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Untersuchungen zur Epidemiologie und Diagnostik von Infektionen in der Hämatologie und Medizinischen Onkologie

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aus Wernigerode

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Solange du nicht aufgibst,
kannst du nicht verlieren.

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Abkürzungsverzeichnis

AGIHO	Arbeitsgemeinschaft Infektionen in der Hämatologie und Onkologie
AML	aktue myeloische Leukämie
AUC	*area under the curve*
BMI	*body mass index*
CDI	*Clostridum difficile*-Infektion
CRBSI	*central venous catheter-related bloodstream infection*
CRP	C-reaktives Protein
DTP	*Differential-Time-to-Positivity*
ELISA	*enzyme-linked immunosorbent assay*
ENTRY	*Effects of delayed entry into blood culture systems on culture positivity*
HR	*hazard ratio*
IPS	*Infection Probability Score*
KI	Konfidenzintervall
MARTINA	*Optimal control of clinically relevant cancer chemotherapy schedules in patients with acute myeloid leukaemia – with special emphasis on neutropenia*
MRGN	multiresistente Gram-negative Stäbchenbakterien
NPW	negativer prädiktiver Wert
NSCLC	*non-small cell lung cancer*
NVI	Norovirus-Infektion
OR	*odds ratio*
PCT	Procalcitonin
PCR	Polymerasekettenreaktion
ROC	*receiver operation characteristic*
SECRECY	*Study to evaluate central venous catheter-related infections in haematology and oncology*
SIMPLY	*Study on the impact of anaerobe blood cultures in catheter-related bacteraemia in haematology*
TTP	*Time-to-Positivity*
ZVK	zentral-venöser Katheter

1 Einleitung

In der Hämatologie und Medizinischen Onkologie wurden in den letzten Jahrzehnten zweifelsohne sehr bedeutende Fortschritte in der Behandlung von Patienten mit Krebserkrankungen erzielt. So konnten z. B. die Überlebensraten von Patienten mit chronischer myeloischer Leukämie (CML) durch die Entwicklung bzw. den Einsatz neuer zytoreduktiver Substanzen, Zytostatika, der allogenen Knochenmark- oder Blutstammzelltransplantation (alloSCT), und letzten Endes vor allem der molekularen, zielgerichteten Medikamente dramatisch verbessert werden. Die Wahrscheinlichkeit des Überlebens 5 Jahre nach Diagnosestellung lag für Patienten, die im Rahmen der Deutschen CML-Studiengruppe behandelt wurden (*n*=3615), im Zeitraum von 1983-1994 mit Busulfan bei 38%, 1983-1994 mit Hydroxyurea bei 44%, 1986-1994 mit Interferon bei 53%, 1995-2001 mit Interferon oder alloSCT bei 63%, 1997-2003 mit Interferon oder alloSCT bei 71% und 2002-2011 mit Imatinib bei 90% [Hochhaus *et al.* 2013]. Ein wesentlicher Baustein in der Behandlung von Krebspatienten ist die Supportivtherapie, ohne die die meisten (kurativen) Krebstherapien gar nicht erst möglich wären – oder wie die *Multinational Association of Supportive Care in Cancer* (MASCC) in ihrem Leitbild treffend formuliert: *Supportive Care makes excellent Cancer Care possible* [MASCC 2015]. Auch in der Supportivtherapie sind in den letzten 10-20 Jahren erhebliche Fortschritte erreicht worden [Egerer 2015], die insgesamt gesehen dazu beigetragen haben, die Überlebenswahrscheinlichkeiten der Patienten deutlich zu verbessern [MASCC 2015]. Die Infektiologie stellt einen wichtigen Pfeiler in der Supportivtherapie dar, da aufgrund der myelosuppressiven Therapien infektiologische Komplikationen bei vielen Patienten zu erwarten sind. Die Hämatologie und Medizinische Onkologie ist spätestens seit Einführung moderner Chemotherapieregimes mit der klinischen Infektiologie sehr eng verbunden.

Infektionen stellen – weltweit gesehen – eine der häufigsten Todesursachen dar. In den Industrieländern fordern nosokomiale Infektionen und die Ausbreitung multiresistenter Erreger das moderne Gesundheitssystem heraus. Die Prävalenz und Inzidenz von Infektionen werden aufgrund der stetig wachsenden Anzahl immunsupprimierter und immer älter werdender Patienten zunehmen und das Spektrum immer breiter werden [Vehreschild *et al.* 2013a]. Infektionen sind in bis zu 70% der Fälle für fatale Komplikationen bei Patienten mit akuten Leukämien verantwortlich [Buchheidt *et al.* 2003]. In den letzten Jahren hat sich die Überlebenswahrscheinlichkeit von Krebspatienten, die auf einer Intensivstation invasiv beatmet werden mussten deutlich verbessert: So konnte die Mortalitätsrate von etwa 90% im Jahr 1983 auf etwa 60% im

Jahr 2011 reduziert werden [Schellongowski 2013]. Infektionen stellen einen nicht unerheblichen Anteil der Ursachen für die Aufnahme von Krebspatienten auf eine Intensivstation dar [Staudinger *et al.* 2013]. Eine intensivmedizinische Behandlung von Krebspatienten verschlechtert die Prognose substantiell, ist aber mit der von kritisch-kranken Patienten ohne maligne Grunderkrankung vergleichbar [Staudinger *et al.* 2000]. Überleben Krebspatienten das akute kritische Problem, haben diese erfreulicherweise dieselbe Langzeitprognose wie vor der Aufnahme auf die Intensivstation [Staudinger *et al.* 2013]. Durch verbesserte antimikrobielle Therapieprotokolle, u. a. auch durch Ergänzung einer antibiotischen um eine antimykotische empirische Therapie, konnte die Prognose von Patienten mit Fieber in Neutropenie verbessert werden. In den prospektiven, multizentrischen Studien der Paul-Ehrlich-Gesellschaft für Chemotherapie (PEG) konnte durch medikamentöse Intervention die Mortalitätsrate für Patienten mit febriler Neutropenie im Jahr 1994 von 6,1% auf 1,6% im Jahr 2006 in der PEG-I-Studie gesenkt werden. In den gleichen Zeiträumen verbesserte sich in der Studie PEG-II die Mortalitätsrate für Patienten mit Bakteriämie/Fungämie von 13,5% auf 5,5% [Link *et al.* 1994; Schiel *et al.* 2006]. Die Fortschritte in der Hämatologie und Medizinischen Onkologie sind insgesamt gesehen also auch auf die Fortschritte im Bereich der Infektiologie zurückzuführen.

Die Hämatologie und Medizinische Onkologie arbeitet also Hand in Hand mit der klinischen Infektiologie bei der Betreuung von Krebspatienten zusammen. Ein positiver Verlauf bzw. Ausgang des einen ist ohne einen positiven Verlauf bzw. Ausgang des anderen nur schwer möglich. Eine fortgeschrittene bzw. nicht kontrollierte Krebserkrankung ist ein prognostisch ungünstiger Faktor für Patienten, die Infektionen wie z. B. Blutstrominfektionen in der Neutropenie entwickeln [Marín *et al.* 2015].

Die Prophylaxe, Diagnostik und Therapie von Infektionen haben daher bei der Therapie von Krebspatienten eine sehr große klinische und prognostische Bedeutung. Während für Infektionen bei Patienten, die nicht an einer Krebserkrankung leiden, auch in Deutschland Standards zur Prophylaxe, Diagnostik und Therapie existierten, gab es solche Vorgaben für Krebspatienten bis Mitte der 1990er Jahre nicht. Die *Arbeitsgemeinschaft Infektionen in der Hämatologie und Onkologie* (AGIHO) ist eine Fachgruppe der Deutschen Gesellschaft für Hämatologie und Medizinische Onkologie (DGHO), die 1996 mit dem Ziel gegründet wurde, diesem Mangel entgegenzutreten und Konzepte zur Kontrolle therapieassoziierter infektiologischer Komplikationen zu entwickeln. Die AGIHO setzt sich aus etwa 150 Ärztinnen und Ärzten aus Deutschland und Österreich zusammen, die ein besonderes Interesse an der Erforschung und Behandlung von Infektionen bei Krebspatienten haben. Ein wesentliches Ziel der AGIHO

ist es daher, Leitlinien zur Prophylaxe, Diagnostik und Therapie von Infektionen bei Krebspatienten zu erstellen. Diesem Ziel kommt die AGIHO durch Bildung von themenspezifischen Arbeitsgruppen nach, die diese Leitlinien regelmäßig aktualisieren und auf Treffen der Arbeitsgemeinschaft zur Diskussion stellen. Viele evidenzbasierte Leitlinien der AGIHO sind bereits in internationalen Fachzeitschriften erschienen, an denen auch der Kandidat aktiv mitgearbeitet hat [Vehreschild *et al.* 2013b; Hentrich *et al.* 2014; Penack *et al.* 2014; Schmidt-Hieber *et al.* 2016; von Lilienfeld-Toal *et al.* 2016; Schmidt-Hieber *et al.* 2018]. Ein zweites Ziel der AGIHO ist die Unterstützung klinischer Studien zur Epidemiologie, Prophylaxe, Diagnostik und Therapie von Infektionen bei Krebspatienten [AGIHO 2018]. Auch hier sind international publizierte Studienergebnisse unter Mitarbeit des Kandidaten verfügbar [Herrmann *et al.* 2017].

Für manche infektiologische Krankheitsbilder, wie z. B. Infektionen im Bereich des Zentralnervensystems, waren nur wenige Daten zu deren klinischen Charakteristika sowie zur optimalen Diagnostik und Therapie verfügbar, oder sie waren auf ganz bestimmte Erreger oder Subgruppen immunsupprimierter Patienten, wie allogen stammzelltransplantierte Patienten, beschränkt. Eine allumfassende klinische Leitlinie zu dieser Problematik war international bislang nicht verfügbar [Schmidt-Hieber *et al.* 2016]. Mit den Leitlinien aus der AGIHO heraus sollte ein für den auf diesem Gebiet unerfahrenen ärztlichen Kollegen ein Handwerkzeug geschaffen werden, um den Patienten optimal zu diagnostizieren und zu therapieren, ohne dass der Arzt sich mit verschiedenen Empfehlungen und Papieren im Einzelnen auseinandersetzen muss.

Leitlinien sind systematisch entwickelte Instrumente des Qualitätsmanagements im Sinne von wissenschaftlich begründeten, praxisorientierten Handlungsempfehlungen, von denen in begründeten Fällen abgewichen werden kann oder sogar muss. Sie stellen den nach einem definierten, transparent gemachten Vorgehen erzielten Konsens mehrerer Experten aus unterschiedlichen Fachbereichen und Arbeitsgruppen zu bestimmten ärztlichen Vorgehensweisen dar. In Richtlinien hingegen wird Handeln oder Unterlassen geregelt. Richtlinien werden von einer rechtlich legitimierten Institution übereinstimmend genehmigt, schriftlich fixiert und veröffentlicht. Für den Rechtsraum dieser Institution sind Richtlinien verbindlich und deren Nichtbeachtung zieht definierte Sanktionen nach sich [Ollenschläger *et al.* 2001].

Die Leitlinien der AGIHO beruhen auf einer systematischen Literaturrecherche und einer einheitlichen Bewertung der Empfehlungsstärke und Qualität der Evidenz nach den Kategorien der *Infectious Diseases Society of America* (IDSA) [Kish 2001] (**Tabelle 1**). Die Empfehlungen basieren auf Konsensusdiskussionen der Expertengruppen und werden in Leitlinientreffen ratifiziert.

Tabelle 1. Graduierung von Empfehlungen für klinische Leitlinien (nach IDSA)

Kategorie, Grad	Definition
Empfehlungsstärke	
A	Gute Evidenz *für* den Einsatz
B	Moderate Evidenz *für* den Einsatz
C	Schwache Evidenz *für* den Einsatz
D	Moderate Evidenz *gegen* den Einsatz
E	Gute Evidenz *gegen* den Einsatz
Qualität der Evidenz	
I	Ergebnisse aus ≥1 guten randomisierten klinischen Studie
II	Ergebnisse aus ≥1 guten klinischen Studie, ohne Randomisation; aus Kohorten- oder Fall-Kontroll-Studien (möglichst aus >1 Zentrum); aus mehreren Langzeitstudien; Dramatische Ergebnisse aus nicht kontrollierten Versuchen
III	Basierend auf Meinungen angesehener Experten, basierend auf klinischer Erfahrung, deskriptiven Studien oder Berichten aus Expertengruppen

IDSA, Infectious Diseases Society of America. Nach Kish 2001.

Im Verlauf der Jahre hat die AGIHO das bewehrte IDSA-Graduierungssystem verlassen und das von der *European Society of Clinical Microbiology and Infectious Diseases* (ESCMID) vorgeschlagene angenommen [Ullmann *et al.* 2012]. Dieses vierstufige System unterscheidet eindeutiger *für* bzw. ganz klar *gegen* eine bestimmte Maßnahme und erlaubt eine eindeutigere Zuordnung der Evidenz (in der Stufe II) – z. B. Generierung der Evidenz aus Metaanalysen oder Übersichtsarbeiten, Übertragung der Evidenz aus anderen Patientenkohorten bzw. ähnlichen Immunstatus-Situationen.

Die Umsetzungen von Empfehlungen und Leitlinien bzw. Adhärenz an eben diese kann das Überleben der Patienten signifikant verbessern. So zeigte eine Studie zur Therapie von Fieber in Neutropenie bei Krebspatienten, dass die Beachtung und Umsetzung von Empfehlungen zu dieser Problematik mit einer verbesserten Überlebenswahrscheinlichkeit einhergeht (HR=0,36 [95% KI 0,14-0,92]; p=0,02) [Rosa *et al.* 2014]. Dies unterstreicht noch einmal nachhaltig die Bedeutung der Implementierung von allumfassenden Empfehlungen zur Prophylaxe, Diagnostik und Therapie von infektiologischen Komplikationen bei unserem Patientengut. Wie wichtig die Infektiologie in der klinischen Routine eines Hämatologen und Medizinischen Onkologen ist und tatsächlich auch ernst genommen wird, zeigen Daten einer Tertiärklinik aus Deutschland: Trotz naturgemäß breiter Expertise des Hämatologen und Medizinischen Onkologen in infektiologischen Fragen wurden die meisten konsiliarischen Anfragen an den Infektiologen aus diesem Bereich gestellt (17%) – operative Disziplinen, wie Orthopädie und Chirurgie, folgten erst auf den Rängen 3 und 4 (jeweils 12%); die zweitmeisten Anfragen kamen aus der Neurologie (13%). Die Adhärenz an die Empfehlungen des

Spezialisten korrelierte dabei mit einer verbesserten Behandlung der Patienten und dem Ausgang der infektiologischen Komplikation [Vehreschild *et al.* 2013a]. Infektionen bei immunsupprimierten Patienten, wie aus dem Bereich der Hämatologie und Medizinischen Onkologie, sind mitunter eine Herausforderung, da sie sich *in puncto* Diagnostik und klinischer Manifestation von nicht-immunsupprimierten Patienten unterscheiden können [Benito *et al.* 2015].

Die Infektiologie ist nicht nur ein integraler Bestandteil bei der Behandlung von Patienten aus dem Bereich der Hämatologie und Medizinischen Onkologie, sondern wird sich sicherlich auch in Zukunft in ausgewählten Fällen therapeutischen Methoden aus der Krebstherapie in der Behandlung von Infektionen bedienen, wie z. B. die bereits erfolgreich eingesetzte Immuntherapie mit artifiziell veränderten chimären Antigen-T-Zell-Rezeptoren (CAR) [Mancini *et al.* 2015], die bereits zur Behandlung verschiedener Krebserkrankungen eingesetzt werden [Couzin-Frankel 2013]. So konnte bereits im Mausmodell gezeigt werden, dass CAR-Zellen, die Dectin-1 exprimieren und somit β-Glucan von *Aspergillus* spp. erkennen, das Hyphenwachstum im Vergleich zur unbehandelten Kontrollgruppe verringern [Kumaresan *et al.* 2018].

Bei Patienten, die unter Chemotherapie stehen, gibt es eine ganze Reihe von Faktoren, die infektiologische Komplikationen begünstigen können. Neben patientenseitigen „intrinsischen“ Faktoren (**Abbildung 1**) gibt es auch Faktoren wie Mukositis oder Gefäßzugänge [Maschmeyer *et al.* 2015a], die man als „extrinsische“ Faktoren bezeichnen könnte. Diese „extrinsischen“ Faktoren sind durch direkte toxische Schäden der Chemotherapie (oder auch durch Radiatio) oder aber durch unser ärztliches Handeln verursacht.

Unter all diesen Faktoren ist und bleibt die Neutropenie der primäre bzw. wichtigste Risikofaktor [Rolston 2015]. Der Nadir der neutrophilen Granulozyten tritt für gewöhnlich am Ende der zweiten Woche nach Beginn einer Chemotherapie, zwischen Tag 10 und 14, auf. Dies ist die Zeit, bei der das Maximum der zytotoxischen Wirkung der Chemotherapie auf die intestinale Mukosa zu erwarten ist. Dies bedeutet auch, dass Fieber in Neutropenie typischerweise zwischen Tag 10 und 14 eines Chemotherapiezyklus auftritt – ganz unabhängig vom eingesetzten Protokoll [Bow 2015]. Die Mehrzahl der Episoden von Fieber in Neutropenie treten im ersten Zyklus auf. In solch einem Fall besteht dann auch ein größeres Risiko, dass in weiteren Zyklen erneut Fieber in Neutropenie auftritt [Cullen et al. 2007].

Abbildung 1. Prädisponierende Faktoren für infektiologische Komplikationen (nach Schmidt-Hieber *et al.* 2017).

Auch im Zeitalter der hoch-technisierten Medizin basiert die Diagnose einer so wesentlichen Komplikation wie Fieber in Neutropenie im Prinzip also nicht auf laborchemischen Markern wie Lipopolysacharid-Bindungsprotein, Procalcitonin, C-reaktives Protein oder Interleukin 6 [García de Guadiana-Romualdo *et al.* 2015], sondern auf den „einfachen“ klinischen Blick sowie der Tatsache einer stattgehabten Chemotherapie. Einzig das Differentialblutbild zur Bestimmung der neutrophilen Granulozyten (siehe Abschnitt 2.1.1) spielt dabei eine nicht zu vernachlässigende Rolle.

In dieser kumulativen Habilitationsschrift sollen ausgewählte Aspekte zur Epidemiologie von Infektionen sowie Aspekte zur laborhämatologischen, laborchemischen, mikrobiologischen und klinischen Diagnostik von infektiologischen Komplikationen bei Krebspatienten unter Zuhilfenahme aktueller AGIHO-Leitlinien und eigenen Arbeiten des Kandidaten der Jahre 2007 bis 2018 aus Sicht des klinisch tätigen Hämatologen und Medizinischen Onkologen näher beleuchtet und diskutiert werden. Die Daten und Untersuchungsergebnisse aus den hier beschriebenen Arbeiten des Kandidaten stammten dabei von Patienten bzw. Probanden aus der Klinik für Hämatologie und Onkologie (Universitätsklinikum Magdeburg [UKMD]; Direktor: Prof. Dr. med. Th.

Fischer), der Klinik für Gastroenterologie, Hepatologie und Infektiologie (UKMD; ehemaliger Direktor: Prof. Dr. med. Drs. h.c. em. P. Malfertheiner) und dem Institut für Transfusionsmedizin und Immunhämatologie mit Blutbank (UKMD; ehemaliger Direktor: Prof. Dr. med. em. M. Heim) bzw. dem Institut für Medizinische Mikrobiologie und Krankenhaushygiene (UKMD; ehemaliger Direktor: Prof. Dr. med. em. W. König, jetziger Direktor: Prof. Dr. med. D. Schlüter) sowie der Klinik für Pneumologie, Allergologie, Schlaf- und Beatmungsmedizin und Thorakale Onkologie der Lungenklinik Lostau (Chefarzt: Dr. med. H. Achenbach).

Publikation I

Schmidt-Hieber M, Silling G, **Schalk E**, Heinz W, Panse J, Penack O, Christopeit M, Buchheidt D, Meyding-Lamadé U, Hähnel S, Wolf HH, Ruhnke M, Schwartz S, Maschmeyer G. CNS infections in patients with hematological disorders (including allogeneic stem cell transplantation) – Guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Medical Oncology (DGHO). **Ann Oncol 2016**;27(7):1207-1225

2 Ergebnisse und Disskussion

2.1 Laborparameter

2.1.1 Kapilläre Blutbildbestimmung

Die Bestimmung der Leukozyten bzw. neutrophilen Granulozyten hat in der Hämatologie in der täglichen Routine eine immense Bedeutung. In der Phase der Leuko- bzw. Neutropenie erfolgt deren Bestimmung täglich. Seit Jahrzehnten wissen wir bereits, dass nicht nur die Tiefe der Neutropenie, sondern auch deren Dauer das Risiko für Fieber und Infektionen bestimmt [Bodey *et al.* 1966]. Je nach Dauer der Neutropenie werden Patienten einem Standard- oder hohem Risiko zugeordnet [Heinz *et al.* 2017]. Patienten, die in der Neutropenie eine Sepsis entwickeln, weisen eine Krankenhausmortalität von etwa 50% auf [Legrand *et al.* 2012]. Deshalb ist es wichtig, die richtige und schnelle Diagnose zu stellen, um eine adäquate Therapie unmittelbar beginnen zu können [Penack *et al.* 2014; Heinz *et al.* 2017]. Die Therapie von Fieber bzw. Infektionen unterscheidet sich, je nachdem, ob eine Neutropenie vorliegt bzw. wie lange sie andauert [Buchheidt *et al.* 2003; Heinz *et al.* 2017]. Weiterhin ist die Kenntnis der Leukozyten bzw. insbesondere der neutrophilen Granulozyten wichtig für oder gegen die Entscheidung einer antimikrobiellen Prophylaxe oder den Einsatz von Granulozyten-kostimulierenden Faktoren (G-CSF) [Neumann *et al.* 2013; Vehreschild *et al.* 2014a]. Fieber in Neutropenie gilt als infektiologischer Notfall. Um die Diagnose einer Neutropenie stellen zu können, bedarf es, aufgrund fataler Konsequenzen für den Patienten bei „Übersehen“ einer Neutropenie, valider Methoden in der Blutbildbestimmung.

In unserem Zentrum war es über lange Zeit im stationären und ambulanten Bereich Standard, dass die Blutbildbestimmungen durch kapilläre Punktion einer Fingerbeere erfolgen. Aufgrund dieser so erstellten Blutbilder wurden klinischen Entscheidungen getroffen. Wir stellten uns daraufhin die Frage, wie valide die von unserem hämatologischen Speziallabor so bestimmten Blutbildparameter im Vergleich zur venösen Blutentnahme, die immer noch als Standard gilt, sind [Daae *et al.* 1991]. Auch wenn kapilläre Blutbildanalysen in der Hämatologie seit vielen Jahrzehnten etabliert sind [Lewis *et al.* 1965], gibt es nur wenige, akzeptable kapillär-venös vergleichende Studien zu Blutbildparametern bei Erwachsenen und Patienten – also mit pathologischen Werten. Wir führten daher an unserem Zentrum in Kooperation mit dem Institut für Transfusionsmedizin und Immunhämatologie mit Blutbank eine prospektive

Studie durch, insbesondere, um unsere interne Methode der kapillären Blutbildbestimmung zu validieren [Schalk *et al.* 2007].

Wir untersuchten 463 zeitgleich von einer Fingerbeere und peripheren Vene entnommene Blutproben bei 428 Erwachsenen (Advia 120, Bayer, Deutschland). Dabei handelte es sich um 303 Patienten (70,8%) und um 125 (29,2%) Probanden, wobei darunter 70 (56,0%) potentielle Blutspender waren. Das mittlere Alter der Gesamtkohorte betrug 51 Jahre (Spanne 18-82 Jahre). Das Geschlechterverhältnis war ausgeglichen. Die meisten Patienten litten an malignen Lymphomen (172; 56,8%), Leukämien (42; 13,9%) und myeloproliferativen Neoplasien (41; 13,5%). Interessanterweise fanden wir keinerlei infektiologische Komplikationen nach Punktion der Fingerbeere bei neutropenen Patienten oder vermehrte Blutungen bei Patienten mit Thrombopenie.

Insgesamt fanden wir höhere kapilläre Werte für Hämoglobin (+0,2 mmol/l) und Leukozyten (+200/µl) im Vergleich zu den korrespondierenden venösen Werten sowie niedrigere Thrombozytenwerte (-1000/µl) in der kapillären Messung. Diese Unterschiede sind statistisch signifikant bzw. zeigen einen Trend zur Signifikanz (**Tabelle 2**). Die statistische Signifikanz ist bei jeweils sehr hohen Korrelationskoeffizienten (Pearson's *r*; ≥0,98) am ehesten auf den großen Stichprobenumfang zurückzuführen. Allenfalls für die Differenz im Hämoglobinwert wurde auch von einer klinischen Relevanz ausgegangen, wenn man sich an strikte Grenzwerte zur Frage der Erythrozytentransfusion halten würde. Dies würde dann möglicherweise zu häufigeren/früheren Transfusionen führen, wenn die Hämoglobinbestimmung kapillär erfolgt [Schalk *et al.* 2007]. Große Zellen werden bei der kapillären Blutentnahme bzw. Messung „bevorzugt", was die entsprechend höheren Leukozyten- und niedrigeren Thrombozytenwerte erklären könnte [Schalk *et al.* 2009].

Tabelle 2. Vergleich von kapillär-venösen Blutbildparametern (*n*=463)

Parameter	Δ-Wert[a]	*p*-Wert	Pearson's *r*[b]	Cohen's *d*[c]
Hämoglobin [mmol/l]	+0,2	<0,001	0,98	0,13
Leukozyten [x/µl]	+200	0,002	1,00	0,01
Neutrophile Granulozyten[d] [x/µl]	-70	0,05	0,98	0,02
Thrombozyten [x/µl]	-1000	0,08	0,99	0,01

[a]Mittlere Differenz zwischen kapillärer *vs.* venöser Messung. [b]Korrelationskoeffizient. [c]Effektstärke. [d]*n*=447. Daten aus Schalk *et al.* 2007, tlw. unveröffentlicht.

Statistisch signifikante Ergebnisse müssen allerdings nicht notwendigerweise auch von klinischer Relevanz sein [Schulz 2012] – *et vice versa*. Um die praktische, klinische Relevanz der kapillär-venösen Differenzen zu messen, wurde nach Publikation die Effekt-

stärke Cohen's *d* berechnet (**Tabelle 2**) [Schalk 2015; unveröffentlichte Daten]. Cohen's *d* misst die Effektgröße für Mittelwertunterschiede zwischen zwei Gruppen und hilft die praktische Relevanz eines signifikanten Mittelwertunterschieds zu beurteilen. Eine Effektstärke von 0,8 zeigt einen großen, 0,5 einen mittleren und 0,2 einen kleinen Effekt an. Im Allgemeinen wird ein Cohen's *d* von kleiner 0,2 als nicht klinisch relevant angesehen [Cohen 1988]. Demnach sind die beobachten Unterschiede zwischen kapillärer und venöser Messung aus unserer Sicht klinisch nicht relevant (jeweils Cohen's *d* <0,2).

Die interessante Frage war dann anschließend, inwieweit sich kapillär bestimmte Blutbildparameter für die klinisch wichtigen Grenzwerte wie Neutropenie, Agranulozytose, Anämie und Thrombopenie im Vergleich zu venös bestimmten Werten verhalten. Da gemeinhin eine Neutropenie auch bei Gesamtleukozyten <1000/µl anzunehmen ist und in der Klinik breite Anwendung findet, betrachteten wir auch diese Laborkonstellation. Dazu führten wir an den zuvor erhobenen Datensätzen nochmals eine Analyse durch [Schalk *et al.* 2007; Schalk *et al.* 2008]. Dabei erschien uns die Frage nach den neutrophilen Granulozytenwerten am wichtigsten. Die Kenntnis reeller Werte der neutrophilen Granulozyten ist für die Abschätzung des Infektionsrisikos von Patienten – insbesondere bei schwerkranken und infektgefährdeten Patienten in der Hämatologie – essentiell. Das Risiko steigt mit der Abnahme eben dieser Werte, also der Tiefe der Neutropenie. So besteht bereits bei leichtgradiger Neutropenie von <1000/µl eine deutlich gesteigerte Infektneigung. Bei neutrophilen Granulozyten <500/µl liegt eine Beeinträchtigung der Kontrolle der körpereigenen mikrobiellen Flora vor. Liegen die neutrophilen Granulozyten bei <200/µl, so kann keine lokale Entzündungsreaktion mehr stattfinden. Bis *dato* gab es nur eine kleine Studie mit 40 gesunden Erwachsenen, die höhere Werte in der kapillären Blutentnahme zeigte [Daae *et al.* 1988]. Wir konnten nun zeigen, dass für neutrophile Granulozyten <1500/µl (+30/µl) und <500/µl (+20/µl) sowie für Thrombozyten <20.000/µl (+1000/µl) ebenfalls nur sehr geringe Unterschiede zwischen der kapillären und venösen Bestimmung bestehen, die nicht bzw. nur grenzwertig signifikant sind. Die Korrelation der kapillären und venösen Wertepaare war ebenfalls sehr hoch (≥0,97). Da die Effektstärke Cohen's *d* für all diese Werte insgesamt bzw. die Grenzwerte <0,2 war, haben die gemessenen Unterschiede aus unserer Sicht ebenfalls keine klinische Relevanz. Einzig für die Leukopenie <1000/µl sowie für die Diagnose der Anämie (Hämoglobin <6,0 mmol/l) besteht ein grenzwertig signifikanter bzw. signifikanter Unterschied zwischen kapillärer und venöser Bestimmung. Der Unterschied von +100/µl bzw. +0,2 mmol/l ist aber von nur sehr geringer klinischer Relevanz, wie Cohen's *d* von 0,25 bzw. 0,29 noch einmal (statistisch) belegt (**Tabelle 3**).

Tabelle 3. Vergleich von wichtigen klinischen kapillär-venösen Blutbildparametern

Parameter	Δ-Wert[a]	Sens.	Spez.	*p*-Wert	Pearson's *r*[b]	Cohen's *d*[c]
Leukopenie[d] [x/µl] (*n*=18)	+100	1,00	1,00	0,06	0,87	0,25
Neutropenie[e] [x/µl] (*n*=43)	+30	0,95	1,00	0,07	0,98	0,06
Agranulozytose[f] [x/µl] (*n*=19)	+20	0,95	1,00	0,15	0,97	0,12
Anämie[g] [mmol/l] (*n*=55)	+0,2	0,89	0,99	<0,001	0,93	0,29
Thrombopenie[h] [x/µl] (*n*=21)	+1000	0,91	1,00	0,06	0,98	0,18

Sens., Sensitivität; Spez., Spezifität. [a]Mittlere Differenz zwischen kapillärer *vs.* venöser Messung. [b]Korrelationskoeffizient. [c]Effektstärke. [d]Leukozyten <1000/µl. [e]Neutrophile Granulozyten <1500/µl. [f]Neutrophile Granulozyten <500/µl. [g]Hämoglobin <6,0 mmol/l. [h]Thrombozyten <20.000/µl. Daten aus Schalk *et al.* 2007, Schalk *et al.* 2008, tlw. unveröffentlicht.

Aufgrund der ermittelten statistischen Kennzahlen Sensitivität und Spezifität (**Tabelle 3**), kann für die Diagnostik einer Leukopenie, Neutropenie, Agranulozytose, Anämie und Thrombopenie mittels kapillärer Blutbildbestimmung jeweils eine extrem hohe diagnostische Odds Ratio (DOR) berechnet werden (DOR >800), was der kapillären Blutbildbestimmung, als diagnostische Methode, zusätzlich eine sehr hohe Aussagekraft für die genannten klinischen Situationen bescheinigt [Glas *et al.* 2003].

Bei Kindern werden größere kapillär-venöse Differenzen bei der Messung der neutrophilen Granulozyten beobachtet. Die relativen Differenzen vermindern sich mit zunehmenden Alter: +17,2% bei Kindern von 3 Monaten bis 14 Jahren, +12,6% bei jungen Erwachsenen im Alter von 20-22 Jahren und +8,2% im Alter von 22-62 Jahren [Daae *et al.* 1988; Daae *et al.* 1991; Yang *et al.* 2001]. Wir fanden eine relative Differenz von +1,0% (Alterspanne 18-81 Jahre; etwa 60% der Untersuchten waren älter als 50 Jahre). Es scheint also so zu sein, dass die (relativen) kapillär-venösen Differenzen mit dem Alter abnehmen. Bei Kindern wird auch eine Makrozytose diskutiert [Schalk *et al.* 2009], was die größeren kapillär-venösen Werte erklären könnte (siehe oben).

Unsere Studie war zum damaligen Zeitpunkt die größte zu diesem Thema [Schalk *et al.* 2009]. Bislang ist auch keine weitere Studie mit solch einem Stichprobenumfang (*n*=463) sowie Einschluss von Patienten mit pathologischen Werten in der Fachliteratur erschienen [PubMed 2018]. Die Analyse der Literatur zu 6475 kapillär-venösen Blut-

bildparametern erbrachte, dass kapilläre Bestimmungen zuverlässig, risikoarm, präzise und valide sind und demnach mit hoher Wahrscheinlichkeit *richtig*-positive und *richtig*-negative Werte erbringen. Kapilläre Blutbildmessungen sind daher auch, oder gerade deswegen, für die Bestimmung der neutrophilen Granulozyten und Thrombozyten bei thrombopenen Patienten geeignet. Letzteres spielt bei ZVK-Infektionen (siehe Abschnitt 2.4) keine unerhebliche Rolle. Wichtig für die kapilläre Blutbildbestimmung ist allerdings, dass die Punktion einer Fingerbeere erfolgt, und nicht die eines Ohrläppchens, und dass der erste Blutstropfen verworfen wird. Letzteres ist insbesondere für die Bestimmung der Thrombozyten wichtig [Schalk *et al.* 2009].

Publikation II
Schalk E, Heim MU, Koenigsmann M, Jentsch-Ullrich K. Use of capillary blood count parameters in adults. **Vox Sang 2007**;93(4):348-353

Publikation III
Schalk E, Scheinpflug K, Mohren M. Correlation of capillary and venous absolute neutrophil counts in adult hematological patients and normal controls. **Am J Hematol 2008**;83(7):605

Publikation IV
Schalk E, Scheinpflug K, Mohren M. Capillary blood count analyses in the clinical practice: a safe, reliable and valid method. **J Lab Med 2009**;33(5):303-309

2.1.2 C-reaktives Protein und Procalcitonin beim Lungenkarzinom

Das C-reaktive Protein (CRP) ist ein Akute-Phase-Protein, was Inflammation anzeigt. Dies kann zum einen infektionsbedingt durch Bakterien oder Pilze sein, zum anderen kann es aber auch durch nicht-infektionsbedingte Ursachen zu erhöhten CRP-Werten kommen. So werden erhöhte CRP-Werte regelhaft bei soliden Tumoren, wie z. B. bei Patienten mit Lungenkrebs, beobachtet, ohne dass Infektionen vorliegen, wenngleich Lungenkrebs-Patienten oft Infektionen erleiden, zumeist Pneumonien. Die diagnostische Aussagekraft des CRP-Wertes ist daher oft eingeschränkt [Penel *et al.* 2004; Hong *et al.* 2012; Srimuninnimit *et al.* 2012; Tulek *et al.* 2013]. Ein Parameter der hier weiterhelfen kann, ist Procalcitonin (PCT). PCT vermag zwischen infektionsbedingten und nicht-infektionsbedingten inflammatorischen Reaktionen durch Antwort auf zirkulierende bakterielle Endotoxine und inflammatorische Zytokine zu differenzieren. Wie beim CRP ist auch beim PCT die Aussagekraft bei Krebspatienten eingeschränkt bzw. sind die Daten aus der Literatur uneinheitlich [Maruna *et al.* 2000; Nijsten *et al.* 2000; Carrol *et al.* 2002; Penel *et al.* 2004; Schüttrumpf *et al.* 2006; Masago *et al.* 2010]. In der klinischen Routine wird zur Diagnostik einer Infektion zumeist das CRP verwendet, und zur Absicherung oft noch das PCT im Nachgang hinzugezogen. Aufgrund der

Synthese von PCT unter physiologischen Bedingungen in den C-Zellen der Schilddrüse [Maruna *et al.* 2000], ist durchaus verständlich, dass PCT auch in Tumoren mit neuroendokriner Differenzierung gebildet werden kann. Es konnte gezeigt werden, dass PCT bei Lungenkarzinomen mit neuroendokriner Komponente, also kleinzellige Lungenkarzinome, erhöht ist [Patout *et al.* 2014]. Wir stellten uns daher die Frage, inwieweit PCT einen zusätzlichen Nutzen zum CRP bringt, um zwischen infektionsbedingter CRP-Erhöhung und nicht-infektionsbedingter CRP-Erhöhung bei Patienten mit nicht-kleinzelligem Lungenkarzinom (NSCLC), also ohne neuroendokriner Komponente, zu unterscheiden.

Wir führten daher eine retrospektive Untersuchung an der Abteilung Thorakale Onkologie der Klinik für Pneumologie, Allergologie, Schlaf- und Beatmungsmedizin und thorakale Onkologie, Lungenklinik Lostau, durch [Scheinpflug *et al.* 2015]. Es wurden dabei 100 Fälle von 63 Patienten im Zeitraum von 01/2013 bis 10/2013 eingeschlossen. All diese Patienten litten an einem NSCLC und hatten bei Aufnahme eine CRP-Erhöhung. Bei jedem dieser 100 Patienten wurde gleichzeitig auch das PCT bestimmt. Infektionen wurden anamnestisch, klinisch sowie durch weiterführende bildgebende und mikrobiologische Untersuchungen diagnostiziert. Für die CRP-Bestimmung wurde der Latex-Agglutinations-Test COBAS INTEGRA System, Roche Diagnostics, Deutschland, verwendet. CRP-Werte <0,5 mg/l wurden als normal angesehen. Der Enzyme-linked Fluorescent Assay VIDAS BRAHMS PCT, Brahms Diagnostica, Deutschland, wurde für die PCT-Bestimmung eingesetzt. Ein Wert <0,5 ng/ml wurde als normal definiert. Es wurden Patienten mit Infektionen mit Patienten ohne Vorliegen einer Infektion verglichen. Eine sog. Receiver Operation Characteristic- (ROC) Analyse wurde durchgeführt und die Fläche unter der Kurve (AUC) berechnet, um die Genauigkeit der Diskriminierung zwischen Infektionen und Nicht-Infektionen zu bestimmen. Dabei sagt eine AUC <0,5 aus, dass keine diagnostische Genauigkeit besteht; bei einer AUC zwischen 0,5 und 0,7 besteht eine mittlere, bei einer AUC zwischen 0,7 und AUC=0,9 eine hohe diagnostische Genauigkeit [Swets 1988].

Das mittlere Patientenalter betrug 65,6 Jahre; 69,8% der Patienten waren Männer. Die Mehrzahl der Patienten befand sich im metastasierten Stadium IV (76,2%). In 79 Fällen (79,0%) wurde eine Infektion diagnostiziert. Dabei handelte es sich zumeist um Pneumonien (47; 59,5%), gefolgt von akuten Exazerbationen chronisch obstruktiver Lungenerkrankungen (14; 17,8%), Empyeme (12; 15,2%) und Harnwegsinfektionen (4, 5,0%); Sepsis oder febrile Neutropenie kamen nicht vor. Die gleichzeitige CRP- und PCT-Erhöhung ging nicht mit einem höheren Risiko für das Vorliegen einer Infektion einher (OR=0,8 [95% KI 0,3-2,6]; p=0,93). Es fand sich kein Unterschied in der

mittleren CRP-Erhöhung zwischen der Gruppe der Patienten mit Infektionen und der Gruppe ohne Infektionen (144,6 mg/l *vs.* 108,8 mg/l; *p*=0,09). Das gleiche konnte für die Frage der PCT-Erhöhung beobachtet werden: 0,37 ng/ml *vs.* 0,50 ng/ml (*p*=0,47). Sowohl für die Gruppe der Patienten mit Infektionen als auch für die Patienten ohne Infektionen fanden wir trotzdem eine positive Korrelation (Pearson's *r*) zwischen den CRP- und PCT-Werten (*r*=0,48 bzw. *r*=0,80). Bezüglich der Vorhersage von Infektionen in unserer NSCLC-Kohorte konnten wir eine AUC von 0,59 für CRP und eine AUC von 0,46 für PCT ermitteln. Insbesondere die niedrige AUC für PCT <0,5 in der Vorhersage von Infektionen, aber auch die nicht-signifikant positive und höhere PCT-Erhöhung und der höhere Korrelationskoeffizient jeweils in der Gruppe der Patienten ohne Infektion, zeigt, dass das PCT bei Patienten mit NSCLC offenbar nicht hilfreich ist, um zwischen einer infektionsbedingten und einer nicht-infektionsbedingten CRP-Erhöhung zu unterscheiden respektive in der Diagnostik von Infektionen in dieser Patientenkohorte keine Rolle spielt. Das heißt also, dass nicht jede PCT-Erhöhung bei NSCLC-Patienten, die eine CRP-Erhöhung aufweisen, gleichzusetzen ist mit dem Vorliegen einer Infektion. Infektionen müssen daher in dieser Patientenkohorte durch andere – anamnestische, klinische, bildgebende und mikrobiologische – Untersuchungen bzw. Parameter ausgeschlossen bzw. bewiesen werden. Dieses Wissen könnte dazu führen, dass Antibiotika nicht in jeden Fall einer CRP- bzw. PCT-Erhöhung in diesem Patientengut primär eingesetzt werden müssen. Dies könnte wichtig *in puncto* eines sog. Antimicrobial Stewardship sein.

In der klinischen Routine werden CRP und PCT in der Diagnostik und im Verlauf von Infektionen bestimmt. Für die Diagnose einer Sepsis ist die Bestimmung des PCT gegenüber dem CRP vorteilhafter [Maruna *et al.* 2000; Nijsten *et al.* 2000; Carrol *et al.* 2002]. Es gibt allerdings nur wenige Berichte über die Anwendung von PCT bei Patienten mit Lungenkrebs, die zum Teil widersprüchliche Ergebnisse zeigen oder gar keine Patienten mit Infektionen einschlossen [Masago *et al.* 2010; Tulek *et al.* 2013]. PCT hat seine Wertigkeit in der Diagnostik von Bakteriämie und Sepsis [Hoeboer *et al.* 2015]. Die meisten Patienten in unserer Kohorte hatten eine Pneumonie als Infektfokus. Eine PCT-Erhöhung ist nur bei solchen Patienten mit Pneumonie zu verzeichnen, die auch bakteriämisch sind [Johansson *et al.* 2014]. Nicht jede Pneumonie geht jedoch notwendiger Weise mit einer Bakteriämie einher [Hagel *et al.* 2013], was die Ergebnisse aus unserer Arbeit erklären könnte. Denn, PCT vermag sehr wohl Infektionen bei Patienten mit Lungenkarzinom anzuzeigen, sofern sich diese mit Fieber präsentieren [Masago *et al.* 2010].

Publikation V
Scheinpflug K*, **Schalk E***, Grabert E, Achenbach HJ. Procalcitonin is not useful to discriminate between infectious and non-infectious CRP elevation in patients with non-small cell lung cancer. **Infect Control Hosp Epidemiol 2015**;36(9):1117-1118
*Geteilte Erstautorenschaft

2.2 Fieber in Neutropenie

2.2.1 Epidemiologie und Klinik

Hämatologische Patienten, insbesondere solche mit akuten Leukämien oder myelodysplastischen Syndromen, haben mit 85-95% die höchste Rate an Fieber in Neutropenie – verglichen mit Patienten mit Sarkomen, Lymphomen oder soliden Tumoren, wo die Raten maximal 25% betragen [Bow 2015]. Das hohe Risiko bei Patienten mit akuten Leukämien ist auf die Leukämie *per se* und die Therapiefolgen zurückzuführen [Crawford *et al.* 2004] – wobei die Neutropenie der primäre und wichtigste Risikofaktor ist [Bodey *et al.* 1966]. Wie bereits im Abschnitt 2.1.1 dargestellt, geht das Risiko für Infektionen mit der Tiefe und der Dauer der Neutropenie einher. Andere Risikofaktoren für Infektionen sind die eingeschränkte zelluläre und humorale Immunität, zerstörte Barrieren, wie Haut und vor allem Schleimhäute und venöse Katheter [Maschmeyer *et al.* 2015a]. Oft liegen bei ein und demselben Patienten mehrere Risikofaktoren vor. Man kann annehmen, dass mehr als die Hälfte der Patienten mit Fieber in Neutropenie oder Bakteriämie eine Sepsis bzw. einen septischen Schock entwickeln. Eine schwere Sepsis wurde bei 20-30% und ein septischer Schock bei 5-10% der Patienten mit Fieber in Neutropenie beobachtet [Penack *et al.* 2014]. Diese epidemiologischen Daten gewinnen vor dem Hintergrund der sehr hohen Mortalitätsraten, die bei bis zu 85% in diesem Patientengut liegen [Azoulay *et al.* 2013], nochmal besonders an Bedeutung. Wie bereits im Abschnitt 2.1.1 diskutiert, ist es daher wichtig, den neutropenen Patienten adäquat anhand des (Differential-) Blutbildes zu diagnostizieren. Angemerkt werden muss bei der Diagnose der Sepsis [Levy *et al.* 2003] bei Patienten mit hämatologischen Krebserkrankungen bzw. in Neutropenie jedoch, dass naturgemäß die Leukozytenwerte bzw. die Werte der neutrophilen Granulozyten nicht mit zur Diagnostik herangezogen werden können [Penack *et al.* 2014]. In der Literatur sind viele Leitlinien zum Management von Patienten mit Sepsis verfügbar, jedoch zielt keine davon speziell auf Patienten mit Neutropenie ab. Einzig die Leitlinie der AGIHO hat sich bislang dieses speziellen Themas unter Mitwirkung des Kandidaten angenommen [Penack *et al.* 2014].

In der Hämatologie hat sich „eingebürgert“, dass man von Neutropenie spricht bei Vorliegen der neutrophilen Granulozyten von <500/µl bzw. weniger als 1000/µl oder wenn ein Abfall in den kommenden zwei Tagen auf 500/µl zu erwarten ist [Heinz *et al.* 2017]. Vor dem Hintergrund der deutlich verminderten Abwehrlage mit fehlender Kontrolle der körpereigenen mikrobiellen Flora (siehe Abschnitt 2.1.1) bei Neutropenie <500/µl ist dies nachvollziehbar. Mindestens 500/µl neutrophile Granulozyten sind also für das „Überleben“ notwendig. Man spricht von Fieber (in Neutropenie), wenn die Körpertemperatur einmalig ≥38,3°C beträgt, mindestens für eine Stunde bei ≥38,0°C liegt oder innerhalb von zwölf Stunden zweimal gemessen ≥38,0°C beträgt [Heinz *et al.* 2017].

Liegt Fieber in Neutropenie vor, so ist bis zum Beweis des Gegenteils von einer Infektion auszugehen, da dies in der Regel in über 90% bei Patienten mit akuten Leukämien der Fall ist [Rolston 2015]. Die Diagnose Fieber bei Patienten in Neutropenie rechtfertigt den sofortigen Beginn einer empirischen Antibiotikatherapie [Link *et al.* 2003; Penack *et al.* 2014]. Bei fiebernden Patienten in der Neutropenie ist die Mortalitätsrate mindestens um 15% höher als bei neutropenen Patienten, die kein Fieber entwickeln [Lyman *et al.* 2010]. Eine Verzögerung des Beginns einer antibiotischen Therapie innerhalb der ersten sechs Stunden bei Patienten im septischen Schock geht mit einer verminderten Überlebenswahrscheinlichkeit von 7% pro verzögerter Stunde einher [Kumar *et al.* 2006]. Ähnlich, wenn nicht noch kritischer, dürfte die Situation bei Patienten mit Sepsis in Neutropenie sein, wenn es zu einem verzögerten Beginn der Antibiotikatherapie von mehr als einer Stunde kommt: In einer Studie wurde ein extrem hohes Mortalitätsrisiko für diese Patientenkohorte angegeben (OR=10,0 [95% KI 2,5-33,0)] [Mokart *et al.* 2014].

In etwa 40-50% der Fälle handelt es sich bei den Infektionen um ungeklärtes Fieber (auch als Fieber ohne Ursache [FUO] bezeichnet), gefolgt von jeweils 25-30% klinisch-dokumentierten und mikrobiologisch-dokumentierten Infektionen. Klinisch-dokumentierte Infektionen sind solche mit einem klinischen oder radiologischen Hinweis auf eine Infektion, ohne dass diese jedoch mikrobiologisch bestätigt wurde (z. B. Pneumonie, Enterokolitis). Für mikrobiologisch-dokumentierte Infektionen bedarf es einem signifikanten kulturellen Erregernachweis [Buchheidt *et al.* 2003; Rolston 2015]. Patienten mit dokumentierten Infektionen weisen höhere Mortalitätsraten auf als Patienten, die sich „nur“ mit Fieber in Neutropenie präsentieren [Kuderer *et al.* 2006]. Diese Beobachtung konnten wir in einer sehr kleinen retrospektiven Analyse an Patienten mit akuten Leukämien (n=75) so nicht bestätigen: Bei Patienten mit einer positiven Blutkultur war das mediane Krankenhaus-Überleben länger (p=0,04, Cohen’s d=0,6) als bei Patienten

ohne positive Blutkulturen [Schalk 2013]. Dies könnte bedeuten, dass die gezielte Antibiotikatherapie bei einem Erregernachweis einen Überlebensvorteil gegenüber einer empirischen bzw. kalkulierten Therapie erringt. Der Respirationstrakt stellt die häufigste Infektionsquelle bei Patienten mit akuten Leukämien dar (**Tabelle 4**); etwa 25% der Patienten mit akuten Leukämien entwickeln Lungeninfiltrate [Maschmeyer *et al.* 2015b; Rolston 2015], wenngleich nicht alle Infiltrate auf Infektionen zurückzuführen sind [Schalk *et al.* 2005].

Tabelle 4. Häufige Infektionen/Infektionsherde bei Patienten mit akuten Leukämien

Infektion/Infektfokus	Häufigkeit [%]
Respirationstrakt	30-40
Blutbahn	15-20
Harntrakt	10-15
Haut	8-10
Intestinaltrakt	5-8
Andere	10-15

Nach Rolston 2015.

Publikation VI
Penack O, Becker C, Buchheidt B, Christopeit M, Kiehl M, von Lilienfeld-Toal M, Hentrich M, Reinwald M, Salwender H, **Schalk E**, Schmidt-Hieber M, Weber T, Ostermann H. Management of sepsis in neutropenic patients: 2014 updated guidelines from the Infectious Diseases Working Party of the German Society of Hematology and Medical Oncology (AGIHO). **Ann Hematol 2014**;93(7):1083-1095

2.2.2 Erregerspektrum

In entwickelten Ländern überwiegen bei Krebspatienten Gram-positive Erreger, wobei die Zahl der Gram-negativen Bakteriämien in den Zentren, in denen eine antibiotische Prophylaxe durchgeführt wird, noch niedriger ist [Feld 2008; Rolston 2015]. Allerdings ist die Mortalitätsrate bei Gram-negativen Bakeriämien höher als bei Gram-positiven (18% *vs.* 5%) [Feld 2008]. Der hohe Anteil bzw. die Zunahme Gram-positiver Bakteriämien ist möglicherweise auf die vermehrt durchgeführte Antibiotikaprophylaxe, vornehmlich mit Fluorochinolonen, den vermehrten Gebrauch zentral-venöser Katheter (ZVK) sowie das vermehrte Auftreten oraler Mukositis zurückzuführen [Zinner 2000].

Die Kenntnis des – zu erwartenden – Erregerspektrums ist bei Patienten mit hämatologischen Krebserkrankungen insbesondere in der Phase der Neutropenie essentiell. Die empirische oder dann auch kalkulierte antimikrobielle Therapie richtet sich nach

dem zu erwartenden Erreger. In der frühen Phase der Neutropenie sind vor allem bakterielle Infekte zu erwarten. Erst bei prolongierter Neutropenie über 10 Tage gewinnen andere (opportunistische) Erregergruppen, wie Pilze und Viren, an Bedeutung und müssen dann bei der Wahl der antimikrobiellen Therapie mit bedacht werden [Rolston 2015]. Invasive Pilzinfektionen können jedoch auch bei einer Neutropeniedauer von weniger als 10 Tagen auftreten [Schalk *et al.* 2006]. Der häufige Einsatz antimikrobieller Substanzen für die verschiedenen Indikationen, wie prophylaktische, empirische, präemptive oder zielgerichtete Therapien, beeinflusst die Natur und das Spektrum der Infektionen, mit der Gefahr des vermehrten Auftretens multiresistenter Erreger [Rolston 2015]. Die in einem Krankenhaus bzw. in einer Klinik auch außerhalb der Gruppe von Krebspatienten sowie in der Gemeinschaft als solche primär und routinemäßig angewandte Antibiotikastrategie beeinflusst die „Mikrobiologie“ (Erregerspektrum, Resistenzlage) bei hämatologischen Krebspatienten [Akova 2015]. Die Umsetzung der sog. Tarragona-Strategie – *Look at your Patient* und *Listen to your Hospital* [Sandiumenge *et al.* 2003] – ist daher von großer Bedeutung für eine erfolgreiche Therapie von Infektionen in unserem Patientengut. Eine inadäquate Antibiotikatherapie hat einen negativen prognostischen Einfluss (OR=3,0 [95% KI 1,6-5,7]) auf das Überleben von Patienten mit Bakteriämie [Retamar *et al.* 2012]. Die Empfehlungen zur primären empirischen Therapie von Fieber in der Neutropenie [Link *et al.* 2003; Penack *et al.* 2014] basieren auf Erhebungen zum Erregerspektrum und der Resistenzlage. Da sich die Epidemiologie und die Resistenzlage im Laufe der Zeit (auch relativ kurzfristig) ändern können, sind regelmäßige Analysen empfohlen [Rolston 2015].

Wir stellten uns die Frage, inwieweit sich das mikrobielle Erregerspektrum bei Patienten aus der Hämatologie von anderen Patienten unterscheidet. Dieses Wissen um ein unterschiedliches Erregerspektrum kann die primäre, empirische antimikrobielle Therapie in der ambulanten Versorgung bzw. in einer Notaufnahme eines Krankenhauses grundlegend beeinflussen. In einer retrospektiven Untersuchung wurden daher alle kulturellen Erreger im Zeitraum von 01/1992 bis 12/2009 untersucht, die im Universitätsklinikum Magdeburg isoliert wurden. Dabei wurden das Erregerspektrum aus der Klinik für Hämatologie und Onkologie mit dem aller anderen Kliniken verglichen [Schalk *et al.* 2014a].

Insgesamt wurden 603.944 Erreger aus allen in Frage kommenden Materialien kulturell isoliert. Nur ein kleiner Bruchteil (21.431; 3,5%) stammte davon aus der Hämatologie. Es überwogen Gram-positive Bakterien, wobei der Anteil in der Hämatologie größer als der bei allen anderen Patienten war (67,4% *vs.* 58,4%; p<0,001). Anaerobier waren häufiger bei den Patienten außerhalb der Hämatologie nachweisbar (1,0% *vs.* 0,6%;

p=0,02). Keinen signifikanten Unterschied gab es hingegen für den Nachweis von Hefepilzen (Hämatologie: 9,0%, andere Patienten: 9,5%; *p*=0,70). Interessanterweise fanden sich die vor allem in der Hämatologie gefürchteten *Pseudomonadaceae* [Link *et al.* 2003; Penack *et al.* 2014] hier seltener als in der anderen Patientenkohorte (2,6% *vs.* 5,6%; *p*<0,001). Gefürchtet deswegen, da Infektionen durch *Pseudomonas aeruginosa* mit einer sehr hohen Mortalitätsrate von bis zu 32% einhergehen [Trecarichi *et al.* 2011]. Ähnlich verhielt es sich für *Staphylococcus aureus* (4,9% *vs.* 9,6%; *p*<0,001) und für *Enterobacteriaceae* (12,4% *vs.* 19,3%; *p*<0,001). Wie zu erwarten war [Rolston *et al.* 2006], ließen sich bei den hämatologischen Patienten am häufigsten Koagulase-negative *Staphylococcus* spp. isolieren, die im Vergleich zu den nicht-hämatologischen Patienten auch deutlich überwogen (31,6% *vs.* 19,6%; *p*<0,001) (**Abbildung 2**). Dies ist am ehesten auf die relativ vielen ZVK-Infektionen in der Hämatologie zurückzuführen, bei denen diese Erregergruppe eine große Rolle spielt (Abschnitt 2.4.2). Die Frage, die sich an die Analyse des Erregerspektrums *per se* anschloss, war, inwieweit sich dieses in dem Zeitraum von 18 Jahren entwickelt hatte. Wir konnten zeigen, dass im Zeitraum 2001-2009, verglichen mit 1992-2000, sowohl bei den hämatologischen (+9,0%; *p*=0,002) als auch bei den nicht-hämatologischen Patienten (+2,7%; *p*=0,002) ein Anstieg der Gram-positiven Bakterien zu verzeichnen war. Kein Unterschied in der Häufigkeit, im Vergleich der beiden Zeiträume, war bei den Gram-negativen und anaeroben Bakterien zu beobachten. Der große relative Zuwachs an Gram-positiven Bakterien in der Hämatologie ist auch auf die verminderte relative Häufigkeit der Hefepilze zurückzuführen (-6,0%; *p*=0,006). Dies ist sicherlich durch eine bessere antimykotische Prophylaxe und Therapie bedingt, die sich in den letzten Jahren erfreulicherweise gut entwickelt hat [Tacke *et al.* 2014; Mousset *et al.* 2014].

Im gleichen Zeitraum von 01/1992 bis 12/2009 untersuchten wir retrospektiv alle Blutkulturen, die von unserer Klinik zur mikrobiologischen Diagnostik eingesandt wurden [Schalk *et al.* 2010a; Schalk *et al.* 2014a]. Auch hier verglichen wir die Zeiträume 1992-2000 und 2001-2009. Dieser Vergleich der beiden Zeiträume ist insofern wichtig, als das im ersten Zeitraum primär empirisch Imipenem/Cilastatin eingesetzt wurde. Im zweiten untersuchten Zeitraum wurde primär empirisch Ceftazidim eingesetzt, und es wurde bei Patienten mit akuter lymphatischer Leukämie eine Antibiotikaprophylaxe mit Levofloxacin durchgeführt.

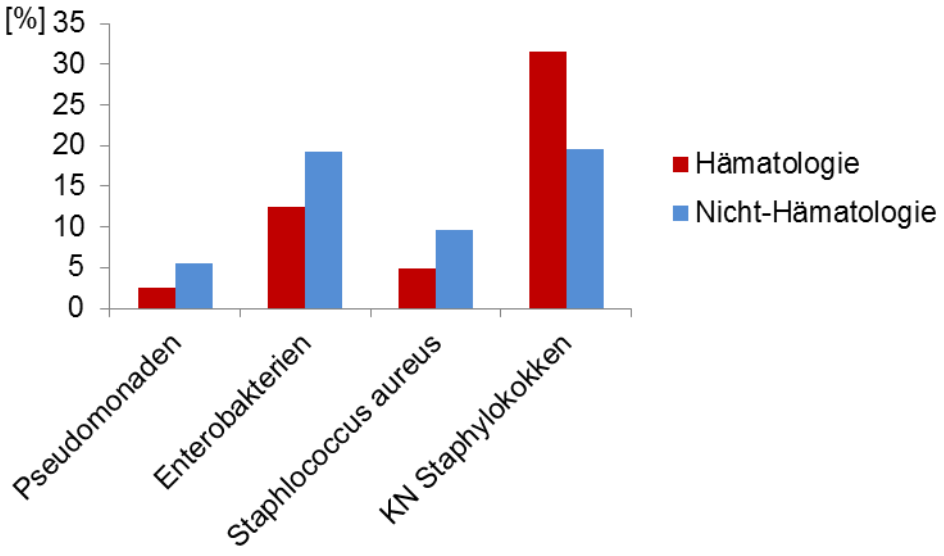

Abbildung 2. Vergleich der Häufigkeiten von aus allen Materialen isolierten Erregern von Patienten aus der Hämatologie und aus anderen Kliniken. Für alle Vergleiche $p<0{,}001$. Daten aus Schalk *et al.* 2014a.
KN Staphylokokken, Koagulase-negative Staphylokokken.

Insgesamt wurden 24.413 Blutkulturen eingesandt, von denen 2226 positive aerobe Blutkulturen in diese Analyse eingeschlossen wurden. Hauptsächlich konnten Koagulase-negative *Staphylococcus* spp. nachgewiesen werden (46,3%), gefolgt von *Enterobacteriaceae* (19,0%) und *Streptococcus* spp. (9,4%). *Pseudomonadaceae* spielten auch hier mit 4,5% eine eher untergeordnete Rolle (**Abbildung 3**). Insgesamt gesehen überwogen also auch bei den Blutkulturen Gram-positive Bakterien (72,8% *vs.* 27,2%; $p<0{,}001$).

Die beiden Zeiträume vergleichend fiel auf, dass die Rate an Gram-positiven Bakterien abnahm (76,0% *vs.* 69,6%; $p=0{,}02$). Dieser Wandel des Erregerspektrums ist hauptsächlich auf den Rückgang von Isolaten durch Koagulase-negative *Staphylococcus* spp. (-8,3%; $p=0{,}01$) sowie einen Zuwachs an *Enterobacteriaceae* (+9,5%; $p<0{,}001$) zurückzuführen. Letzteres ist möglicherweise einer relativ hohen Fluorochinolon-Resistenz bei den *Enterobacteriaceae* (Ciprofloxacin: 14,9%) zurückzuführen, die, wie oben erwähnt, prophylaktisch und nachfolgend auch häufig therapeutisch, kalkuliert eingesetzt wurden. Von besonderem Interesse und Wichtigkeit ist die Tatsache, dass immerhin 19,0% aller Bakterien aus den Blutkulturen zu der sog. ESKAPE-Gruppe (*Enterococcus faecium*, *S. aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *P. aeruginosa*, *Enterobacter* spp.) gehörten, die nicht nur ursächlich den Löwenanteil nosokomialer Infektionen darstellen, sondern auch ein Paradigma in der Pathogenese, Transmission und Resistenz präsentieren [Rice 2008]. Wir konnten ebenfalls

beobachten, dass weitere sog. „Bad Bugs“, wie Methicillin-resistente *S. aureus* (MRSA), Vancomycin-resistente *Enterococcus* spp. (VRE) und Breitspektrum β-Laktamase bildende *Enterobacteriaceae* (ESBL-Bildner), vor allem im zweiten Untersuchungszeitraum (2001-2009) erstmals auftraten bzw. im Verlauf an Häufigkeit zunahmen.

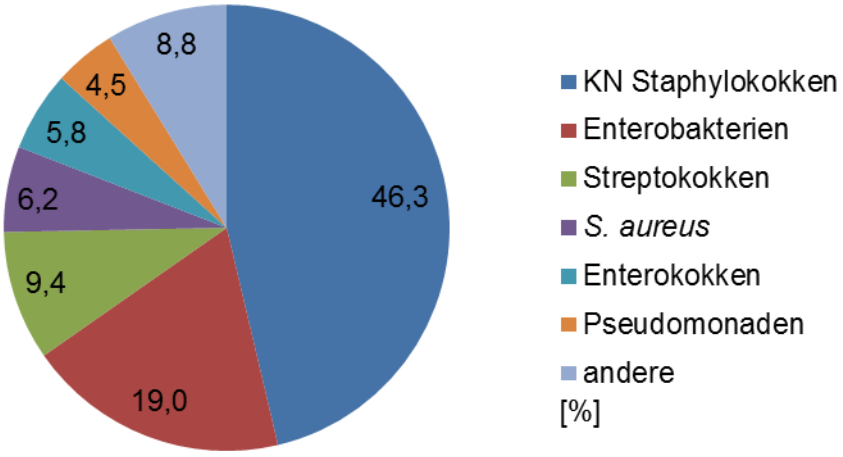

Abbildung 3. Häufigkeiten von aus Blutkulturen isolierten Erregern von Patienten aus der Hämatologie. Daten aus Schalk *et al.* 2014a.
KN Staphylokokken, Koagulase-negative Staphylokokken.

Multiresistente Erreger, insbesondere multiresistente Gram-negative Stäbchenbakterien (MRGN) spielen eine große und zunehmende Rolle [Tacconelli *et al.* 2014], insbesondere vor dem Hintergrund der erforderlichen Isolier- und Hygienemaßnahmen [RKI 2012]. Screening-Untersuchungen auf das Vorhandensein von MRGN sind daher vor dem Hintergrund der Infektionskontrolle und Verhinderung der Transmission im stationären Bereich [RKI 2012; Tacconelli *et al.* 2014], aber auch vor dem Hintergrund einer Antibiotikaresistenz *per se* und des Fehlens adäquater Antibiotika heute und in naher Zukunft empfohlen und angebracht [Bassetti *et al.* 2013]. MRGN sind weltweit das zurzeit dringendste infektiologische Problem [Schröppel *et al.* 2013]. Epidemiologische Daten zu Gram-negativen Stäbchen, die *in vitro* gegen 3 und 4 der entsprechenden Antibiotikagruppen resistent sind (3MRGN bzw. 4MRGN), waren bislang nicht verfügbar. Wir führten daher eine retrospektive Erhebung von 07/2012 bis 12/2013 an unserem Zentrum durch und analysierten alle stationären Patienten [Schalk *et al.* 2014b].

Von den 493 konsekutiv stationär aufgenommenen Patienten waren 118 Patienten mit Gram-negativen Stäbchen kolonisiert oder infiziert. Die Prävalenz mit 3/4MRGN von 3,7% (18/493) scheint eher gering zu sein. Vor dem Hintergrund der Prävalenz der anderen „Bad Bugs“ – MRSA, VRE und ESBL-Bildner –, die im gleichen Zeitraum bei 1,6%, 0,6% bzw. 2,0% lag, sind 3/4MRGN hier in unserem Patientengut nicht zu vernachlässigen. Unter allen Erstisolaten Gram-negativer Stäbchen (*n*=173) waren 12,7% 3/4MRGN nachweisbar. Dabei überwogen *Escherichia coli* (36,4%), *P. aeruginosa* (31,8%) und *K. pneumoniae* (9,1%), die hauptsächlich für Harnwegsinfekte verantwortlich waren. Die ermittelte hohe Inzidenz der 3/4MRGN unter allen Erstisolaten Gram-negativer Stäbchen von 6,4 pro 1000 Patiententage [Schalk *et al.* 2014b] und die eingeschränkten therapeutischen Möglichkeiten unterstreichen die Wichtigkeit rationaler Screening-Maßnahmen im Sinne einer MRGN-Surveillance, Isolier- und Hygienemaßnahmen sowie Antibiotic Stewardship-Programme in der Hämatologie und Medizinischen Onkologie [Schröppel *et al.* 2013]. Die MRGN-Prävalenz und -Inzidenz werden in Zukunft weiter steigen, da diese Patienten im Verlauf zur weiteren Chemotherapie oder aber aufgrund von Komplikationen unter/nach Therapie wieder stationär aufgenommen werden müssen, was die entsprechenden Stationen aufgrund der oft nur eingeschränkt vorhandenen Isoliermöglichkeiten an ihre Grenzen bringen kann. Der Nachweis von MRGN in einem früheren Krankenhausaufenthalt ist sehr häufig mit einer weiterhin nachweisbaren MRGN-Besiedlung bei einem Folgeaufenthalt in der Klinik vergesellschaftet [Schröppel *et al.* 2013]. In einem in unserer Klinik systematisch durchgeführten Aufnahme- und wöchentlichen Screening aller stationären Patienten im Zeitraum von 03/2015 bis 05/2015 beobachteten wir, dass die 3/4MRGN-besiedelten Patienten bis zu dreimal in dem untersuchten Zeitraum stationär betreut wurden und demnach isoliert werden mussten. Überproportional häufig handelte es sich dabei um 3MRGN (85,7%) aus Rektalabstrichen (66,7%) [Schalk 2015; unveröffentlichte Daten]. Die durch Sreening-Untersuchungen nachgewiesenen Erreger führen zwar nur in seltenen Fällen zu Blutstrominfektionen, d. h. der positive prädiktive Wert ist sehr gering [Liss *et al.* 2012; Vehreschild *et al.* 2014b; Sidler *et al.* 2015]. Die Vorabkenntnis von Erregern mit ganz bestimmter Antibiotikaresistenz kann aber im Einzelfall lebensrettend für den einzelnen Patienten sein, wie die Erfahrung in unserem Zentrum zeigt. Aufgrund der hohen Antibiotikaverbrauchsdichte [Schröppel *et al.* 2013] in der Hämatologie scheinen 3/4MRGN häufiger in unserem Patientengut aufzutreten, wie die Inzidenz von 3/4MRGN an der Gesamtheit aller Erreger mit 1,09 Fällen pro 1000 Patiententage [Schalk *et al.* 2014b], im Vergleich zur Gesamtheit aller Patienten in einem Tertiär-Krankenhaus, aufzeigt, wo eine Inzidenz von 0,43 Fällen pro 1000

Patiententage angegeben wurde [Vonberg *et al.* 2008] – unter Vorbehalt der Vergleichbarkeit und des Zeitraumes der beiden Erhebungen.

Publikation VII
Schalk E, Tammer I, Heidel FH. Germ and hematology: underlying disease influences diversity of germ spectra and antibiotic therapy. **Infect Control Hosp Epidemiol 2014**; 35(2):208-210

Publikation VIII
Schalk E, Färber J, Fischer T. Multidrug-resistant Gram-negative bacteria (MRGN) in hematology and oncology. **Infect Control Hosp Epidemiol 2014**;35(9):1203-1204

2.2.3 Rationale Blutkulturdiagnostik

Ein nicht unerheblicher Anteil von 15-20% der Patienten mit akuten Leukämien und Neutropenie entwickelt Blutstrominfektionen (**Tabelle 4**, Abschnitt 2.2.1) [Rolston 2015]. Blutkulturen spielen in der Hämatologie gegenüber anderen Patientengruppen eine große Rolle. So erfolgt die mikrobiologische Diagnostik in der Hämatologie zu einem viel größeren Anteil anhand von Blutkulturen als im Vergleich zu nicht-hämatologischen Kliniken bzw. Patienten (43,2% *vs.* 15,8%; p<0,001) [Schalk *et al.* 2014a]. Die Blutkulturdiagnostik stellt auch heute noch den Goldstandard in der Diagnostik der Bakteriämie bzw. Sepsis dar [Penack *et al.* 2014]. Daneben finden auch molekularbiologische Methoden in der Diagnostik der Bakteriämie Anwendung [Chen *et al.* 2010]. Vor allem die Polymerasekettenreaktion (PCR) hat hier das Interesse geweckt [Mancini *et al.* 2008; von Lielienfeld-Toal *et al.* 2009]. Der Vorteil der PCR der schnelleren Erregeridentifizierung liegt auf der Hand. Wie im Abschnitt 2.2.2 dargestellt, reicht die alleinige Identifizierung eines Erregers oft nicht aus, da eine Empflindlichkeitstestung auf die verschiedensten Antibiotika aufgrund der zunehmend schlechter werdenden Resistenzlagen unbedingt erforderlich ist. Dies kann aktuell in der breiten klinischen Anwendung nur durch die Kultur erfolgen. Auch die Massenspektrometrie (matrix-assisted laser desorption/ionization time-of-flight mass spectrometry [MALDI-TOF]) kann bei der Erregeridentifizierung hilfreich sein [Egil *et al.* 2015], ersetzt aber auch hier nicht die Kultur zur Resistenztestung und benötigt vorher bereits *per se* eine positive Blutkultur.

Die Positivraten von Blutkulturen liegen bei Patienten mit Neutropenie nicht über 30% [Feld 2008; Hagel *et al.* 2013] und vermindern sich dramatisch nach Beginn einer antibiotischen Therapie [Serody *et al.* 2000; Ritchie *et al.* 2007]. Hier, d. h. in der Diagnostik unter laufender Antibiotikatherapie (z. B. bei einem Patienten, der trotz Antibiotika weiterhin fiebert), kann die PCR hilfreich sein [von Lilienfeld-Toal *et al.* 2009]. Anhand

eigener, retrospektiv erhobener Daten an unserer Klinik konnten wir zeigen, dass die Positivrate der Blutkulturen bei 100 konsekutiv behandelten Patienten mit akuten Leukämien im Zeitraum von 10/2011 bis 05/2013 bei 19,0% (134/704) lag, was sich mit aktuellen Daten aus der Literatur zu Patienten mit Fieber in Neutropenie deckt (Mittelwert=20%, Spanne 9-27%) [Schalk 2013].

Ein Problem in der Blutkulturdiagnostik stellt das Zeitfenster zwischen Blutentnahme, inklusive Transport in das mikrobiologische Institut, und die Inkubation dar. Sollte eine sofortige Inkubation nicht möglich sein, so wird eine Lagerung der Blutkulturflaschen bei Raumtemperatur empfohlen [Sautter *et al.* 2006; Lamy *et al.* 2012]. Das Risiko von *falsch*-negativen Ergebnissen erhöht sich signifikant ab einer Verzögerung von 12 Stunden nach Inokulation [Akan *et al.* 2006]. Wie in den meisten anderen Kliniken auch, erfolgt in unserem Klinikum die Inkubation innerhalb der Regelarbeitszeit. Demzufolge ist es möglich, dass bei einem am Abend fiebernden Patienten die Blutkulturen mit entsprechender Zeitverzögerung erst am nächsten Morgen inkubiert werden können. Bislang gab es keine ausreichend publizierten Daten darüber, ob und in welchem Ausmaß sich eine verzögerte Inkubation inokulierter Blutkulturen negativ auswirkt – z. B. auf das Zeitfenster bis zum Positivwerden (Time-to-Positivity [TTP]) oder den Anteil *falsch*-negativer Resultate. Eine falsche Befundinterpretation (*falsch*-negativ bzw. noch nicht positive gewordene Blutkultur) hätte möglicherweise einen Einfluss auf die weitere antibiotische Behandlung des Patienten. Es war bekannt, dass bei Saponin-beinhaltenden Blutkulturflaschen die TTP im Vergleich zu „Standard-Blutkulturen“ bis zu 6 Stunden kürzer ist (Rohner *et al.* 1997). Dies könnte die Qualität, und auch die Quantität, der Diagnostik in der klinischen Routine verbessern. Es war jedoch noch nicht bekannt, ob dieser positive TTP-Effekt auch bei einer verzögerten Inkubation aufrechterhalten werden kann. Um diese Frage beantworten zu können, führten wir eine *ex vivo*/*in vitro*-Studie durch, in dem die verzögerte Inkubation bei einem fiebernden Patienten nachempfunden wurde [Schalk *et al.* 2015a]. Dabei wurde Blut von gesunden Freiwilligen auf 38,3°C erwärmt und in BACTEC Plus Aerobic/F-, Anaerobic/F- und Lytic 10 Anaerobic/F- sowie Mycosis-IC/F-Blutkulturflaschen überführt sowie in BACTEC-Brutschränken inkubiert (alles Becton Dickinson, Deutschland) nach Beimpfung mit *S. aureus*, *S. epidermidis*, *E. coli*, *P. aeruginosa*, *S. mitis*, *E. faecium* und *Candida albicans* (American Type Culture Collection- [ATCC] Stämme), entsprechend der Erregerstatistik *in domo* [Schalk *et al.* 2014a]. Die Lytic 10 Anaerobic/F-Flaschen enthielten Saponin, was zur Lyse der Blutzellen (Leukozyten) führt. Nach Beimpfung der Blutkulturflaschen wurden diese bei Raumtemperatur 0, 2, 4, 8, 12 und 16 Stunden stehen gelassen und erst dann mit dieser Zeitverzögerung entsprechend inkubiert.

Insgesamt wurden 520 Blutkulturflaschen untersucht. Es bestand kein signifikanter Unterschied bezüglich der TTP bei den aeroben und lytisch-anaeroben Flaschen beim Vergleich der verzögerten Inkubation nach 2, 4, 8, 12 oder 16 Stunden. Interessanterweise verkürzte sich die TTP bei Inkubation der anaeroben Flaschen nach einer Verzögerung von 12 und 16 Stunden um 7,7 Stunden (p=0,006) bzw. um 6,4 Stunden (p=0,01) (**Tabelle 5**). Eine weitere wichtige Beobachtung war, dass *falsch*-negative Ergebnisse häufig bei *P. aeruginosa* und *C. albicans* in den lytisch-anaeroben Flaschen zu verzeichnen waren. Unsere Ergebnisse zeigten zudem, dass die Mykosis-Flasche unbedingt für die frühzeitige Diagnostik von *C. albicans* erforderlich ist, da die TTP im Vergleich der Mykosis- mit den anaeroben Flaschen um 17,4 Stunden (p<0,001) kürzer ist. Die Tatsache, dass *P. aeruginosa* offensichtlich in Blutkulturen seltener nachgewiesen wird als es eigentlich der Fall sein müsste – es also oft zu *falsch*-negativen Ergebnissen kommt und dies vom eingesetzten Kulturmedium abhängt [Seegmüller *et al.* 2004; Schalk *et al.* 2015a] – muss dem Klinker bewusst sein, und trotzdem bzw. gerade deswegen, bei der Auswahl der primären empirischen Antibiotikatherapie bei Patienten mit Fieber mit Neutropenie in der Hämatologie mit bedenken [Link *et al.* 2003; Penack *et al.* 2014].

Tabelle 5. Vergleich einer verzögerten Blutkulturinkubation

	TTP-Differenz [h]		
Inkubation	**Aerob Plus**	**Anaerob Plus**	**Anaerob Lytisch**
0 *vs.* 2 Stunden	0,58	2,06	-1,01
0 *vs.* 4 Stunden	-0,87	0,72	-1,02
0 *vs.* 8 Stunden	-0,68	-1,25	-2,40
0 *vs.* 12 Stunden	-1,29	-7,69*	-4,01
0 *vs.* 16 Stunden	-3,72	-6,38*	1,04

TTP, Time-to-Positivity. *p<0,05. Daten aus Schalk *et al.* 2015a.

Im Allgemeinen werden zur Diagnostik der Bakteriämie aerobe und anaerobe Blutkulturen empfohlen [Link *et al.* 2003]. Da allerdings auch von Experten betont wird, dass aerobe Flaschen für die Diagnostik von Bakteriämien ausgehend von ZVK ausreichend sind [Bouza *et al.* 2012], stellten wir uns die Frage, was den diagnostischen Gewinn von anaeroben Blutkulturen in unserem Patientengut ausmacht. Wir analysierten daraufhin 704 Blutkulturen (jeweils ein Set, bestehend aus einer aeroben und anaeroben Flasche) der zuvor genannten 100 Patienten mit akuten Leukämien [Schalk 2013]. Dabei zeigte sich, dass 83% aller anaeroben Flaschen ebenfalls positiv waren, wenn die aerobe Flasche positiv war. Interessanterweise waren 41% der anaeroben Flaschen vor den aeroben Flaschen positiv geworden. Der Unterschied in der TTP

(anaerob *vs.* aerob) betrug 101 Minuten (95% KI 73-130 Minuten). Dies bedeutet, dass in einem nicht unerheblichen Anteil der Blutkulturen die Vorabinformation z. B. „positive Blutkultur, Gram-negative Stäbchen“ aus dem Labor von den Ergebnissen der anaeroben Flaschen stammt. Diese Information kann durchaus wichtig für die antibiotische Therapie und Prognose des Patienten sein (siehe Abschnitt 2.2.1 und 2.2.2 sowie 2.4.2).

Die Frage, was bei weiterhin fieberndem Patienten mit Neutropenie wiederholte Blutkulturen diagnostisch erbringen können, wenn in der ersten Blutkultur kein Erregernachweis gelang, war in der Literatur nicht eindeutig beantwortet [Serody *et al.* 2000; Rosenblum *et al.* 2013]. Von den in der o. g. Analyse initial negativen Blutkulturen konnten durch wiederholte Blutentnahmen in 28% (20/71) der Fälle im Verlauf dann doch Erreger nachgewiesen werden [Schalk 2013]. Durch solche Informationen kann im Verlauf die empirische Antibiotikatherapie auf eine zielgerichtete umgestellt werden, was den Verlauf bzw. Ausgang der Infektion positiv beeinflussen kann. Man könnte annehmen, dass sich im Krankheitsverlauf des weiterhin fiebernden Patienten das Erregerspektrum zwischen der ersten und weiteren Blutkulturen ändert, da sich möglicherweise eine Mukositis entwickelt oder der ZVK weiter *in situ* verbleibt, und so vermehrt Gram-positive Erreger Blutstrominfektionen verursachen könnten [Zinner 2000). Dies konnten wir in unserer Analyse jedoch nicht beobachten: Der Anteil von Gram-positiven und Gram-negativen Bakterien änderte sich im Verlauf nicht (p=0,17) [Schalk 2013].

Ein Parameter der Qualitätssicherung in der Blutkulturdiagnostik ist die Rate an eingesandten Blutkulturen. Diese sollte zwischen 100-200 pro 1000 Patiententage für die Diagnostik von Blutstrominfektionen liegen [Seifert *et al.* 2007]. Die Evidenz für diese Empfehlung ist jedoch schwach und nicht gut nachvollziehbar. Für Intensivstationen in Deutschland wurde ein mittlerer Wert von 86 pro 1000 Patiententage ermittelt, was eine „Unterdiagnostik“ entsprechend der Empfehlungen bedeuten würde [Gastmeier *et al.* 2011]. Für unsere Klinik konnte eine Rate von 126 pro 1000 Patiententage ermittelt werden [Schalk 2013], was demnach einer sehr hohen Rate entspricht [Gastmeier *et al.* 2011]. In einer Arbeit wurde die Assoziation zwischen Blutkulturrate und nachgewiesen Blutstrominfektionen untersucht. Dabei konnte ein „Grenzwert“ von 87 Blutkulturen pro 1000 Patiententage (95% KI 54-120) ermittelt werden [Karch *et al.* 2015]. Dies bedeutet, dass oberhalb dieses „Grenzwertes“ keine Erhöhung der Sepsisrate mehr zu beobachten ist. Übertragen auf die Blutkulturdiagnostik bei unseren Patienten bedeutet dies, dass mit jeder weiteren Abnahme von Blutkulturen (diagnostische Episode) die Positivrate abnimmt (p=0,01, r=1,00) und dass die Abnahme von mehr als 2-

3 Blutkulturen (entsprechend einer Blutkulturrate von 79 bzw. 96 pro 1000 Patiententage) im Verlauf keinen weiteren Vorteil/Zugewinn in der Diagnostik mehr erbringen würde (**Tabelle 6**) [Schalk 2013].

Tabelle 6. Blutkulturrate und Positivrate

	Diagnostische Episode					
Parameter	**1**	**2**	**3**	**4**	**5**	**Gesamt**
Blutkulturrate [x/1000 Tage]	48	79	96	108	114	126
Positivrate [%]	39	27	24	22	21	19

Analyse von 704 Blutkulturen von 100 Patienten mit akuten Leukämien; Daten aus Schalk 2013. Für die Diagnose einer Blutstrominfektion wurde ein „Grenzwert" der Blutkulturrate von 87 pro 1000 Patiententage (95% KI 54-120) berechnet [Karch *et al.* 2015].

2.3 Abdominelle Infektionen

2.3.1 Diarrhoen

Patienten mit Krebserkrankungen können Diarrhoen nicht-infektiöser sowie infektiöser Genese entwickeln. Als Diarrhoen werden im Allgemeinen ≥3 ungeformte Stühle pro Tag angesehen. Nicht-infektiöse Diarrhoen können paraneoplastischer oder therapiebedingter Ursache sein [Vehreschild *et al.* 2013b]. Diarrhoen können aber auch durch die Grunderkrankung *per se* verursacht werden, wie z. B. bei einer gastrointestinalen Manifestation einer AL-Amyloidose [Syed *et al.* 2016], einem Lymphom-Befall im Magen-Darm-Trakt [*Li et al.* 2014] oder auch einer Graft-*vs.*-Host-Erkrankung (GvHD) nach alloSCT [Cox *et al.* 1994]. Paraneoplastische Diarrhoen sind selten. Die Sekretion von vasoaktiven intestinalen Polypeptiden spielt bei den nicht-β-Inselzell-Tumoren des Pankreas typischerweise eine Rolle, was zu wässrigen Diarrhoen, Hypokaliämie und Hypochloridämie führt [Nasir *et al.* 2008]. Flush und Diarrhoen sind ein typisches Phänomen bei Serotonin-produzierenden Karzinoiden [Udenfriend *et al.* 1956]. Andere Hormone, die paraneoplastische Diarrhoen hervorrufen können, sind Glucagon (Glucagonome), Gastrin (Gastrinome oder hepatozelluläre Karzinome), Somatostatin (Somatostatinome oder Phäochromozytome) und Prostaglandine (hepatozelluläre Karzinome) [Domen *et al.* 1980; Interlandi *et al.* 1985; Steiner *et al.* 1986; Saban *et al.* 1986; Strohm, 1996]. Bei Patienten mit kleinzelligem Lungenkarzinom kann es durch autonome Neuropathien, vermittelt durch Antikörper gegen neuronale Proteine, zu Diarrhoen kommen [Winkler *et al.* 2001]. In den meisten Fällen der paraneoplastischen

Diarrhoen ist die Diagnose und Therapie der Grunderkrankung die einzige Möglichkeit die Diarrhoen zu reduzieren. Einzig bei Karzinoiden und einigen anderen neuroendokrinen Tumoren kann eine Blockade der Somatostatin-Rezeptoren durch Octreotid oder Lanreotid eine Therapieoption darstellen [Vehreschild *et al.* 2013b]. Bei Krebspatienten sind direkte toxische Effekte der Chemotherapeutika der häufigste Grund für abdominelle Komplikationen. 5-Fluorouracil, Irinotecan, Capecitabin, Anthrazykline, viele sog. small molecules und monoklonale Antikörper können therapieassoziierte Diarrhoen hervorrufen [Vehreschild *et al.* 2013b]. Die Inzidenzrate von Diarrhoen bei Patienten mit Neutropenie wurde mit 27-76% angegeben. In nur 5-17% dieser Fälle waren die Diarrhoen infektiöser Genese [Avery *et al.* 2000; Gorschlüter *et al.* 2001; Aksoy *et al.* 2007; Vehreschild *et al.* 2011]. Die Zerstörung der gastrointestinalen Mikroflora nach Verabreichung von Antibiotika führt bei 5-62% der Patienten aufgrund von Alterationen im Kohlenstoff-Stoffwechsel zu osmotischen Diarrhoen und einer verminderten Absorption kurzkettiger Fettsäuren [Wiström *et al.* 2001; Owens *et al.* 2008; McFarland, 2008]. In 7-50% dieser Fälle kommt es dann zu einer Überwucherung durch *Clostridium difficile*, was dann eine *C. difficile*-Infektion (CDI) bedingen kann [Plummer *et al.* 2004; Hickson *et al.* 2007]. Auch eine abdominelle Radiatio führt nach etwa 7-14 Tagen zu Diarrhoen durch Zerstörung der Darmmukosa. Durch chirurgische Eingriffe am Gastrointestinaltrakt kann die Physiologie im Darm durch verkürzte Magen- oder Darmpassage, bakterielle Überwucherung, veränderte Sekretion und Absorption von Gallensäuren beeinträchtigt werden, was ebenfalls zu Diarrhoen führen kann [Vehreschild *et al.* 2013b]. Sofern nach entsprechender Diagnostik infektiöse Ursachen der Diarrhoen ausgeschlossen sind, ist Loperamid Mittel der Wahl [Vehreschild *et al.* 2013b].

Treten Diarrhoen im Zeitraum von weniger als 72 Stunden nach Aufnahme des Patienten in das Krankenhaus auf, so ist an ambulant erworbenen Diarrhoen zu denken und die Diagnostik initial hinsichtlich *C. difficile* (insbesondere dann, wenn zuvor eine Chemotherapie durchgeführt oder Antibiotika verabfolgt wurden) und *Salomenella* spp., *Shigella* spp., *Yersinia enterocolitica* oder *Campylobacter coli/jejuni* (SSYC) durchzuführen. Eine erweiterte Diagnostik sollte dann im Verlauf auf Adenovirus, Astrovirus, Cytomegalievirus (CMV), Norovirus, Rotavirus und Parasiten erfolgen [Vehreschild *et al.* 2013b]. Treten Diarrhoen frühestens 72 Stunden nach Aufnahme des Patienten in das Krankenhaus auf, so handelt es sich um nosokomiale Diarrhoen. Hier sollte die initiale Diagnostik *C. difficile* und Norovirus beinhalten. Die erweiterte Diagnostik zielt dann auf SSYC, Adenovirus, Astrovirus, CMV, Rotavirus und Parasiten ab. In allen Fällen ist auch immer ein lokales Ausbruchsgeschehen mit in Betracht zu ziehen [Vehreschild *et al.* 2013b], was zu einem sehr großen und ernst zu nehmenden

Problem für Patienten und Mitarbeiter werden kann [Schwartz *et al.* 2011]. Im Allgemeinen sollten Untersuchungen im Verlauf auf ein und dasselbe Pathogen unterbleiben, um *falsch*-positive Ergebnisse zu vermeiden [Vehreschild *et al.* 2013b]. Im Einzelnen kann die Wiederholung von Untersuchungen, wie z. B. bei *C. difficile*, jedoch dazu beitragen, die Rate an *falsch*-negativen Ergebnissen zu verringern [Rau *et al.* 2008].

Unter einer CDI wird das Auftreten von Diarrhoen, Ileus oder toxisches Megacolon in Kombination mit dem Nachweis Toxin-produzierender *C. difficile* im Stuhl oder Nachweis einer pseudomembranösen Kolitis in der Endoskopie verstanden [Bauer *et al.* 2009; Vehreschild *et al.* 2013b]. Dabei soll eine Probe ungeformten Stuhls unmittelbar nach Entnahme zur Diagnostik eingesandt werden [Crobach *et al.* 2009; Cohen *et al.* 2010]. In der Regel ist eine Probe zu Beginn der Symptomatik ausreichend [Deshpande *et al.* 2011]. Der Zytotoxin-Assay ist zwar sehr sensitiv (94-100%), hat aber eine sehr lange Bearbeitungszeit [Cohen *et al.* 2010]. Deshalb sollten die Stuhlproben mit einem enzyme-linked immunosorbent assay (ELISA) auf das Vorhandensein von Zytotoxin A und B (Sensitivität 50-80%, Spezifität 89-99%) [O'Connor *et al.* 2001] oder dem *C. difficile*-Antigen Glutamatdehydrogenase (GDH; Sensitivität 85-95%, Spezifität 89-99%) [Ticehurst *et al.* 2006] untersucht werden. Alternativ steht eine PCR zum Nachweis von Toxin B zur Verfügung (Sensitivität 97%, Spezifität 93%) [Huang *et al.* 2009]. Negative Testergebnisse können als negativ ausgegeben werden. Positive Testergebnisse sollten allerdings mit einer zweiten Methode bestätigt werden [Crobach *et al.* 2009]. Bei Patienten mit Neutropenie oder schwerer Kolitis sollte eine diagnostische Endoskopie wegen eines erhöhten Risikos von Darmperforationen oder Blutungen unterbleiben [Hookman *et al.* 2009]. In verschiedenen Leitlinien [Bauer *et al.* 2009; Cohen *et al.* 2010] wird zwischen schweren und nicht-schweren CDI-Verläufen unterschieden. Dabei ist die Leukozytose ein Kriterium zur Unterscheidung. Die Leukozytose ist jedoch bei Krebspatienten, insbesondere bei hämatologischen Patienten, in Neutropenie naturgemäß nicht nützlich. Es wird daher empfohlen, neutropene Patienten mit CDI, die ein Chemotherapie-assoziiertes Darmsyndrom (CABS; Temperatur ≥37,8°C, abdominelle Schmerzen und/oder Ileuszeichen über mindestens 72 Stunden) aufweisen, einem schweren Verlauf zuzuordnen. Patienten mit CABS erleiden häufiger Komplikationen bis hin zum Tod [Vehreschild *et al.* 2011] und sollten daher im Fall von CDI als schwere CDI klassifiziert werden [Vehreschild *et al.* 2013b]. Die Klassifizierung des Schweregrades einer CDI ist insofern wichtig, als dass schwere und nicht-schwere CDI anders behandelt werden [Vehreschild *et al.* 2013b].

Die häufigsten Erreger viraler Gastroenteritis sind Noroviren (früher auch als Norwalk-ähnliches Virus bezeichnet), Rotaviren, Adenoviren und CMV [Vehreschild *et al.* 2013b]. Die PCR (Sensitivität 94%, Spezifität 92%) ist aktuell Mittel der Wahl zur Diagnostik einer NVI. Als Alternative stehen der Antigennachweis sowie die Elektronenmikroskopie zur Verfügung [Rabenau *et al.* 2002; Höhne *et al.* 2004]. Letztere findet in der klinischen Routine jedoch keine breite Anwendung.

Publikation IX
Vehreschild MJGT, Vehreschild JJ, Hübel K, Hentrich M, Schmidt-Hieber M, Christopeit M, Maschmeyer G, **Schalk E**, Cornely OA, Neumann S. Diagnosis and management of gastrointestinal complications in adult cancer patients: evidence-based guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO). **Ann Oncol 2013**; 24(5):1189-1202

Anmerkung: Diese Leitlinie wurde im Verlauf unter erneuter Mitarbeit des Kandidaten aktualisiert und publiziert [Schmidt-Hieber *et al.* 2018].

2.3.2. *Clostridium difficile*-Infektionen bei AML

Patienten mit akuter myeloischer Leukämie (AML) entwickeln eine schwere Neutropenie – entweder durch die leukämische Tumorlast *per se* oder die zytotoxische Chemotherapie, die in der Regel aus einer Kombination aus Cytarabin und einem Anthrazyklin (z. B. Daunorubicin, Idarubicin) besteht [Estey *et al.* 2005; Miller *et al.* 2005] – was die Patienten dann für lebensbedrohliche Infektionen sehr empfänglich macht. Da Infektionen einen wichtigen Grund für Morbidität und Mortalität darstellen [Hiddemann *et al.* 1997], ist der Beginn einer empirischen Antibiotikatherapie bereits erforderlich, sobald Fieber in Neutropenie auftritt [Link *et al.* 2003]. Antibiotika stellen einen wichtigen Risikofaktor für CDI dar, da Antibiotika die vorhandene, originäre Darmflora unterdrücken und so eine Überwucherung des Darmes mit *C. difficile* bedingen [Gerding *et al.* 1995; Starr *et al.* 2003; Barlett *et al.* 2008; Owens *et al.* 2008; Vehreschild *et al.* 2014c]. *C. difficile* ist der häufigste Grund für Diarrhoen, die durch medizinische Maßnahmen (sog. health-care associated) hervorgerufen werden und sind für in bis zu 50% der Fälle für antibiotikabedingte Diarrhoen verantwortlich. CDI, insbesondere Patienten mit Rezidiven, stellen ein großes ökonomisches Problem dar [Heimann *et al.* 2015]. Weitere Risikofaktoren für die Entwicklung einer CDI sind ein höheres Patientenalter, darmmotilitätsenkende Medikamente, Beatmung, Protonenpumpen-Inhibitoren, H_2-Antagonisten und Hypalbuminämie [Vehreschild *et al.* 2013b]. Interessanterweise können zytotoxische Chemotherapeutika *per se*, wie Cytarabin, eine CDI induzieren [Roda 1987; Anand *et al.* 1993]. Bei erwachsenen Krebspatienten treten CDI in 5-9% der Chemotherapiezyklen bzw. bei 5-20% aller Patienten auf

[Vehreschild *et al.* 2013b]. CDI ist demnach eine häufige Komplikation bei Patienten mit Krebserkrankungen nach myelosuppressiver Chemotherapie [Gorschlüter *et al.* 2001]. Patienten mit CDI entwickeln Diarrhoen, Fieber, Abdominalschmerzen und Abwehrspannung. Der Schweregrad dieser Infektion reicht von milden Diarrhoen bis zur fulminanten pseudomembranösen Enterokolitis, einhergehend mit einem paralytischen Ileus, toxischem Megacolon oder Darmperforation. Das Auftreten von Diarrhoen kann zu jedem Zeitpunkt während einer Antibiotikatherapie und bis zu 2 Wochen nach Beendigung eben dieser auftreten. Therapieoptionen der CDI bei Krebspatienten unterscheiden sich im Vergleich zu immunkompetenten Patienten und beinhalten im Wesentlichen Antibiotika, wie Metronidazol, Vancomycin oder Fidaxomicin [Vehreschild *et al.* 2013b; Schmidt-Hieber *et al.* 2018].

Wir beobachteten eine merkliche Zunahme von Diarrhoen bei Patienten mit AML und entschieden uns daher, eine retrospektive Studie durchzuführen. Das Ziel dieser monozentrischen Studie war es, klinische Daten und Risikofaktoren von Patienten mit AML zu generieren, die eine CDI nach intensiver Chemotherapie entwickelten [Schalk *et al.* 2010b]. Dabei wurden alle Patienten mit AML eingeschlossen, die zwischen 01/2003 und 03/2008 konsekutiv in unserem Zentrum stationär zur AML-Therapie aufgenommen wurden. Für die Analyse kamen nur solche Patienten in Betracht, die eine Cytarabin-/Anthrazyklin-basierte, intensive Chemotherapie erhielten, d. h., Patienten, die nur eine zytoredekutive, palliative Therapie mit niedrig dosiertem Cytarabin s. c. oder Hydroxyurea erhielten, wurden ausgeschlossen. Bei allen Patienten, die Diarrhoen entwickelten, wurden Stuhlproben bezüglich des Vorhandenseins von *C. difficile*-Enterotoxin und -Zytotoxin (Toxin A und B) mittels ELISA untersucht (RIDASCREEN, R-Biopharm, Deutschland). Als Diarrhoen wurden ≥3 ungeformte Stühle pro 24 Stunden definiert. Unter einer Neutropenie wurde ein Wert der neutrophilen Granulozyten von <1000/µl verstanden. Eine schwere Enterokolitis aufgrund von *C. difficile* wurde diagnostiziert, wenn blutige Diarrhoen, Fieber (≥38,3°C) und abdominelle Schmerzen auftraten. Eine prophylaktische Antibiotikatherapie in der Phase der Neutropenie wurde nicht durchgeführt. Patienten mit Fieber in Neutropenie erhielten primär Ceftazidim als antibiotische Therapie. Verglichen wurden klinische Merkmale von Patienten die Diarrhoen aufgrund von *C. difficile* (CDI) entwickelten mit denen, die Diarrhoen ohne Nachweis von *C. difficile* (*non*-CDI) aufwiesen.

Insgesamt wurden 134 Patienten mit intensiver Therapie einer AML in dieser Studie untersucht. Das mittlere Alter betrug 53 Jahre (Spanne 18-75 Jahre); das Geschlechtsverhältnis war genau ausbalanciert. Fast die Hälfte der Patienten (43%) war mindestens 60 Jahre alt. Es wurden 301 Chemotherapiezyklen verabfolgt (im Mittel=2

Zyklen, Spanne 1-5 Zyklen). Die Mehrheit der Patienten erhielt eine Cytarabin-Dosis von mindestens 6000 mg/m^2 pro Zyklus (202; 67,1%). In 6 Zyklen (2,0%) wurde kein Cytarabin verabfolgt, sondern nur Idarubicin als Monotherapie oder Busulfan/Cyclophosphamid. Diarrhoen traten bei 40,6% aller Patienten auf. In einem Drittel aller Chemotherapiezyklen (100, 33,2%) traten Diarrhoen auf, die im Mittel 6 Tage (Spanne 1-31 Tage) andauerten. Dabei handelte es sich in etwa einem Viertel (28; 28,0%) um Diarrhoen, die auf *C. difficile* zurückzuführen waren. Diese 28 CDI-Episoden traten bei 24 Patienten auf, was zu einer Häufigkeit von CDI bei AML-Patienten von 17,9% bzw. von 9,3% pro Chemotherapiezyklus führt. Interessanterweise traten die meisten CDI-Fälle – 44,0% – im ersten Zyklus auf, gefolgt von 24,0% im zweiten, 12,0% im dritten und 8,0% im vierten Zyklus. Bei einem Patienten kam es zu einer CDI, ohne dass vorher Antibiotika verabfolgt wurden.

Im Vergleich der klinischen Merkmale von Patienten/Episoden mit CDI (*n*=28) und *non*-CDI (*n*=72) zeigte sich, dass die Patienten mit CDI im Vergleich zu denen mit *non*-CDI älter waren (58 Jahre *vs.* 50 Jahre; *p*=0,02), häufiger vor dem Auftreten von Diarrhoen Antibiotika erhielten (2 *vs.* 1; *p*=0,03), häufiger Ceftazidim erhielten (75,0% *vs.* 54,2%; *p*=0,046), die Dauer einer Antibiotikatherapie vor Auftreten von Diarrhoen länger war (7 Tage *vs.* 4 Tage; *p*=0,01) und auch die Dauer der Neutropenie vor Auftreten von Diarrhoen länger war (12 Tage *vs.* 7 Tage; *p*=0,01). Kein Unterschied bestand hingegen für die Dauer der Diarrhoen und die verabfolgte Cytarabin-Dosis pro Chemotherapiezyklus (**Tabelle 7**).

Tabelle 7. Vergleich von klinischen Merkmalen von Patienten mit Diarrhoen

Klinisches Merkmal	**CDI (*n*=28)**	***non*-CDI (*n*=72)**	***p*-Wert**
Alter [a]	58 (22-75)	50 (18-70)	0,02
Dauer der Diarrhoen [Tage]	8 (2-31)	6 (1-31)	0,25
Anzahl der Antibiotika[a] [*n*]	2 (0-5)	1 (0-3)	0,03
Ceftazidim-Therapie [%]	75,0	54,2	0,046
Dauer der Antibiotikatherapie[a] [Tage]	7 (0-21)	4 (0-17)	0,01
Dauer der Neutropenie[a] [Tage]	12 (0-33)	7 (0-22)	0,01
Cytarabin-Dosis pro Zyklus [mg/m^2]	5336 (0-18.000)	5774 (0-10.000)	0,66

CDI, *Clostridium difficile*-Infektion; *non*-CDI, Diarrhoen ohne Nachweis von *C. difficile*; Spanne in Klammern. [a]Vor Auftreten der Diarrhoen. Daten aus Schalk *et al.* 2010b.

In der univariaten Analyse konnte gezeigt werden, dass das Risiko für das Auftreten einer CDI bei einer Dauer der Neutropenie von mindestens 10 Tagen vor Auftreten der Diarrhoen erhöht war (OR=2,7 [95% KI 1,1-6,5]; *p*=0,04), nicht aber für ältere Patienten

(≥60 Jahre), Antibiotikatherapie *per se*, Dauer der Antibiotikatherapie von mindestens 10 Tagen vor Auftreten der Diarrhoen oder eine Cytarabin-Dosis von mindestens 6000 mg/m^2 pro Chemotherapiezyklus. Allein für die Verabfolgung von Ceftazidim vor Auftreten der Diarrhoen bestand ein Trend für ein erhöhtes CDI-Risiko (OR=2,5 [95% KI 0,96-6,7]; *p*=0,07) (**Tabelle 8**). Bei Patienten mit CDI betrug die Dauer der Neutropenie in mehr als der Hälfte der Fälle länger als 10 Tage (16; 57,1%), aber nur bei etwa einem Drittel der Patienten, die keine CDI entwickelten (24; 33,3%).

Tabelle 9. Risiko für die Entwicklung von CDI

Klinisches Merkmal	OR	*p*-Wert
Alter ≥60 Jahre	1,7 [0,7-4,1]	0,35
Antibiotikatherapie *per se*	2,6 [0,8-8,5]	0,13
Antibiotikatherapie ≥10 Tage[a]	1,7 [0,6-4,8]	0,40
Ceftazidim-Therapie[a]	2,5 [0,96-6,7]	0,07
Neutropenie ≥10 Tage[a]	2,7 [1,1-6,5]	0,04
Cytarabin ≥6000 mg/m^2 pro Zyklus	0,5 [0,2-1,3]	0,16

CDI, *Clostridium difficile*-Infektion; OR, Odds Ratio; 95% Konfidenzintervall in Klammern. [a]Vor Auftreten der Diarrhoen. Daten aus Schalk *et al.* 2010b.

In 92,9% der CDI-Episoden (*n*=26) erfolgte die Therapie initial mit Metronidazol (19; 73,1%) oder mit Vancomycin (7; 26,9%). In 2 Episoden (7,1%) erhielten die Patienten keine antibiotische Therapie, weil die Diarrhoen bereits wieder verschwanden, ehe das positive Testergebnis für *C. difficile* eintraf. In 84,2% der Fälle (*n*=16) war nach Metronidazol ein Therapieansprechen zu verzeichnen; bei Vancomycin war es in allen Episoden der Fall (*n*=7). Ein Therapieversagen war bei 3 Patienten nach Metronidazol und bei keinem Patienten nach Vancomycin zu beobachten. Bei 4 Patienten kam es zu CDI-Rezidiven – 3 nach Metronidazol, 1 nach Vancomycin. Alle Rezidive traten im nächstfolgenden Chemotherapiezyklus auf. Eine schwere Enterokolitis entwickelten 5 Patienten (17,9%) mit CDI. Von diesen wurden initial 4 (80,0%) mit Metronidazol und nur 1 Patient mit Vancomycin behandelt. Keiner der Patienten verstarb an den Folgen einer CDI.

Diarrhoen sind eine häufige Komplikation bei Patienten mit AML [Gorschlüter *et al.* 2002]. Dieses konnte in unserer Analyse bestätigt werden. In einem Viertel bis einem Drittel der Fälle sind Diarrhoen in unserem Patientengut auf *C. difficile* zurückzuführen. CDI sind demnach deutlich häufiger bei Patienten mit AML als Infektionen durch Noroviren (Abschnitt 2.3.3) [Schalk *et al.* 2014c; Vehreschild *et al.* 2014c]. Interessanterweise fanden wir keinen Fall von Diarrhoen, die auf SSYC zurückzuführen waren. Dies ist insofern eine wichtige Beobachtung, als dass Diarrhoen bei AML-Patienten ent-

weder auf die Grunderkrankung oder auf die Therapie selbst zurückzuführen sind und deutlich seltener durch Hygienemängel im Krankenhaus verursacht werden [Schalk *et al.* 2010b]. Bei AML-Patienten, die mit Cytarabin behandelt wurden, entwickelten Patienten in einer älteren Studie in bis zu 100% der Fälle Diarrhoen [Meusers *et al.* 1985], die teilweise von der Cytarabin-Dosis und Therapiedauer abhängig sind [Kuse *et al.* 1985]. Weder diese hohe Häufigkeit der Diarrhoen, noch die Cytarabin-Dosis konnten als Risikofaktor in unserer Studie bestätigt werden. In heterogenen Patientenpopulationen, bestehend aus Patienten mit AML, akuter lymphatischer Leukämie, CML im Blastenschub und aggressivem Non-Hodgkin-Lymphom, wurde eine CDI-Häufigkeit von 5-7% pro Chemotherapiezyklus angegeben [Gorschlüter *et al.* 2001; Gorschlüter *et al.* 2002], was in etwa auch der Häufigkeit in unserer homogenen AML-Kohorte entspricht. Interessanterweise traten in etwa zwei Drittel aller CDI-Episoden in den ersten beiden Chemotherapiezyklen auf. Dies ist möglicherweise auf die leukämische Tumorlast zurückzuführen [Schalk *et al.* 2010b]. In einigen Fällen konnten Wandverdickungen im Darm auf eine leukämische Infiltration zurückgeführt werden [Gorschlüter *et al.* 2002]. Leukämien konnten als ein unabhängiger Risikofaktor für CDI identifiziert werden [Dubberke *et al.* 2007], was diese Beobachtungen erklären könnte. In einer *in vitro*-Studie konnte gezeigt werden, dass Cytarabin keine zytotoxische Wirkung auf *C. difficile* hat. Cytarabin stellt allerdings einen Risikofaktor in Hinblick auf Alteration der intestinalen Flora dar, die dadurch eine verminderte Kolonisationsresistenz bedingt, was dann letztendlich zu einer Überwucherung von *C. difficile* führt, wenn zusätzlich Antibiotika eingesetzt werden [Vetere *et al.* 1984]. Interessanterweise scheint eine höhere Cytarabin-Dosis protektiv für CDI zu sein, da die OR mit 0,5 kleiner als 1,0 ist, auch wenn dies nicht statistisch signifikant ist [Schalk *et al.* 2010b]. Eine ähnliche Beobachtung konnte in einer Studie zuvor gemacht werden: Die Häufigkeit von Diarrhoen war bei Patienten, die hochdosiertes Cytarabin erhielten, signifikant niedriger als bei Patienten, die die Standarddosis erhielten. Diese Beobachtung steht allerdings in Kontrast zu Berichten, in denen gezeigt wurde, dass die Zerstörung der Mukosa durch hoch-dosiertes Cytarabin die Pathogenese von invasiven bakteriellen Infektionen begünstigt [Gorschlüter *et al.* 2002]. In unserer Studie konnten weitere bekannte Risikofaktoren für CDI bestätigt werden: der Einsatz von Ceftazidim [Baxter *et al.* 2008] und das vermehrte Auftreten von CDI bei älteren Patienten [Starr *et al.* 2003; Gifford *et al.* 2006]. Eine weitere wichtige Beobachtung und Bestätigung war die Dauer der Neutropenie für die Entwicklung einer CDI. Die CDI-Rate war bei Patienten höher, die sich einer alloSCT unterzogen [Altclas *et al.* 2002; Dettenkofer *et al.* 2003] oder eine konventionelle AML-Chemotherapie erhielten [Bilgrami *et al.* 1999; Schalk *et al.* 2010b], verglichen mit Patienten nach autologer Blutstammzelltransplantation. Diese Beob-

achtung spiegelt die Dauer der Neutropenie in den verschiedenen Therapieansätzen wider. Mehr als die Hälfte der CDI-Fälle (58%) traten in einer Kohorte allogen stammzelltransplantierter Patienten in der Phase der Neutropenie auf [Dettenkofer *et al.* 2003]. Etwa 85% aller Patienten mit akuten Leukämien und intensiver Chemotherapie entwickeln Infektionen und/oder Fieber in Neutropenie [Hiddemann *et al.* 1997]. Die höhere CDI-Rate bei Patienten mit (prolongierter) Neutropenie ist möglicherweise in diesem Zusammenhang auch auf den vermehrten Gebrauch von Antibiotika zurückzuführen [Schalk *et al.* 2010b], wenngleich nicht alle Antibiotika gleichermaßen CDI verursachen [Vehreschild *et al.* 2014c]. Die Ansprechraten in unserer Studie entsprechen in etwa auch denen, die in der Literatur angegeben sind [Gohrschlüter *et al.* 2001; Pépin *et al.* 2007; Gerding *et al.* 2008; Vehreschild *et al.* 2013b].

Ab 07/2014 wurde die *C. difficile*-Diagnostik im Klinikum auf die international empfohlene Zwei-Schritt-Diagnostik umgestellt [Crobach *et al*. 2009; Vehreschild *et al.* 2013b, Schmidt-Hieber *et al.* 2018]. Mittels immunologischer Methode wurde ab diesem Zeitraum nun zunächst ein Screening auf *C. difficile*-Glutamatdehydrogenase durchgeführt. Im positiven Fall werden also dadurch nur *C. difficile* nachgewiesen. Durch eine PCR wird anschließend Toxin B nachgewiesen, um so toxigene, sprich pathogene *C. difficile*-Stämme zu identifizieren und dadurch eine eigentliche CDI nachzuweisen. Es konnte in einer Untersuchung in unserer Klinik an Patienten mit akuten Leukämien gezeigt werden, dass durch die Umstellung der Diagnostikmethode nur 50% der im ersten Schritt nachgewiesenen *C. difficile*-Stämme dann im zweiten Schritt tatsächlich einen Toxinnachweis erbrachten. Die Häufigkeit von CDI-Fällen nahm in dieser Patientenkohorte nach Einführung der Zwei-Schritt-Diagnostik um 27% ab (Vergleich gleichlanger Zeiträume vor und nach der Umstellung der Diagnostikmethode) [Ionita 2018]. Dies bedeutet, dass in der Kohorte der AML-Patienten in der zuvor diskutierten Arbeit die CDI-Häufigkeit tatsächlich noch niedriger sein könnte, oder, dass einige Patienten unnütz bezüglich einer vermeintlichen CDI behandelt wurden.

Publikation X
Schalk E, Bohr URM, König B, Scheinpflug K, Mohren M. *Clostridium difficile*-associated diarrhoea, a frequent complication in patients with acute myeloid leukaemia. **Ann Hematol 2010**;89(1):9-14

2.3.3 Norovirus-Infektionen

Weltweit gesehen spielen Norovirus-Infektionen (NVI) eine bedeutende Rolle als Ursache infektiöser Gastroenteritiden in den Wintermonaten und sind eine der häufigsten Gründe für virale Gastroenteritiden bei Krebspatienten [Vehreschild *et al.* 2013b], ein-

hergehend mit einer hohen Mortalitätsrate von bis zu 25%, insbesondere bei Patienten nach alloSCT [Schwartz *et al.* 2011]. Die Transmission von Noroviren geschieht durch Kontakt mit Exkrementen, aber auch durch Aerosole. Es bedarf für eine NVI nur 100 bis 1000 Viren. Die Inkubationszeit ist mit 12-48 Stunden sehr kurz. NVI gehen einher mit Erbrechen, Diarrhoen und Abdominalschmerzen, Myalgien und mit niedrigem Fieber. Die Diagnostik der NVI ist bereits im Abschnitt 2.3.1 dargestellt. Spezifische Therapien sind bis *dato* nicht bekannt [Vehreschild *et al.* 2013b]. NVI sind bei immunkompetenten Patienten nach 12-72 Stunden selbstlimitierend, doch das Ausscheiden der Viren ist noch bis zu 3 Wochen später möglich [Ludwig *et al.* 2008]. Die Epidemiologie von NVI unterscheidet sich zwischen immunkompromittierten und immunkompetenten Patienten [Bok *et al.* 2012]. Daten bezüglich NVI bei Krebs-patienten waren bis *dato* jedoch kaum publiziert.

Um nähere Informationen zur Epidemiologie von NVI bei Krebspatienten zu generieren, führten wir eine retrospektive, monozentrische Studie an unserem Zentrum durch [Schalk *et al.* 2014c]. Dabei wurden Patienten aus der Klinik für Hämatologie und Onkologie mit Patienten aus der Klinik für Gastroenterologie, Hepatologie und Infektiologie unseres Klinikums verglichen. Weiterhin wurden Fälle der kalten Jahreszeit (Oktober-März) mit Fällen aus der warmen Jahreszeit (April-September) verglichen, sowie Patienten mit hämatologischen Krebserkrankungen (akute Leukämien, maligne Lymphome) mit Patienten mit gastroenterologischen Krebserkrankungen. Weiterhin wurden die Fälle des gesamten Spektrums der Hämatologie (d. h. auch Patienten mit Anämien oder anderen benignen Erkrankungen) mit dem gesamten Spektrum der Gastroenterologie (d. h. auch Patienten mit Magenblutungen) verglichen. Es wurden Stuhlproben von allen konsekutiv aufgenommenen stationären Patienten im Zeitraum von 01/2009 bis 12/2012 auf Noroviren hin untersucht, bei denen der Verdacht auf eine Gastroenteritis bestand. Als Test wurde der ELISA RIDASCREEN Norovirus 3rd Genertion von R-Biopharm, Deutschland, verwendet.

Insgesamt wurden 1766 Stuhlproben von 673 Patienten untersucht. Das mittlere Alter betrug 58,6 Jahre; 54,5% der Patienten waren männlich. Es konnten 66 *de novo* NVI bei 60 verschiedenen Patienten nachgewiesen werden. In 31 Fällen trat die NVI bei Krebspatienten auf, dabei die meisten Fälle (23; 74,2%) bei Patienten mit hämatologischen Krebserkrankungen. Die Prävalenz und Inzidenz von NVI unterschied sich nicht zwischen hämatologischen und gastroenterologischen Patienten. So lag die Prävalenz in der Hämatologie bei 0,7%, verglichen mit 0,5% in der Gastroenterologie (p=0,36). Die Inzidenz der NVI war bei den hämatologischen Patienten mit 7,1 pro 1000 Patientenjahre zwar etwas höher als die der gastroenterologischen Patienten (4,6

pro 1000 Patientenjahre), was jedoch statistisch nicht signifikant war (p=0,44). In der Gesamtheit der hämatologischen Patienten war demnach das Risiko für eine NVI genauso groß, wie für die Gesamtheit der gastroenterologischen Patienten (OR=1,3 [95% KI 0,8-2,2]; p=0,40). Für die Subgruppe der Patienten mit hämatologischen Krebserkrankungen war das Risiko für eine NVI allerdings deutlich höher als für die Patienten mit gastroenterologischen Krebserkrankungen (OR=83,1 [95% KI 9,8-702,5]; p<0,001). Das Risiko für das Auftreten von NVI war in der kalten Jahreszeit – verglichen mit der warmen Jahreszeit – höher, sowohl für die Gesamtheit der hämatologischen als auch für die Gesamtheit der gastroenterologischen Patienten. Allerdings bestand kein erhöhtes Risiko für NVI in der kalten Jahreszeit, sowohl für die Subgruppe aller Krebspatienten (OR=2,1 [95% KI 0,6-6,9]; p=0,36) als auch für die Subgruppe der Patienten mit hämatologischen Krebserkrankungen (OR=1,8 [95% KI 0,2-13,2]; p=0,92). Die Ergebnisse sind in **Tabelle 9** zusammengefasst.

Tabelle 9. Epidemiologie und Risikofaktoren von Norovirus-Infektionen (n=66)

Parameter	Wert	p-Wert
NVI-Prävalenz [%]		
alle HO-Patienten	0,7 [0,2-1,2]	0,36
alle GHI-Patienten	0,5 [0,2-0,7]	
NVI-Inzidenz [pro 1000 Patientenjahre]		
alle HO-Patienten	7,1 [0-16,2]	0,44
alle GHI-Patienten	4,6 [0-9,5]	
NVI-Risiko [OR]		
alle HO-Patienten *vs.* alle GHI-Patienten	1,3 [0,8-2,2]	0,40
HO-Krebserkrankung *vs.* GHI-Krebserkrankung	83,1 [9,8-702,5]	<0,001
NVI-Risiko für Auftreten Winter *vs.* Sommer [OR]		
alle HO-Patienten	3,5 [1,1-10,5]	0,03
alle GHI-Patienten	2,9 [1,4-5,9]	0,003
alle Krebspatienten	2,1 [0,6-6,9]	0,36
nur HO-Krebspatienten	1,8 [0,2-13,2]	0,92

NVI, Norovirus-Infektion; HO, Hämatologie und Onkologie; GHI, Gastroenterologie, Hepatologie und Infektiologie; OR, Odds Ratio; 95% Konfidenzintervall in Klammern. Daten aus Schalk *et al.* 2014c.

Im Allgemeinen findet sich eine Prädominanz von NVI in den Wintermonaten [Bok *et al.* 2012]. Im Gegensatz dazu zeigten ein paar wenige Berichte, dass die Inzidenz von NVI bei Krebspatienten eine weniger ausgeprägte saisonale Variabilität aufwies. Diese Beobachtung bei Krebspatienten stützt sich allerdings auf nur wenige Fälle, wie n=9 bei Kindern [Ludwig *et al.* 2008], n=12 bei Erwachsenen [Roddie *et al.* 2009] oder n=11 im Ausbruch [Schwartz *et al.* 2011]. Diese vorherigen Ergebnisse werden durch unsere etwas größere Serie mit n=31 Fällen bestätigt. Aufgrund der offensichtlichen Seltenheit

der NVI bei Krebspatienten – die Prävalenz liegt in unserer Analyse bei unter 1% – sind größere Fallserien, insbesondere monozentrische, wahrscheinlich nur über einen sehr langen Beobachtungszeitraum möglich. Immunsuppressive Therapien, also auch Chemotherapie, stellen einen Risikofaktor für NVI dar. Noroviren können bei immunsupprimierten Patienten oft über Wochen bis Jahre – im Gegensatz zum Immunkompetenten (siehe oben) – persistieren [Bok *et al.* 2012] und auch zu Rezidiven führen (Ye *et al.* 2015]. Dies könnte das nicht-saisonale Auftreten von NVI bei Krebspatienten erklären [Schalk *et al.* 2014c].

Publikation XI
Schalk E, Geginat G, Schulz C, Schlüter D, Fischer T. The incidence of norovirus infections in cancer patients shows less seasonal variability compared to patients with other diseases. **Ann Hemtol 2014**;93(5):889-890

2.4 ZVK-Infektionen

2.4.1 Diagnostik

Die Diagnose von ZVK-Infektionen basiert auf klinischen Symptomen und Laborparametern und hält nicht immer klaren Definitionen stand. Es existieren in der Literatur von verschiedenen Fachgesellschaften bzw. Expertengruppen unterschiedliche Definitionen für ZVK-Infektionen [Pearson 1996; O'Grady *et al.* 2002; Wolf *et al.* 2008; O'Grady *et al.* 2011]. Meist sind diese aber kaum in der täglichen Praxis anwendbar. Die Leitliniengruppe „ZVK-Infektionen" der AGIHO hatte daher versucht, praktikablere Definitionen zu entwickeln – als eine gemeinsame Schnittmenge aller gebräuchlichen Definitionen. Dieses wurde in der Leitlinien-Gruppe maßgeblich unter Federführung des Kandidaten realisiert.

Die *Centers for Disease Control and Prevention* (CDC) unterscheidet bei ZVK-Infektionen zwischen

- ZVK-Kolonisation,
- lokalen ZVK-Infektionen,
- Infusions-bedingten Blutstrominfektionen und
- ZVK-*bedingten* Blutstrominfektionen (central venous catheter-*related* bloodstream infection [CRBSI]) [Pearson 1996; O'Grady *et al.* 2002; O'Grady *et al.* 2011].

2.4.1 Diagnostik

Die größte Bedeutung in der klinischen Praxis haben die CRBSI. Die CDC unterscheiden noch einmal CRBSI von ZVK-*assoziierten* Blutstrominfektionen (central

venous catheter-*associated* bloodstream infection [CABSI]), was bedeutet, dass der ZVK höchstens 48 Stunden *in situ* lag bevor eine Blutstrominfektion auftrat, und dass diese Blutstrominfektion nicht durch Infektionen an anderer Stelle bedingt war [O'Grady *et al.* 2011]. Damit die Definitionen von ZVK-Infektionen in der klinischen Praxis besser anwendbar sind, schlug die AGIHO in der neuen Leitlinie 2012 vor, bei den CRBSI zwischen

- *definitiven* CRBSI,
- *wahrscheinlichen* CRBSI und
- *möglichen* CRBSI

zu unterscheiden [Hentrich *et al.* 2014]. Diese Unterscheidung ist abgeleitet von den internationalen Konsensus-Empfehlungen zur Diagnostik von invasiven Pilzinfektionen, bei denen ebenfalls klinische und apparative/mikrobiologische Parameter Anwendung finden und zwischen *bewiesenen*, *wahrscheinlichen* sowie *möglichen* invasiven Pilzinfektionen unterschieden wird [De Pauw *et al.* 2008]. In **Tabelle 10** sind die diagnostischen Kriterien für CRBSI nach AGIHO 2012 dargestellt.

Die eindeutigste und wichtigste Definition der CRBSI ist die für *definitive* CRBSI. Bei Verdacht auf eine CRBSI sollen Blutkulturen (≥20 ml) – also ein Paar, bestehend aus einer aeroben und anaeroben Flasche – jeweils aus dem ZVK und aus einer peripheren Vene abgenommen werden [DesJardin *et al.* 1999; Bouza *et al.* 2007]. Bei Multilumen-ZVK, wie sie herkömmlicherweise in der Hämatologie eingesetzt werden, sollten aus jedem der Schenkel Blutkulturen abgenommen werden, da eine Kolonisation der Erreger auch nur in einem Schenkel möglich ist. Ein negatives Kulturergebnis schließt eine Kolonisation/Infektion bei Abnahme der Blutkulturen aus einem zufällig gewählten ZVK-Schenkel nicht aus. Bei letzterer Verfahrensweise liegt die Wahrscheinlichkeit für den Nachweis einer Kolonisation bei 60% [Dobbins *et al.* 2003].

Tabelle 10. Diagnosekriterien für CRBSI nach AGIHO 2012

Diagnose	Kriterien (I)	Kriterien (II)
Definitive CRBSI	Wachstum des gleichen Erregers in Kultur aus peripherem Blut und an ZVK- Spitze	±*in vitro* Testung zeigt gleiches Resistenzmuster (AI)
	Wachstum des gleichen Erregers in Kultur aus ZVK-Blut und peripherem Blut	**und** DTP ≥2 h (AII) **oder** ≥3-fach höhere Koloniezahl aus ZVK-Blut als aus peripherem Blut (AII)
Wahrscheinliche CRBSI	Wachstum des gleichen Erregers in Kultur aus ZVK-Blut und peripherem Blut	**und** keine Kriterien für *definitive* CRBSI **und** Nachweis von Koagulase-negativen *Staphylococcus* spp., *S. aureus* oder *Candida albicans* **und** Ausschluss anderer Infektionen (BIII)
Lokale Infektionen, verschiedene	Klinische Zeichen, verschiedene Ausprägungen	**und** Blutstrominfektion ohne Kriterien für *definitive* CRBSI (BIII)
Mögliche CRBSI	Nachweis von typischen Erregern (*S. epidermidis*, *S. aureus*, *Candida* spp.) in Blutkultur	**und** kein anderer Fokus (BIII)
	Entfieberung in <48 h nach ZVK-Entfernung	**und** kein anderer Fokus (BIII)
Kolonisation	Wachstum von Erregern an ZVK-Spitze	**und** klinische oder labor-chemische Infektions-zeichen **und** keine Blutstrominfektion (BIII)

Adaptiert und gekürzt nach AGIHO 2012 [Hentrich *et al.* 2014]. In Klammern das Evidenzniveau (**Tabelle 1**, Abschnitt 1) [Kish 2001]. DTP, Differential-Time-to-Positivity.

Ein wichtiges diagnostisches Instrument zum Nachweis von *definitiven* CRBSI ist die sog. Differential-Time-to-Positivity (DTP), d. h., der Unterschied in der Zeit zwischen dem Positivwerden der Blutkultur aus dem ZVK-Blut und jener aus dem Blut aus einer peripheren Vene. Bei CRBSI ist zu erwarten, dass die Bakteriendichte aus dem ZVK-Blut deutlich höher ist als im peripheren Blut, da der ZVK die eigentliche Infektionsquelle darstellt. Da eine höhere Bakteriendichte durch vermehrte CO_2-Produktion schneller zum Positivwerden der Blutkulturflasche führt, sollten die Blutkulturen aus dem ZVK-Blut bei Vorliegen einer CRBSI auch eher positiv werden, als die Blutkulturen aus dem peripheren Blut. Wenn die Blutkulturen aus dem ZVK-Blut mindestens 2 Stunden vor jenen aus dem peripheren Blut positiv werden (DTP ≥2 Stunden für zentrale *vs.* periphere Blutkultur), so liegt mit großer Sicherheit eine (*definitive*) CRBSI

vor. Dieser diagnostische Test weist eine Sensitivität von 81% und eine Spezifität von 92% auf [Raad *et al.* 2004]. Die DTP als Methode des CRBSI-Nachweises ist für Patienten auf Intensivstationen [Blot *et al.* 1999], für Patienten nach hämatopoetischer Stammzelltransplantation [Abdelkefi *et al.* 2005] und für neutropene Krebspatienten [Seifert *et al.* 2003] untersucht. In unserem SECRECY-Register (siehe Abschnitt 2.4.2) lag die mittlere DTP für *definitive* CRBSI bei 7,0 Stunden (95% KI 4,3-9,8 Stunden) [Schalk 2015; unveröffentlichte Daten], was mit den Daten aus der Literatur vergleichbar ist [Seifert *et al.* 2003]. Um die DTP zu bestimmen, bedarf es keinerlei weiterer Ressourcen, da die Zeit bis zum Positivwerden jeder Blutkulturflasche vom Inkubator automatisch angezeigt wird. Dies bedeutet, dass *definitive* CRBSI leicht und durch jedes mikrobiologische Labor in der klinischen Routine zu diagnostizieren sind, wenn Blutkulturen simultan aus dem ZVK und einer peripheren Vene abgenommen werden und die Zeiten bis zum Positivwerden der Blutkulturen dem Kliniker durch den Mikrobiologen zeitnah mitgeteilt werden.

Ein weiterer und wichtiger Punkt bei der Diagnostik von CRBSI ist die ZVK-Spitze nach ZVK-Entfernung. Die ZVK-Spitze spielt bei der Definition bzw. Diagnostik von *definitiven* und *möglichen* CRBSI eine wichtige Rolle (**Tabelle 10**). So konnte eine Analyse des zuvor genannten SECRECY-Registers (Abschnitt 2.4.2) zeigen, dass in etwa einem Drittel der Fälle das Anlegen einer Kultur von der ZVK-Spitze [Hentrich *et al.* 2014] zur Diagnose einer CRBSI beigetragen hat: Durch Nachweis eines Erregers an der Spitze nach ZVK-Entfernung war dieser Erreger in Zusammenschau aller diagnostischen Kriterien (**Tabelle 10**) in 35,7% der Fälle ursächlich verantwortlich für eine *definitive* CRBSI bzw. in 31,9% für eine *mögliche* CRBSI [Schalk 2015; unveröffentlichte Daten].

Publikation XII
Hentrich M, **Schalk E**, Schmidt-Hieber M, Chaberny I, Mousset S, Buchheidt B, Ruhnke M, Penack O, Salwender H, Wolf H, Christopeit M, Neumann, Maschmeyer M, Karthaus M. Central venous catheter-related infections in hematology and oncology: 2012 updated guidelines on diagnosis, management and prevention by the Infectious Diseases Working Party of the German Society of Hematology and Medical Oncology. **Ann Oncol 2014**;25(5):936-947

2.4.2 Vorhersage von ZVK-Infektionen

ZVK werden bei Patienten mit hämatologischen Neoplasien, wie z. B. akute Leukämien oder maligne Lymphome häufig verwendet, um die myelosuppressiven Chemotherapien oder autologe oder allogene Stammzelltransplantationen durchzuführen. In diesem Patientengut stellen CRBSI wichtige und häufige Komplikationen, insbe-

sondere in der Phase der Neutropenie, dar. CRBSI sind mit hoher Morbidität und Mortalität assoziiert. Leider ist die Diagnosestellung einer CRBSI oft schwierig und basiert häufig auf klinischen Zeichen bevor der ZVK entfernt wird [O'Grady *et al.* 2011; Hentrich *et al.* 2014]. Die CRBSI-Diagnose bleibt daher eine klinische Herausforderung, bevor mikrobiologische Ergebnisse vorliegen. Die Entfernung und Neuanlage von ZVK gehen mit einem erhöhten Risiko einher, insbesondere bei kritisch kranken Patienten mit Thrombopenie, was die klinische Entscheidung für diese Prozedur erschwert. Es wäre daher von großem klinischem Interesse, ein Instrument zur Verfügung zu haben, was die Wahrscheinlichkeit von CRBSI vorhersagen könnte.

Im Jahre 2003 wurde der sog. *Infection Probability Score* (IPS) entwickelt. Der IPS kann dazu genutzt werden, um die Wahrscheinlichkeit von Infektionen bei kritisch Kranken vorherzusagen [Peres Bota *et al.* 2003]. In den IPS gehen die allgemein und auch am Krankenbett genutzten sowie einfach zu bestimmenden Parameter

- Körpertemperatur,
- Herzfrequenz,
- Atemfrequenz,
- Leukozyten,
- C-reaktives Protein sowie der
- SOFA- (Sequential Organ Failure Assessment) Score [Vincent *et al.* 1996]

ein. Letzterer beinhaltet die Parameter

- Oxygenierungsindex,
- Kreatinin,
- Bilirubin,
- arterieller Mitteldruck,
- Thrombozyten und
- Bewusstseinstrübung (Glasgow-Koma-Skala).

Der SOFA-Score geht nur in den IPS ein, sofern >5 Punkte erreicht wurden. Der IPS kann zwischen 0 und 26 Punkten betragen. Der Grenzwert von 14 Punkten zeigt ein moderates Risiko für das Vorliegen einer Infektion von etwa 10% (negativer prädiktiver Wert [NPW]=89,5%) an. Der IPS wurde validiert bzw. angewandt für verschiedene Infektionen bei kritisch kranken Patienten und Patienten auf Normalstation [Martini *et al.* 2008; Apostolopoulou *et al.* 2010a; Apostolopoulou *et al.* 2010b; Apostolopoulou *et al.* 2011; Ratzinger *et al.* 2013] sowie für die Frage des Erfordernisses der invasiven Beatmung [Safavi *et al.* 2007; Honarmand *et al.* 2009] – jedoch bislang noch nicht für CRBSI.

Wir stellten uns daher die Frage, ob der IPS auch für hämatologische Patienten angewendet werden kann, um die Wahrscheinlichkeit von CRBSI vorhersagen zu können. Für die Beantwortung dieser Fragestellung wurden die Daten aus dem vom Kandidaten eingerichteten SECRECY-Register ausgewertet. Das SECRECY-Register war für diese Auswertung hier eine monozentrische, nicht-interventionelle prospektive Beobachtungs-/Kohortenstudie, in der epidemiologische Daten zu ZVK-Infektionen in der Hämatologie und Medizinischen Onkologie generiert wurden.

In diesem Register wurden seit 03/2013 konsekutiv alle Patienten aus unserer Klinik registriert, die einen ZVK für therapeutische Zwecke in der klinischen Routine erhielten. Neben demographischen Daten wurden auch mikrobiologische Daten erhoben. In der hier dargestellten Analyse [Schalk *et al.* 2015b] gingen alle ZVK ein, die bis 09/2014 dokumentiert wurden. Die Definition einer CRBSI erfolge nach den AGIHO-Kriterien von 2012 (siehe Abschnitt 2.4.1) [Hentrich *et al.* 2014]. Es wurden dementsprechend *definitive*, *wahrscheinliche* und *mögliche* CRBSI unterschieden. Der IPS wurde am Tag der ZVK-Anlage (IPS_{in}) sowie am Tag, an dem der ZVK entfernt wurde (IPS_{ex}), bestimmt. Abweichend vom originalen IPS [Peres Bota *et al.* 2003] inkludierten wir den absoluten Granulozytenwert (ANC) anstatt der Gesamtleukozyten (WBC). Dies ist dem Fakt geschuldet, dass die Neutropenie sehr häufig in dieser Patientenkohorte auftritt und die Neutropenie einer der wichtigsten Risikofaktoren für das Auftreten von schweren infektiologischen Komplikationen ist [Link *et al.* 2003]. Bei Neutropenie (ANC <1500/µl) wurden 3 Punkte im IPS vergeben (entsprechend WBC <5000/µl, wie im originalen IPS; WBC <5000/µl müssen nicht notwendigerweise mit einer Neutropenie einhergehen). Hier, sowie in der entsprechenden Publikation [Schalk *et al.* 2015b], wurde daraufhin vom modifizierten IPS (mIPS) gesprochen. Die Berechnung des mIPS ist in **Tabelle 11** dargestellt.

Um einen Grenzwert des $mIPS_{ex}$ zu definieren, der CRBSI vorhersagen kann, wurde sich einer ROC bedient und die AUC bestimmt [Swets 1988]. Um die praktische, klinische Relevanz zu messen, wurde auch die Effektstärke Cohen's *d* berechnet [Cohen 1988] (siehe auch Abschnitt 2.1).

In die Analyse gingen 267 ZVK mit einer Liegedauer ≥1 Tag von 143 verschiedenen Patienten ein. Das mittlere Alter der Patienten lag bei 59,5 Jahren (Spanne 25-81 Jahre), 61,4% waren männlichen Geschlechts. Zumeist wurden die ZVK für Patienten mit akuten Leukämien (53,2%) genutzt, gefolgt von multiplen Myelomen (24,3%) und malignen Lymphomen (11,2%). Die meisten ZVK wurden in die V. jugularis interna inseriert (93,6%). Insgesamt können in dieser Analyse 4044 ZVK-Tage überblickt werden. Im Mittel verblieben die ZVK 15,1 Tage *in situ* (Spanne 1-60 Tage). Bei *n*=66

CRBSI konnte eine CRBSI-Inzidenzrate von 24,7% berechnet werden. Dabei handelte es sich in 18,2% um *definitive* CRBSI, in 19,7% um *wahrscheinliche* und in 62,1% um *mögliche* CRBSI. Die CRBSI-Inzidenz wurde mit 16,3 pro 1000 ZVK-Tage angeben. Dabei lag die Inzidenz für *definitive* CRBSI bei 2,9 pro 1000 ZVK-Tage, die für *wahrscheinliche* bei 3,1 pro 1000 ZVK-Tage und die für *mögliche* bei 10,1 pro 1000 Tage. In den meisten Fällen (69,2%) konnte *S. epidermidis* als ursächlicher Erreger für die CRBSI identifiziert werden. In einem Drittel der Fälle wurde der ZVK aufgrund einer (vermuteten) CRBSI vorzeitig entfernt. In 64,0% dieser Fälle konnte dann auch eine CRBSI diagnostiziert werden.

Tabelle 11. Punktesystem für den mIPS

	mIPS-Punkte						
	0	**1**	**2**	**3**	**6**	**8**	**12**
Temperatur [°C]	≤37,5		>37,5				
Herzfrequenz [x/min]	≤80					81-140	>140
Atemfrequenz [x/min]	≤25	>25					
Leukozyten [x1000/µl]		>12					
Granulozyten [x/µl]	>1500			<1500			
CRP [mg/l]	≤6				>6		
SOFA-Score	≤5		>5				

Abweichend vom originalen Infection Probability Score [Peres Bota *et al.* 2003] wurde der mIPS für die Leukozyten-Werte adaptiert (siehe Text). Daten aus Schalk *et al.* 2015b.
mIPS, modifizierter Infection Probability Score; CRP, C-reaktives Protein; SOFA, Sequential Organ Failure Assessment [Vincent *et al.* 1996].

Zum Zeitpunkt der ZVK-Anlage gab es keinen Unterschied im mIPS für die Gruppe der Patienten, die im Verlauf eine CRBSI entwickelten oder nicht (6,7 *vs.* 6,0; p=0,39, d=0,11). In den Fällen, in denen die Patienten eine CRBSI entwickelten, war der mIPs bei der ZVK-Entfernung höher, als bei den Patienten, bei denen keine CRBSI diagnostiziert werden konnte (13,1 *vs.* 7,1; p<0,001). Dieser Unterschied im $mIPS_{ex}$ ist nicht nur signifikant, sondern auch von großer praktischer, klinischer Relevanz wie die hohe Effektstärke anzeigt (d=1,01). Als Grenzwert zur Vorhersage einer CRBSI wurde ein $mIPS_{ex}$ von 8 Punkten berechnet (AUC=0,77). Ein ähnlicher Grenzwert ($mIPS_{ex}$=9 Punkte) wurde für die am häufigsten vorkommenden CRBSI – *mögliche* CRBSI – berechnet; für diese Subgruppe konnten auch ähnliche statistische Kenngrößen wie für die Gesamtheit der CRBSI ermittelt werden (**Tabelle 12**).

Tabelle 12. $mIPS_{ex}$-Grenzwerte zur Vorhersage von CRBSI

Parameter	Alle CRBSI	*Mögliche* CRBSI
$mIPS_{ex}$-Grenzwert	8	9
Fläche unter der Kurve (AUC)	0,77 [0,71-0,83]	0,72 [0,65-0,79]
Sensitivität	84,9%	75,6%
Spezifität	60,7%	62,8%
Negativer prädiktiver Wert	92,4%	93,4%
Positiver prädiktiver Wert	41,5%	27,0%

In Klammern das 95% Konfidenzintervall. Daten aus Schalk *et al.* 2015b.

In der Publikation von Peres Bota *et al.* wurde ein IPS-Grenzwert von 14 Punkten berechnet, um die Wahrscheinlichkeit des Vorliegens von Infektionen anzugeben [Peres Bota *et al.* 2003]. In diesem Bericht wurde ein NPW von 89,5% angegeben, was bedeutet, dass ein moderates Risiko für das Vorliegen von Infektionen von ca. 10% besteht, wenn der IPS kleiner als 14 Punkte ist. Für den Grenzwert von 14 Punkten betrug die AUC der ROC 0,82, was eine moderate Aussagekraft im Sinne der Vorhersage von Infektionen für diesen diagnostischen Test darstellt. Ein Vorteil des IPS könnte darin bestehen, dass zwischen „positiven" von „negativen" Patienten schon sehr früh im Verlauf einer Infektion unterschieden werden kann. Weiterhin kann der IPS dazu verwendet werden, das Therapieansprechen zu beurteilen. Der IPS fällt nach effektiver antibiotischer Therapie im Verlauf ab. So könnte auch die Antibiotikatherapie gesteuert werden, weil ein IPS-Abfall ein Ausheilen der Entzündung anzeigen könnte [Martini *et al.* 2008]. Übertragen auf unsere Anwendung könnte dies bedeuten, dass ein mIPS-Abfall nach Entfernung des ZVK für das Vorliegen einer CRBSI und damit für ein Therapieansprechen spricht. Im Gegenzug dazu könnte ein fehlender Abfall des mIPS nach ZVK-Entfernung auf eine andere Infektionsursache als die des ZVK hindeuten. Da es keinen Unterschied im mIPS bei der ZVK-Anlage im Vergleich der Patienten gab, die im Verlauf eine CRBSI entwickelten oder nicht, kann der mIPS bei der ZVK-Anlage nicht dazu beitragen, eine CRBSI vorherzusagen. Mit Ausnahme der Studie von Ratzinger *et al.* [Ratzinger *et al.* 2013] zeigen die hier vorgestellten Daten zum IPS vergleichbare Ergebnisse mit der Literatur. Der mittlere IPS aus den bislang publizierten Studien betrug 12 Punkte (Spanne 10-14 Punkte), mit einer mittleren Sensitivität von 63% (Spanne 46-75%), einem mittleren NPW von 88% (Spanne 80-93%) und einer mittleren AUC von 0,75 (Spanne 0,62-0,96). Eine Übersicht der bislang bekannten Daten zum IPS zeigt **Tabelle 13**. Es fällt allerdings auf, dass der durch uns berechnete mIPS-Grenzwert von 8 Punkten deutlich unter den bislang aus der Literatur bekannten liegt. Eine mögliche Erklärung dafür könnte sein, dass die hier untersuchte Kohorte von Patienten mit hämatologischen Neoplasien sich von den zuvor unter-

suchten Patienten von Intensivstationen unterscheidet [Apostolopoulou *et al.* 2010a; Apostolopoulou *et al.* 2010b]. Ein weiterer Grund könnte sein, dass wir eine hohe Inzidenz sowie eine hohe *a priori* Wahrscheinlichkeit der CRBSI fanden, im Vergleich zu anderen infektiologischen Komplikationen. Wie bereits dargestellt, verwendeten wir eine modifizierte Version des originalen IPS, die mehr die Neutropenie *per se* wichtet. Dies könnte potentiell den mIPS erhöhen (im Vergleich zum originalen IPS), wenn die ANC-Werte anstatt der WBC-Werte verwendet werden. Insgesamt gesehen ist der mIPS-Grenzwert für die Vorhersage einer CRBSI potentiell vermindert, weil strengere Kriterien für einen definierten Risikofaktor (Neutropenie) in unserem Patientengut angewendet wurden.

Tabelle 13. Literaturübersicht zum IPS und dessen statistische Kennzahlen

Autor	Indikation	IPS	Sens. [%]	Spez. [%]	NPW [%]	PPW [%]	AUC
Peres Bota *et al.* 2003	Infektion, Intensivstation	14	74	78	90	54	0,96
Martini *et al.* 2008	Infektion, Intensivstation	14	-	-	86	80	-
Apostolopoulou *et al.* 2010a	Bakteriämie, Hämatologie	10	75	71	93	37	0,72
Apostolopoulou *et al.* 2010b	HCAI, Hämatologie	10	59	74	80	51	0,70
Apostolopoulou *et al.* 2011	*C. difficile*-Infektion, Hämatologie	13	46	82	92	26	0,62
Ratzinger *et al.* 2013	Sepsis, allgemein	16	30	65	26	69	0,51
Ratzinger *et al.* 2013	Bakteriämie, allgemein	16	21	65	71	17	0,58
Schalk *et al.* 2015b	**CRBSI, Hämatologie**	**8**	**85**	**61**	**92**	**42**	**0,77**

IPS, Infection Probability Score; HACI, healthcare-associated infection; CRBSI, catheter-related bloodstream infection; Sens., Sensitivität; Spez., Spezifität; NPW, negativer prädiktiver Wert; PPW, positiver prädiktiver Wert; AUC, area under the curve.

Das Risiko für eine CRBSI bei der Entfernung des ZVK und Vorliegen des berechneten $mIPS_{ex}$-Grenzwertes von ≥8 Punkten war hoch (OR=5,9 [95% KI 2,8-12,6]; p<0,001). Diese Wahrscheinlichkeit war noch deutlich höher, wenn der ZVK mindestens 10 Tage *in situ* war und der $mIPS_{ex}$ ≥8 Punkte (OR=9,8 [95% KI 2,9-33,5]; p<0,001). Die ZVK-Liegedauer war an sich kein prädiktiver Risikofaktor für eine CRBSI, da OR=1,4 ([95% KI 0,3-7,3]; p>0,99) bei einer Liegedauer von ≥7 Tagen bzw. OR=1,3 ([95% KI 0,3-5,3); p=0,95) bei einer Liegedauer von ≥14 Tagen.

Es wurde versucht einen Grenzwert für die ZVK-Liegedauer zu ermitteln, ab dem das Risiko für eine CRBSI erhöht ist. Es könnte so die Frage beantwortet werden, nach wie vielen Tagen des ZVK *in situ* es sinnvoll erscheint, den ZVK prophylaktisch zu wechseln, um eine CRBSI zu verhindern. Dazu wurde eine gepoolte Analyse aus Daten des fortlaufenden SECRECY-Registers und der COAT-Studie durchgeführt [Schalk *et al.* 2017a]. Die COAT-Studie (*Antimicrobial Catheter Securement Dressings for the Prevention of CVC-related Bloodstream Infections in Cancer Patients*) war eine prospektive, randomisierte, multizentrische Studie, die den Einfluss zweier verschiedener ZVK-Verbände (Pflaster) auf die CRBSI-Rate bei neutropenen Patienten untersuchte [Biehl *et al.* 2016]. Für die gepoolte Analyse wurden nur über die V. jugularis oder V. subclavia inserierte ZVK mit einer Liegedauer von ≥1 Tag eingeschlossen. Beide Studien verwendeten die Definitionen der ZVK-Infektionen nach AGIHO 2012 [Hentrich *et al.* 2014], wobei nur *definitive* und *wahrscheinliche* ZVK-Infektionen hier betrachtet wurden. Es wurden insgesamt 1194 ZVK mit 20.330 ZVK-Tagen (Median=17 Tage, Spanne 1-60 Tage) untersucht; 610 ZKV (51,1%) kamen dabei aus der COAT-Studie und 584 (48,9%) aus dem SECRECY-Register. Die CRBSI-Rate lag bei 11,5% (137 ZVK-Infektionen) und die entsprechende Inzidenz bei 6,7 pro 1000 ZVK-Tage. Im Median traten die ZVK-Infektionen nach einer ZVK-Liegedauer von 13 Tagen auf. Interessanter Weise gab es keinen Unterschied in der Zeit bis zum Auftreten einer ZVK-Infektion zwischen ZVK, die über die V. jugularis und über die V. subclavia inseriert wurden (mediane Zeit jeweils 13 Tage). Mithilfe der AUC einer ROC wurde versucht einen Grenzwert für die ZVK-Liegedauer anzugeben, ab der ein Risiko für das Auftreten einer ZVK-Infektion besteht. Da die AUC mit 0,42 (95% KI 0,37-0,46) kleiner als 0,5 war, und demnach keine prädiktive Signifikanz vorliegt [Šimundić 2009], kann die ZVK-Liegedauer nicht als Parameter zur Abschätzung des Risikos für ZVK-Infektionen herangezogen werden. Wahrscheinlich liegt dies daran, dass die ZVK-Liegezeit, in der ZVK-Infektionen auftreten, einer sehr großen Spannbreite unterliegt (Spanne 2-40 Tage, Interquartilenspanne 10-17 Tage) [Schalk *et al.* 2017a]. Verdeutlicht wird dies noch einmal in **Abbildung 4**: Die Kurve der kumulativen CRBSI-Rate (11,5%) aus den gepoolten SECRECY/COAT-Daten [Schalk *et al.* 2017a] steigt ab einer ZVK-Liegedauer von 8 Tagen bis zu 22 Tagen relativ gleichmäßig steil an. Wie bereits dargestellt, liegt der Median des Auftretens der ZVK-Infektionen mit Tag 13 ziemlich genau in der Mitte dieses Steilverlaufs der Kurve.

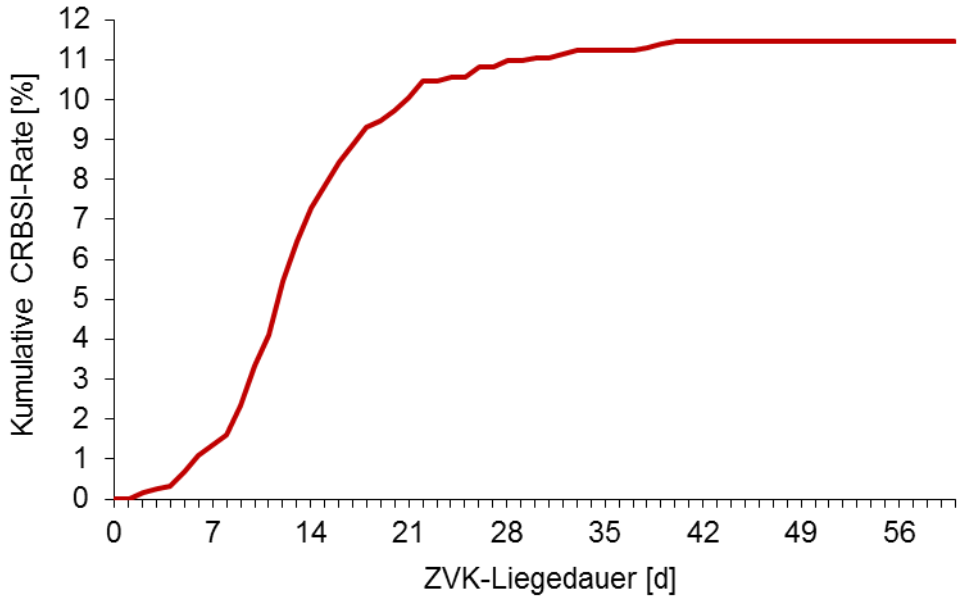

Abbildung 4. Kumulative CRBSI-Rate (11,5%). Gepoolte Daten nach Schalk *et al.* 2017a.
CRBSI, catheter-related bloodstream infection.

Es konnte bereits vor längerer Zeit gezeigt werden, dass die routinemäßige Neuanlage eines ZVK nach einer bestimmten Zeit *in situ* die CRBSI-Raten nicht verringert [Cobb *et al.* 1992]. Deshalb ist diese Prozedur generell nicht empfohlen [Hentrich *et al.* 2014] – insbesondere nicht bei thrombopenen Patienten. Sie ist allerdings eine wichtige Maßnahme bei neutropenen Patienten mit schwerer Sepsis [Legrand *et al.* 2012]. Unterstützt wird dieses durch unsere SECRECY-Analyse, wie bereits dargestellt: Eine längere ZVK-Lage ging nicht mit einem höheren CRBSI-Risiko einher. Das CRBSI-Risiko erhöhte sich erst, wenn klinische oder laborchemische Parameter vorlagen, die eine Entzündung/Infektion anzeigen. Unserer Meinung nach könnten eine ZVK-Liegedauer von etwas mehr als 10 Tagen sowie das Vorliegen des mIPS von mehr als 8 Punkten prädiktive Parameter sein, eine ZVK-Neuanlage vorzunehmen, um so CRBSI zu verhindern. Dies muss selbstverständlich durch prospektive Studien validiert werden.

In der hier vorgestellten SECRECY-Auswertung konnten zum ersten Mal epidemiologische Daten zu CRBSI bei Patienten mit hämatologischen Neoplasien entsprechend den überarbeiteten AGIHO-Kriterien aus 2012 [Hentrich *et al.* 2014] zur Diagnostik von CRBSI präsentiert werden. Die hier gefundene CRBSI-Inzidenz von 16,3 pro 1000 Tage scheint deutlich höher zu sein als im Vergleich zu anderen Berichten erwachsener Krebspatienten: In der Literatur sind CRBSI-Inzidenzen bei diesem Patientengut von 1,1-7,5 pro 1000 ZVK-Tage angegeben [Worth *et al.* 2008; Bénet *et al.* 2009;

Mollee *et al.* 2011]. In einer gepoolten Analyse von 61 prospektiven Studien wurde eine mittlere CRBSI-Inzidenz von 2,3 pro 1000 ZVK-Tagen angegeben [Crnich *et al.* 2002]. Eine ähnliche Inzidenz von 2,7 pro 1000 ZVK-Tage wurde in einer aktuelleren Analyse von 200 prospektiven Studien gefunden [Maki *et al.* 2006]. All diese epidemiologischen Daten bzw. Studien müssen jedoch im Kontext der gewählten Kriterien für die Definitionen der CRBSI gesehen werden [Schalk *et al.* 2016]. So berichteten z. B. Mollee *et al.* über eine CRBSI-Inzidenz von 1,1 pro 1000 ZVK-Tage bei Patienten auf einer hämatologisch-onkologischen Station [Mollee *et al.* 2011]. In dieser Studie handelt es sich jedoch exklusiv nur um *definitive* CRBSI, wie sie hier in der SECRECY-Auswertung angewandt wurden [Hentrich *et al.* 2014]. Die durch uns angegebene Inzidenz von definitiven CRBSI mit 2,9 pro 1000 ZVK-Tage ist dann durchaus mit den Daten aus der Literatur vergleichbar [Maki *et al.* 2006].

Eine Limitation des IPS (oder des mIPS) in der Vorhersage von CRBSI ist die Tatsache, dass andere potentielle Infektfoci ausgeschlossen sein müssen [Hentrich *et al.* 2014], zumindest für die Subgruppen der *wahrscheinlichen* und *möglichen* CRBSI (**Tabelle 10**), die die häufigsten CRBSI ausmachen. Die Wahrscheinlichkeit einer CRBSI mit einem berechneten mIPS ≥8 Punkten bei der ZVK-Entfernung beträgt nur 42%. Dieser Wert verringert sich noch auf 27% für die Subgruppe der *möglichen* CRBSI. Liegt der mIPS bei ZVK-Entfernung unter 8 Punkten, so liegt die Wahrscheinlichkeit des Vorliegens einer CRBSI bei nur 8% [Schalk *et al.* 2015b]. Selbstverständlich darf ein ZVK nicht um jeden Preis erhalten werden, auch wenn der mIPS <8 Punkte beträgt. In 9 der 66 Fälle (13,6%) war der mIPS bei ZVK-Entfernung <8 Punkte (6 von diesen Fällen waren *mögliche* CRBSI) [Schalk *et al.* 2015b]. Es gibt klare Empfehlungen, wann ein ZVK auf jeden Fall entfernt werden sollte, sofern eine CRBSI in Verdacht steht – ganz unabhängig vom mIPS: Bei Zustandsverschlechterung des Patienten, Vorliegen einer Sepsis/eines septischen Schocks, schweren Komplikationen wie Endokarditis, septische Thrombembolien, Abszess, Osteomyelitis oder Nachweis u. a. von *S. aureus*, *P. aeruginosa* oder *C. albicans* in den Blutkulturen [Hentrich *et al.* 2014].

Für ZVK, die <14 Tage *in situ* verbleiben, werden die Infektionen meist durch Ausbreitung der Bakterien an der Außenseite des ZVK verursacht. Im Gegensatz dazu gehen CRBSI bei ZVK mit einer Liegedauer von mehr als 14 Tagen eher von intraluminal aus. Die Ausbreitung von Bakterien an der ZVK-Innenseite innerhalb eines sog. Biofilms geschieht durchaus schon innerhalb der ersten 24 Stunden nach ZVK-Anlage [Raad 1998; Hentrich *et al.* 2014]. Deshalb wurden in der SECRECY-Analyse alle ZVK mit einer Liegedauer von ≥1 Tag eingeschlossen.

Entsprechend den AGIHO-Kriterien für die Diagnose einer CRBSI sind für *mögliche* CRBSI, und zum Teil auch für *definitive* CRBSI, klinische und/oder mikrobiologische Ergebnisse erforderlich (Entfieberung innerhalb von 48 Stunden nach ZVK-Entfernung, kultureller Errgernachweis an der ZVK-Spitze) [Hentrich *et al.* 2014], d. h. die CRBSI-Diagnose kann nicht in jedem Fall bereits bei der ZVK-Entfernung, sondern erst im weiteren Verlauf gestellt werden. Wie anhand der statistischen Kennzahlen für den IPS bzw. mIPS dargestellt (**Tabelle 12 und 13**), liegt der Wert dieses diagnostischen Hilfsmittels insbesondere aufgrund des relativ hohen NPV darin, dass bestimmte Infektionen (wie z. B. *mögliche* CRBSI zum Zeitpunkt der potentiellen ZVK-Entfernung bevor weitere klinische oder mikrobiologische Ergebnisse vorliegen) mit relativ hoher Wahrscheinlichkeit ausgeschlossen werden können, wenn der berechnete IPS/mIPS unterhalb des entsprechenden Grenzwertes liegt.

Publikation XIII
Schalk E, Hanus L, Färber J, Fischer T, Heidel FH. Prediction of central venous catheter-related bloodstream infections (CRBSI) in patients with haematologic malignancies using a modified Infection Probability Score (mIPS). **Ann Hematol 2015**; 94(9):1451-1456

Publikation XIV
Schalk E, Biehl LM, Färber J, Schlüter D, Vehreschild MJGT, Fischer T. Determination of a cut-off time-point for prophylactic exchange of central venous catheters for prevention of central venous catheters-related bloodstream infections in patients with hematological malignancies. **Infect Control Hosp Epidemiol 2017**;38(7):888-889

2.4.3 Adipositas als Risikofaktor für ZVK-Infektionen

Im Allgemeinen wird Adipositas als ein Risikofaktor für CRBSI angesehen. Dieses wird in der Literatur jedoch nicht einheitlich widergeben, und es existieren zu dieser Problematik bislang keine Daten zu Patienten mit hämatologischen Neoplasien. Die ZVK-Anlage gestaltet sich mitunter bei adipösen Patienten schwierig, da die anatomischen Landmarken am Hals „verschleiert“ sind [McGee *et al.* 2003; Graham *et al.* 2007]. Ein weiterer Punkt – das vermehrte Schwitzen adipöser Patienten [Lawrence *et al.* 2004] –, führt häufiger zu Problemen mit den Verbänden an der ZVK-Einstichstelle und erhöht dadurch das Risiko für CRBSI [Trick *et al.* 2006]. Wir stellten daher die Hypothese auf, dass adipöse Patienten, die aufgrund hämatologischer Neoplasien mit Chemotherapie behandelt werden, ein höheres Risiko für CRBSI aufweisen, als nicht-adipöse hämatologische Patienten.

Beim Adipösen ist das Fettgewebe ein dysfunktionelles Gewebe. Chronische Entzündung und Insulinresistenz stellen im viszeralen Fettgewebe wichtige metabolische

Prozesse dar. Als Folge kommt es zu Veränderungen von Serumspiegeln verschiedenster Zytokine und Hormone zur Stimulation von Antiapoptose, Zellproliferation, Angiogense, Invasion, Metastasierung und damit letztendlich zur Tumorprogression [Ungefroren *et al.* 2015]. Adipositas bedingt demnach ein höheres Risiko an unterschiedlichsten Tumoren zu erkranken. So ist z. B. das Leukämierisiko bei adipösen Frauen um den Faktor 1,32 höher, als bei nicht-adipösen Frauen [Dobbins *et al.* 2013]. Weltweit waren im Jahr 2012 etwa 4% aller Krebserkrankungen auf Adipositas zurückzuführen [Arnold *et al.* 2015]. Sachsen-Anhalt ist das deutsche Bundesland mit dem höchsten Anteil an Übergewichtigen: So sind etwa drei Viertel aus der Altersgruppe der 60- bis 75-jährigen übergewichtig [Statistisches Landesamt Sachsen-Anhalt 2012]. Betrachtet man verschiedene Zeiträume in den letzten Jahren, so muss konsterniert werden, dass der Anteil an Übergewichtigen und Adipösen weiter zunimmt [Statistisches Landesamt Sachsen-Anhalt 2012; Völzke *et al.* 2015]. Weiterhin sehen wir eine Zunahme des Körpergewichts, und damit auch des Body Mass Index (BMI), sowie eine Zunahme von Krebserkrankungen im Alter. Damit besteht zumindest eine statistische Korrelation zwischen der Zunahme von Körpergewicht und Krebser-krankungen [Ungefroren *et al.* 2015].

Um den Zusammenhang zwischen Adipositas und CRBSI beantworten zu können, wurden die Daten des zuvor beschriebenen SECRECY-Registers (siehe Abschnitt 2.4.2) im Verlauf noch einmal ausgewertet. In der 03/2015 durchgeführten Auswertung gingen 335 ZVK von 176 verschiedenen Patienten ein [Schalk *et al.* 2015c]. Während der 5094 ZVK-Tage wurden insgesamt 77 CRBSI diagnostiziert. Dabei handelte es sich in 15,6% der Fälle um *definitive*, in 27,3% um *wahrscheinliche* und in 57,1% um *mögliche* CRBSI nach den AGIHO-Kriterien aus 2012 [Hentrich *et al.* 2014]. Die CRBSI-Inzidenz lag bei 15,1 pro 1000 ZVK-Tage (2,4 pro 1000 ZVK-Tage für *definitive* CRBSI) und die Inzidenzrate bei 23,0%. Damit sind diese epidemiologischen Daten mit denen aus der ersten SECRECY-Auswertung aus 09/2014 vergleichbar [Schalk *et al.* 2015b] und aufgrund des größeren Datensatzes durchaus valider. Der mittlere BMI bei der ersten ZVK-Anlage lag bei 28,0 kg/m^2 (Spanne 15-46 kg/m^2), was nach den Kriterien der Weltgesundheitsorganisation Übergewicht darstellt (25,0-29,9 kg/m^2). In 28,4% der Fälle erfolgte die ZVK-Anlage bei adipösen Patienten (BMI>30 kg/m^2).

Die hohe Zahl an übergewichtigen bzw. adipösen Patienten in unserer Kohorte könnte ursächlich mit den zuvor dargestellten Sachverhalten bezüglich Adipositas im Zusammenhang stehen.

Wir nahmen an, dass die Komplikationsrate (Blutung, Hämatom, >2 Punktionsversuche, Probleme mit dem Führungsdraht) bei der ZVK-Anlage bei adipösen Patienten

höher ist, als bei Nicht-Adipösen. Bei Adipösen wurden in 18,3% Komplikationen bei der ZVK-Anlage berichtet, bei den nicht-adipösen Patienten waren es 18,4%. Adipositas ging demnach nicht mit einem erhöhten Komplikationsrisiko bei der ZVK-Anlage einher (OR=0,99 [95% KI 0,53-1,85]; p>0,99). Im Vergleich der CRBSI-Raten fanden wir ebenfalls keine Unterschiede zwischen adipösen und nicht-adipösen Patienten (22,1% *vs.* 23,3%; OR=0,93 [95% KI 0,53-1,65]; p=0,93). Die ZVK-Liegedauer war bei adipösen Patienten kürzer als bei nicht-adipösen (13,5 Tage *vs.* 15,9 Tage; p=0,03). Interessanterweise stellt das Geschlecht bei Adipösen keinen Risikofaktor für CRBSI dar (Männer *vs.* Frauen, OR=0,86 [95% KI 0,32-2,35]; p=0,97). Weder für adipöse Männer (OR=0,68 [95% KI 0,32-1,45]; p=0,42), noch für adipöse Frauen (OR=1,58 [95% KI 0,64-3,92]; p=0,45) war das CRBSI-Risiko im Vergleich zu Nicht-Adipösen erhöht.

Unserer Erfahrung nach ist die ZVK-Anlage bei adipösen Patienten unter Zuhilfenahme der Sonographie eine sichere Prozedur. Überraschenderweise stellt in unserer Kohorte Adipositas keinen Risikofaktor für CRBSI dar. Dies ist noch umso überraschender, da bei der ZVK-Anlage der modifizierte IPS [Schalk *et al.* 2015b] bei adipösen Patienten höher war, als bei Nicht-Adipösen (7,6 *vs.* 5,8; p=0,02) [Schalk *et al.* 2015c]. Wie bereits in Abschnitt 2.4.2 dargestellt, kann der mIPS als ein Instrument angesehen werden, das die Krankheitsschwere von Patienten beschreibt. Da die adipösen Patienten bei der ZVK-Anlage höhere Werte im mIPS aufwiesen, also demnach „kränker“ als die nicht-adipösen Patienten waren, hätte man annehmen können, dass sich dies auch in der CRBSI-Rate widerspiegelt.

Wir wissen, dass das CRBSI-Risiko umso höher ist, je länger ein ZVK *in situ* verbleibt [Schalk *et al.* 2015b; Pepin *et al.* 2015]. Dies könnte unter anderem die Erklärung dafür sein, dass wir kein erhöhtes Risiko für CRBSI bei adipösen Patienten fanden, da in dieser Subgruppe der ZVK im Mittel um 2-3 Tage signifikant kürzer *in situ* war, als bei den nicht-adipösen Patienten. Eine andere Erklärung für unsere Ergebnisse könnte sein, dass eine inverse Assoziation zwischen Adipositas und dem Risiko für die febrile Neutropenie besteht [Chao *et al.* 2014], und damit auch dem Risiko für CRBSI. Ein potentieller Mechanismus ist in der veränderten Pharmakokinetik und/oder einer reduzierten relativen Effektivität der Chemotherapie durch Adipositas zu sehen [Chao *et al.* 2014].

Publikation XV
Schalk E, Färber J, Fischer T, Heidel FH. Central venous catheter-related bloodstream infections in obese hematologic patients. **Infect Control Hosp Epidemiol 2015**;36(8): 995-996

2.5 Influenza-Infektionen

Infektionen durch respiratorische Viren, wie Orthomyxoviren (Influenza A, B und C), Paramyxoviren (Parainfluenza 1-4, respiratorische Synzytial-Viren [RSV] A und B, humane Metapneumoviren), Coronaviren, Picornaviren (Rhinoviren und Enteroviren), Adenoviren, Polyomavirus und Bocavirus, bedingen beim Immunkompetenten oft nur eine gewöhnliche Erkältung, können aber bei immunsupprimierten Patienten lebensbedrohliche Erkrankungen hervorrufen [von Lilienfeld-Toal *et al.* 2016]. Influenza- und RS-Viren zählen dabei zu den häufigsten Erregern [Mikulska *et al.* 2014; RespVir 2017]. Infektionen durch diese Viren sind beim Immunsupprimierten sicherlich ein unterschätztes Problem, da diese Patienten weniger klinische Symptome oder Zeichen bei der klinischen Untersuchung aufweisen, als immunkompetente Patienten [Memoli *et al.* 2014]. Aber insbesondere bei Krebspatienten ist die Gefahr groß, dass sich untere Atemwegsinfektionen/Pneumonien [Mikulska *et al.* 2014] durch diese Erreger entwickeln, was z. B. bei Influenza, und hier zum großen Teil bei Patienten mit hämatologischen Neoplasien [Schnell *et al.* 2010] oft der Fall ist – in bis zu 30% der Fälle, assoziiert mit einer hohen Mortalitätsrate von bis zu 25% [von Lilienfeld-Toal *et al.* 2016]. Da offensichtlich ein Bedarf zur Verbesserung der Behandlung von Krebspatienten mit respiratorischen Virusinfektionen besteht, und es bislang keine allumfassende Empfehlungen zur Diagnostik und Therapie bei Krebspatienten allgemein gab, wurde seitens der AGIHO unter Mitwirkung des Kandidaten eine evidenzbasierte Leitlinie zu dieser Problematik entwickelt [von Lilienfeld-Toal *et al.* 2016].

Influenza tritt, abgesehen von RSV-Infektionen, im Gegensatz zu den vielen anderen respiratorischen Viren, saisonal auf und kann auch zu einem Ausbruchgeschehen führen. Die Influenza-Saison 2014/15 in Deutschland war eine der intensiveren, ging von Oktober 2014 bis Mitte April 2015, erreichte ihren Höhepunkt in der zweiten Woche 2015, und breitete sich vom Südosten zum Nordwesten aus [Buda *et al.* 2015]. Epidemiologische Daten zu Influenza bei immunsupprimierten Patienten gibt es hauptsächlich aus Kohorten von allogen stammzelltransplantierten Patienten. Es ist jedoch erforderlich, Informationen zu Patienten mit verschiedenen Krebserkrankungen zu erhalten, zumal es nur wenige Daten zu Patienten mit soliden Tumoren gibt.

Daher wurden in einer retrospektiven Analyse an acht deutschen Zentren (7 Universitätskliniken für Hämatologie und Medizinische Onkologie, 1 onkologische Schwerpunktpraxis) aus der AGIHO heraus epidemiologische und klinische Daten zur Influenza-Saison 2014/15 bei Krebspatienten generiert, um Hochrisiko-Patienten hinsichtlich schwerem Verlauf und Mortalität zu identifizieren [Herrmann *et al.* 2017]. Ins-

gesamt konnten 203 Patienten mit einer Influenza-Infektion ausgewertet werden. Das mediane Alter der Patienten betrug 61 Jahre. Die Mehrzahl der Patienten litt an einer hämatologischen Neoplasie (78%); insgesamt betrug der Anteil der stammzelltransplantierten Patienten 52%. Passend zu dieser Influenza-Welle insgesamt, war bei den meisten der Patienten Influenza A nachweisbar (77%). Die Mehrzahl der Patienten litt an „Grippe“ (40%). Ein nicht unerheblicher Anteil von 28% der Patienten präsentierten sich mit Pneumonie, andere mit oberen Atemwegsinfektionen (27%) und Magen-Darm-Symptomen (10%). Relevante Superinfektionen durch RSV, *E. coli-, P. aeruginosa*-Bakteriämien oder *Aspergillus* spp.-Pneumonien waren bei 18% der Patienten nachweisbar. Eine antivirale Therapie wurde nur bei 56% der Patienten durchgeführt. Therapiert wurden die Patienten mit Oseltamivir, im Median über 7 Tage. Ein schwerer klinischer Verlauf der Influenza-Infektion mit intensivmedizinischer Betreuung war in 13% der Fälle erforderlich; unter den Patienten mit Pneumonie war dies mit 34% noch häufiger der Fall. Die Mortalitätsrate war mit 9% insgesamt hoch; im Falle einer Pneumonie mit 18% sogar noch deutlich höher. Die Pneumonie stellte sich als Risikofaktor für Mortalität heraus, was sich auch daran zeigte, dass alle Patienten mit Pneumonie verstarben. Als weitere Prognosefaktoren konnten Superinfektionen durch Bakterien oder Pilze identifiziert werden. Die Zeit von Symptombeginn bis zur Diagnose war kürzer bei Patienten, die die Influenza-Infektion überlebten als bei Patienten, die daran verstarben (3 Tage *vs.* 7 Tage; p=0,002). Zudem waren Patienten, die an Influenza verstarben älter als die, die überlebten (63 Jahre *vs.* 57 Jahre; p=0,043). Interessanterweise hatten die Art und Aktivität der malignen Grunderkrankung, eine immunsuppressive Therapie, eine GvHD und – überraschender Weise – eine antivirale Therapie mit Oseltamivir keinen Einfluss auf das Überleben. In der multivariaten Analyse kristallisierten sich die Superinfektion (HR=3,04 [95% KI 1,09-10,6]; p=0,03) und die Dauer von Symptombeginn bis zur Diagnosestellung (HR=1,1 [95% KI 1,01-1,20]; p=0,02) als unabhängige Prognosefaktoren heraus.

Superinfektionen bei Patienten mit Infektionen durch respiratorische Viren gehen mit deutlich erhöhter Mortalität einher [Ustun *et al.* 2010] und müssen unbedingt mit bedacht und dann auch konsequent behandelt werden [von Lilienfeld-Toal *et al.* 2016]. So verstarben in der AGHIO-Kohorte 30% der Patienten mit Superinfektion [Hermann *et al.* 2017]. Krebspatienten mit Influenza gelten als Hochrisiko-Patienten [von Lilienfleld-Toal *et al.* 2016] und sollten bei Symptomen früh, d. h. innerhalb von 48 Stunden nach Auftreten von Symptomen, antiviral behandelt werden [Fiore *et al.* 2011]. Die Intention dabei ist die Verkürzung des natürlichen Verlaufs der Infektion und insbesondere die Verhinderung von unteren Atemwegsinfektionen/Pneumonien [Nichols *et al.* 2004]. Zu beachten ist, dass bei Patienten mit hämatologischen Neoplasien die

Virusausscheidung deutlich länger sein kann, z. B. schieden in einer Untersuchung die Patienten Influenzaviren in 38% der Fälle noch bis zu 2 Wochen nach Symptombeginn aus [Lehners *et al.* 2016]. Die Ausscheidung von Influenza-Viren betrug beim Immunsupprimierten im Mittel 19,0 Tage *vs.* 6,4 Tage bei immunkompetenten Patienten (p=0,047) bzw. im Median 8,0 Tage *vs.* 5,0 Tage (p=0,01) [Memoli *et al.* 2014]. Dies bedeutet, dass bei Krebspatienten die antivirale Therapie länger als gewöhnlich (>5 Tage) durchgeführt werden sollte [von Lilienfeld-Toal *et al.* 2016]. Dies spiegelt sich auch in der AGIHO-Untersuchung wider: Die mediane Therapiedauer betrug hier 7 Tage [Herrmann *et al.* 2017]. Die verlängerte Virusausscheidung ist ein wichtiger Punkt, der in Sachen nosokomialer Transmission, gerade in Ausbruchssituationen, bedacht werden muss. Zum anderen bedeutet dies aber auch, dass ein verzögerter Therapiebeginn (>48 Stunden nach Symptombeginn) bei diesen Patienten nicht von Nachteil ist, da auch dadurch noch effektiv untere Atemwegsinfektionen/Pneumonien verhindert werden können [Choi *et al.* 2011].

Die Untersuchung zeigte, dass Influenza-Infektionen bei Krebspatienten aufgrund der hohen Pneumonie-Rate, unabhängig von der Art der malignen Grunderkrankung, weiterhin potentiell gefährlich sind und bei allen diesen Patienten ernst genommen werden müssen, insbesondere müssen sie schnell diagnostiziert und die Superinfektionen mit behandelt werden. Möglicherweise wird zu selten an andere Auslöser als Influenza bei Patienten mit Pneumonien oder anderweitig kritisch kranken Patienten gedacht, was die Zeitdauer von Symptombeginn bis Diagnose als unabhängigen Prognosefaktor für Mortalität erklären könnte [Hermann *et al.* 2017].

Publikation XVI
Hermann B, Lehners N, Brodhun M, Boden K, Hochhaus A, Kochanek M, Meckel K, Mayer K, Rachow T, Rieger C, **Schalk E**, Weber T, Schmeier-Jürchott A, Schlattmann P, Teschner D, von Lilienfeld-Toal M. Influenza virus infections in patients with malignancies – characteristics and outcome of the season 2014/15. A survey conducted by the Infectious Diseases Working Party (AGIHO) of the German Society of Haematology and Medical Oncology (DGHO). **Eur J Clin Microbiol Infect Dis 2017**;36(3):565-573

Publikation XVII
von Lilienfeld-Toal M, Berger A, Christopeit M, Hentrich M, Heussel CP, Kalkreuth J, Klein M, Kochanek M, Penack O, Hauf E, Rieger C, Silling G, Vehreschild M, Weber T, Wolf HH, Lehners N*, **Schalk E*,** Mayer K*. Community acquired respiratory virus (CRV) infections in cancer patients – guidelines on diagnosis and management by the Infectious Diseases Working Party (AGIHO) of the German Society for Haematology and Medical Oncology (DGHO). **Eur J Cancer 2016**;67:200-212
*Geteilte Letztautorenschaft

3 Zusammenfassung und Ausblick

Die vorliegende kumulative Habilitationsschrift befasste sich mit infektiologischen Komplikationen in der Hämatologie und Medizinischen Onkologie aus Sicht des klinisch tätigen Arztes. Es wurden dabei ausgewählte Aspekte der Epidemiologie sowie der Diagnostik bei Krebspatienten untersucht und diskutiert.

Fieber in Neutropenie ist in unserem Patientengut in der Hämatologie, also zumeist bei Patienten mit akuten Leukämien, eine sehr häufige Komplikation mit weiterhin hoher Letalität. Eine sofortige Initiierung einer empirischen antibiotischen Therapie ist daher unabdingbar. Das Risiko der Entwicklung von infektiologischen Komplikationen hängt u. a. von der Tiefe und von der Dauer der Neutropenie ab. Für die Diagnostik der Sepsis, der schwerwiegendsten infektiologischen Komplikation, können bei unseren Patienten mit Leuko- bzw. Neutropenie naturgemäß die Leukozytenwerte nicht mit zur Diagnosestellung einer Sepsis herangezogen werden. Zum Management, d. h. Diagnostik und Therapie, der Sepsis in Neutropenie wurde durch die AGIHO eine aktualisierte Leitlinie vorgelegt. Um das Infektionsrisiko bei unserem Patientengut anhand der neutrophilen Granulozyten abschätzen zu können, bedarf es valider Werte. Nicht selten erfolgt die Blutabnahme aus einer kapillären Punktion.

Es konnte gezeigt werden, dass die kapilläre Blutbildbestimmung sicher, zuverlässig und valide ist sowie eine hohe diagnostische Aussagekraft hat. Die kapilläre Blutbildbestimmung kann demnach für die Diagnostik einer Neutropenie bzw. Agranulozytose, Anämie und Thrombopenie der venösen Blutbildbestimmung als gleichwertig angesehen werden. Bislang waren zur dieser Problematik nur Studien mit unzureichenden Daten publiziert. Die ermittelten kapillär-venösen Differenzen sind in der klinischen Routine, d. h. auch bei Patienten mit pathologischen Werten, vernachlässigbar gering und daher klinisch nicht bedeutsam. Da Blutentnahmen in der Hämatologie häufig durch kapilläre Punktionen erfolgen, und klinisch wichtige Entscheidungen bzw. Erscheinungsbilder durch so bestimmte Werte getroffen bzw. diagnostiziert werden, bedarf es demnach reeller Blutbildparameter. Diese Arbeit konnte dazu einen wichtigen Beitrag leisten und trägt dazu bei, dass die kapilläre Blutbildbestimmung bei unserem Patientengut in der klinischen Routine auch weiterhin angewendet werden kann.

Wie in dieser Arbeit diskutiert wurde, ist die Neutropenie der wichtigste Risikofaktor für Infektionen bei Patienten mit Krebserkrankungen. Nicht nur die Neutropenie an sich oder deren Grad spielt eine Rolle für die Entwicklung bakterieller oder Pilzinfektionen, sondern auch die Kinetik bzw. Dynamik des Abfalls der neutrophilen Granulozyten

nach Chemotherapie [Akova 2015]. In Kooperation mit dem Institut für Mathematische Optimierung der hiesigen Universität (Direktor: Prof. Dr. rer. nat. S. Sager) soll in dem MARTINA-Projekt (Optimale Steuerung klinisch relevanter Therapiepläne bei Patienten mit akuter myeloischer Leukämie – mit Schwerpunkt auf Neutropenie) versucht werden, in einem mathematischen Modell den Verlauf der Leukozyten bzw. der neutrophilen Granulozyten nach Chemotherapie zu simulieren und schlussendlich durch Einbeziehung patientenspezifischer sowie pharmakokinetischer und -dynamischer Parameter eine Optimierung (sog. Fiting) des Leukozytenverlaufs herbeizuführen. So soll versucht werden, die Dynamik einer sich nach Chemotherapie entwickelnden Neutropenie positiv zu beeinflussen. Erste Daten aus Vorarbeiten konnten bereits präsentiert werden, wobei gezeigt werden konnte, dass eine kondensierte Cytarabin-Abfolge in der Konsolodierungstherapie bei AML-Patienten zu einer schnelleren Erholung der Leukozyten führt [Rinke *et al.* 2014; Jost *et al.* 2016]. Die Modellentwicklung wird fortgesetzt, wobei auch Daten von AML-Patienten untersucht werden, die G-CSF zur Stimulation der Granulopoese erhielten bzw. nicht erhielten.

Für die Diagnose von Fieber in Neutropenie bei Patienten nach Chemotherapie bedarf es im Zeitalter der hoch-technisierten Medizin eigentlich nur der Erfahrung bzw. den guten und richtigen diagnostischen Blick des klinisch tätigen Arztes, da sich eine Neutropenie erfahrungsgemäß nach 10-14 Tagen nach Beginn einer Chemotherapie entwickelt. Laborchemische Parameter, wie z. B. CRP und PCT, sind für diese Diagnose prinzipiell nicht erforderlich, allenfalls das (Differential-) Blutbild. Wie hier ebenso gezeigt werden konnte, ist die diagnostische Wertigkeit von PCT bei Patienten mit NSCLC bei der Frage des Vorliegens von Infektionen eingeschränkt. Offenbar geht die PCT-Erhöhung nicht in jeder klinischen Situation in diesem Patientengut gleichzeitig mit einer Infektion einher. Infektionen bei Patienten mit NSCLC müssen demnach u. a. auch hier klinisch, wie eben Fieber in Neutropenie, ausgeschlossen bzw. bewiesen werden.

Besonders wichtig im Zusammenhang mit der antimikrobiellen Therapie von Infektionen, insbesondere mit der empirischen Therapie bei Fieber in Neutropenie, ist die Kenntnis des (zu erwartenden) Erregerspektrums. Es konnte in der Arbeit gezeigt werden, dass das mikrobielle Spektrum von der Grunderkrankung abhängt, sich das Erregerspektrum also zwischen Patienten aus der Hämatologie von nicht-hämatologischen Patienten grundlegend unterscheidet. Die hier zusammengetragenen Informationen sind wichtig für den Arzt in der Primärbehandlung unserer Patienten und dienen damit der adäquateren antibiotischen Therapie – z. B. in der ambulanten Versorgung oder in der Notaufnahme eines Krankenhauses –, da inadäquate anti-

mikrobielle Therapien mit einer höheren Mortalitätsrate einhergehen. Das Erregerspektrum wandelt sich allerdings im Laufe der Zeit und es ist mit einer weiteren Zunahme multiresistenter Erreger zu rechnen. 3/4MRGN sind in der Hämatologie häufiger als MRSA, VRE oder ESBL-Bildner nachweisbar und demnach bedeutender, als dies zu erwarten gewesen wäre.

Die Problematik mit 3/4MRGN spielt in der Hämatologie eine zunehmende, bedrohliche Rolle. In Kooperation mit dem Institut für Medizinische Mikrobiologie und Krankenhaushygiene (Direktor: Prof. Dr. med. D. Schlüter), Universitätsklinikum Magdeburg, und der Arbeitsgruppe „Mikrobielle Immunregulation“ (Dr. T. Strowig) am Helmholtz-Zentrum für Infektionsforschung, Braunschweig, soll im Rahmen der internationalen Graduiertenschule „Analyse, Bildgebung und Modellierung neuronaler und entzündungsbedingter Prozesse“ (ABINEP) der Einfluss des intestinalen Mikrobioms auf Infektionen, Krankheitsverlauf und Therapieerfolg bei mit Zytostatika-behandelten hämatologisch-onkologischen Patienten untersucht werden. Eine wichtige Fragestellung dabei ist, wie 3/4MRGN „akquiriert“ werden.

Die ermittelten Daten zum Erregerspektrum sowie zu resistenten Erregern basierten auf Ergebnissen aus der kulturell-mikrobiologischen Diagnostik. Es wurde in der Arbeit gezeigt, dass Blutkulturen in der mikrobiologischen Diagnostik in der Hämatologie trotz moderner molekularbiologischer Methoden einen hohen Stellenwert haben und immer noch unabdingbar sind. Entgegen anderslautender Meinungen sollte auf anaerobe Blutkulturen nicht verzichtet werden. Hierzu werden im Rahmen des SIMPLY-Projektes (Prospektive Untersuchung zur Relevanz anaerober Blutkulturflaschen bei Katheter-assoziierten Bakteriämien hämatologischer Patienten) Daten generiert werden. Für die Diagnose einer Blutstrominfektion ist eine adäquat hohe Blutkulturrate erforderlich. Die Praxis in unserer Klinik geht mit den bekannten Empfehlungen einher. Bei initial negativer Blutkultur bei Patienten mit Fieber (in Neutropenie) sind im Verlauf erneute Abnahmen von Blutkulturen durchaus sinnvoll. Mehr als 3 Blutkulturen bringen in der Regel jedoch keinen weiteren diagnostischen Zugewinn bei Blutstrominfektionen. Für den Kliniker wird sehr bedeutsam und erfreulicherweise zu wissen sein, dass eine verzögerte Inkubation von Blutkulturen, wie dies in der klinischen Routine häufig der Fall ist, keinen negativen Einfluss auf das Ergebnis des Positivwerdens der Blutkulturen hat.

Aufgrund der oft vorherrschenden Neutropenie bei unseren Patienten sind die allgemein bekannten Leitlinien bzw. die Einschätzung des Schweregrades einer CDI nicht übertragbar. Die Kenntnis des Schweregrades einer CDI ist jedoch für den Kliniker

wichtig, da dies Auswirkungen auf die Therapie der CDI hat. Mit einer neu entwickelten AGIHO-Leitlinie konnte diesbezüglich nun Abhilfe geschaffen werden.

Es konnte dargestellt werden, dass in der homogenen Kohorte von Patienten mit AML Diarrhoen häufig und oft auf *C. difficile* zurückzuführen sind. Zudem konnte gezeigt werden, dass die (prolongierte) Neutropenie einen Risikofaktor für die Entwicklung einer CDI darstellt. Deshalb sollten Stuhlproben bei AML-Patienten, die Diarrhoen entwickeln, gleich zu Beginn auf *C. difficile* hin untersucht werden, um eine spezifische Therapie bei Vorliegen einer, bzw. bei Hochrisiko-Patienten bereits bei Verdacht auf eine CDI, zu beginnen. Die epidemiologischen Daten zu CDI basierten auf dem einfachen Toxinnachweis. In einer Promotionsarbeit unter Betreuung des Kandidaten wurden nun neue Daten generiert, nachdem die Diagnostik *in domo* auf das in den Leitlinien empfohlene neue Zwei-Stufen-Konzept umgestellt wurde. Die CDI-Rate hat sich nach Umstellung der Diagnostikmethode bei Patienten mit akuten Leukämien seitdem verringert.

Bezüglich NVI konnte gezeigt werden, dass NVI bei hämatologischen Patienten selten sind und dass die Inzidenz von NVI bei Krebspatienten verglichen mit anderen Patientenkohorten eine geringere saisonale Variabilität aufweist. NVI sollten demnach differentialdiagnostisch bei Auftreten von Diarrhoen bei Krebspatienten auch in den Sommermonaten mit bedacht und entsprechende Untersuchungen von Stuhlproben durchgeführt werden. Dies ist insofern von besonderer Bedeutung, als dass NVI besondere und strenge Hygienemaßnahmen erforderlich machen.

Zusammenfassend kann anhand der SECRECY-Analyse festgestellt werden, dass die Inzidenzrate der (*definitiven*) CRBSI aus unserem Zentrum mit denen aus der Literatur vergleichbar ist und dass der modifizierte IPS dazu beitragen könnte, das Risiko für CRBSI bei Patienten mit hämatologischen Krebserkrankungen vorherzusagen bzw. besser auszuschließen und damit die Entscheidung über den Erhalt oder die Entfernung eines ZVK erleichtern könnte. Adipositas ist in unserem Patientengut häufig, zeigt aber kein erhöhtes Risiko für CRBSI, was so nicht unbedingt zu erwarten gewesen wäre. Es wurden zum ersten Mal epidemiologische Daten zu CRBSI anhand der neuen AGIHO-Diagnosekriterien präsentiert.

Mit dem nun multizentrischen SECRECY-Register sollen Faktoren direkt bei ZVK-Anlage identifiziert werden, die es erlauben, Patienten mit Hochrisiko-ZVK hinsichtlich ZVK-Infektionen zu identifizieren. So könnten diese ZVK bei Fieber unklarer Ursache eher entfernt werden. Daten einer Trainingskohorte wurden bereits präsentiert [Schalk *et al.* 2017b]. Dies wird an einer weiteren Kohorte multizentrisch validiert. In einer

kontrollierten klinischen Studie könnte prospektiv und randomisiert untersucht werden, ob ZVK bei Patienten mit Hochrisikokonstellation zu einem bestimmten Zeitpunkt „prophylaktisch“ entfernt werden sollten, um ZVK-Infektionen zu verhindern.

Infektionen durch Influenza-Viren spielen bei Patienten mit Krebserkrankungen eine bedeutende Rolle, insbesondere weil sie oft mit einer Pneumonie einhergehen. Da die Influenza bei immunsupprimierten Patienten oft weniger apparent verläuft, wird sie möglicherweise auch zu spät diagnostiziert – was ein unabhängiger Risikofaktor für Mortalität ist. Neben diesem Fakt gilt es auch an bakterielle und fungoide Superinfektionen zu denken und diese dann konsequent mit zu behandeln, da diese Patienten ein deutlich erhöhtes Mortalitätsrisiko haben.

Infektionen bei Patienten aus der Hämatologie und Medizinischen Onkologie bleiben für den klinisch tätigen Arzt oft eine Herausforderung. Kenntnisse in Epidemiologie und Diagnostik dieser Komplikationen der Krebstherapie tragen dazu bei, die Prognose bei diesen Patienten zu verbessern.

4 Literatur

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5 Anmerkungen

Die im Abschnitt 2.1.1 dargestellte und diskutierte prospektive klinische Studie „Vergleich der Blutbild-Parameter einer kapillären Blutentnahme mit denen einer venösen Blutentnahme“ wurde bei der Ethik-Kommission der Otto-von-Guericke-Universität an der Medizinischen Fakultät und am Universitätsklinikum Magdeburg A.ö.R. unter der Nummer 45/06 zur Begutachtung eingereicht. Die zustimmende Bewertung liegt vor. Die Studie wurde im Studienregister *ClinicalTrials.gov* unter der Nummer NCT00390988 registriert und die Ergebnisse im Verlauf veröffentlicht [Schalk *et al.* 2007; Schalk *et al.* 2008; Schalk *et al.* 2009].

Die im Abschnitt 2.2.3 dargestellte und diskutierte experimentelle Studie „Untersuchung der Effekte einer verzögerten Inkubation von Blutkulturen auf die Kultur-Positivität, ENTRY“ wurde bei der Ethik-Kommission der Otto-von-Guericke-Universität an der Medizinischen Fakultät und am Universitätsklinikum Magdeburg A.ö.R. unter der Nummer 115/14 zur Begutachtung eingereicht. Die zustimmende Bewertung liegt vor. Die Ergebnisse wurden im Verlauf veröffentlicht [Schalk *et al.* 2015a].

Die im Abschnitt 2.4.2 dargestellte und diskutierte prospektive klinische Studie „Studie zur Beurteilung von zentralvenösen Katheter-Infektionen in der Hämatologie und Onkologie, SECRECY“ wurde bei der Ethik-Kommission der Otto-von-Guericke-Universität an der Medizinischen Fakultät und am Universitätsklinikum Magdeburg A.ö.R. unter der Nummer 84/14 zur Begutachtung eingereicht. Die zustimmende Bewertung liegt vor. Die Studie wurde im *Deutschen Register Klinischer Studien* unter der Nummer DRKS00006551 registriert und die Ergebnisse im Verlauf veröffentlicht [Schalk *et al.* 2015b; Schalk *et al.* 2015c; Schalk *et al.* 2016; Schalk *et al.* 2017].

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Olaf Penack (Berlin), Priv.-Doz. Dr. med. Martin Schmidt-Hieber (Berlin) und Frau Prof. Dr. med. Marie von Lilienfeld-Toal (Jena).

Für die gemeinsamen wissenschaftlichen Projekte außerhalb dieser Habilitation danke ich Frau Dr. med. Vanja Zeremski aus unserer Klinik, meinen beiden Doktoranden, Frau Ana-Maria Waldleben und Daniel Geßner aus unerer Klinik, Frau Dipl.-Biomath. Kristine Rinke (Magdeburg), Prof. Dr. rer. nat. Sebastian Sager und seiner Gruppe (Magdeburg) und Dr. rer. nat. Frank Edlich (Freiburg/i.Br.).

Frau Christine Friedrichs und Frau Marlies Kühn aus unserer Klinik dankte ich sehr für ihre Archivarbeit, ohne die viele Projekte nicht möglich gewesen wären.

7 Publikationen der Habilitationsschrift

I. Schmidt-Hieber M, Silling G, **Schalk E**, Heinz W, Panse J, Penack O, Christopeit M, Buchheidt D, Meyding-Lamadé U, Hähnel S, Wolf HH, Ruhnke M, Schwartz S, Maschmeyer G. CNS infections in patients with hematological disorders (including allogeneic stem cell transplantation) – Guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Medical Oncology (DGHO). **Ann Oncol 2016**;27(7):1207-1225

II. **Schalk E**, Heim MU, Koenigsmann M, Jentsch-Ullrich K. Use of capillary blood count parameters in adults. **Vox Sang 2007**;93(4):348-353

III. **Schalk E**, Scheinpflug K, Mohren M. Correlation of capillary and venous absolute neutronphil counts in adult hematological patients and normal controls. **Am J Hematol 2008**;83(7):605

IV. **Schalk E**, Scheinpflug K, Mohren M. Capillary blood count analyses in the clinical practice: a safe, reliable and valid method. **J Lab Med 2009**;33(5):303-309

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*Geteilte Erstautorenschaft

VI. Penack O, Becker C, Buchheidt B, Christopeit M, Kiehl M, von Lilienfeld-Toal M, Hentrich M, Reinwald M, Salwender H, **Schalk E**, Schmidt-Hieber M, Weber T, Ostermann H. Management of sepsis in neutropenic patients: 2014 updated guidelines from the Infectious Diseases Working Party of the German Society of Hematology and Medical Oncology (AGIHO). **Ann Hematol 2014**;93(7):1083-1095

VII. **Schalk E**, Tammer I, Heidel FH. Germ and hematology: underlying disease influences diversity of germ spectra and antibiotic therapy. **Infect Control Hosp Epidemiol 2014**;35(2):208-210

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IX. Vehreschild MJGT, Vehreschild JJ, Hübel K, Hentrich M, Schmidt-Hieber M, Christopeit M, Maschmeyer G, **Schalk E**, Cornely OA, Neumann S. Diagnosis and management of gastrointestinal complications in adult cancer patients: evidence-based guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO). **Ann Oncol 2013**; 24(5):1189-1202

X. **Schalk E**, Bohr URM, König B, Scheinpflug K, Mohren M. *Clostridium difficile*-associated diarrhoea, a frequent complication in patients with acute myeloid leukaemia. **Ann Hematol 2010**;89(1):9-14

XI. **Schalk E**, Geginat G, Schulz C, Schlüter D, Fischer T. The incidence of norovirus infections in cancer patients shows less seasonal variability compared to patients with other diseases. **Ann Hemtol 2014**;93(5):889-890

XII. Hentrich M, **Schalk E**, Schmidt-Hieber M, Chaberny I, Mousset S, Buchheidt B, Ruhnke M, Penack O, Salwender H, Wolf H, Christopeit M, Neumann, Maschmeyer M, Karthaus M. Central venous catheter-related infections in hematology and oncology: 2012 updated guidelines on diagnosis, management and prevention by the Infectious Diseases Working Party of the German Society of Hematology and Medical Oncology. **Ann Oncol 2014**;25(5):936-947

XIII. **Schalk E**, Hanus L, Färber J, Fischer T, Heidel FH. Prediction of central venous catheter-related bloodstream infections (CRBSI) in patients with haematologic malignancies using a modified Infection Probability Score (mIPS). **Ann Hematol 2015**;94(9):1451-1456

XIV. **Schalk E**, Biehl LM, Färber J, Schlüter D, Vehreschild MJGT, Fischer T. Determination of a cut-off time-point for prophylactic exchange of central venous catheters for prevention of central venous catheters-related bloodstream infections in patients with hematological malignancies. **Infect Control Hosp Epidemiol 2017**;38(7):888-889

XV. **Schalk E**, Färber J, Fischer T, Heidel FH. Central venous catheter-related bloodstream infections in obese hematologic patients. **Infect Control Hosp Epidemiol 2015**;36(8):995-996

XVI. Hermann B, Lehners N, Brodhun M, Boden K, Hochhaus A, Kochanek M, Meckel K, Mayer K, Rachow T, Rieger C, **Schalk E**, Weber T, Schmeier-Jürchott A, Schlattmann P, Teschner D, von Lilienfeld-Toal M. Influenza virus infections in patients with malignancies – characteristics and outcome of the season 2014/15. A survey conducted by the Infectious Diseases Working Party (AGIHO) of the German Society of Haematology and Medical Oncology (DGHO). **Eur J Clin Microbiol Infect Dis 2017**;36(3):565-573

XVII. von Lilienfeld-Toal M, Berger A, Christopeit M, Hentrich M, Heussel CP, Kalkreuth J, Klein M, Kochanek M, Penack O, Hauf E, Rieger C, Silling G, Vehreschild M, Weber T, Wolf HH, Lehners N*, **Schalk E***, Mayer K*. Community acquired respiratory virus (CRV) infections in cancer patients – guidelines on diagnosis and management by the Infectious Diseases Working Party (AGIHO) of the German Society for Haematology and Medical Oncology (DGHO). **Eur J Cancer 2016**;67:200-212
*Geteilte Letztautorenschaft

8 Appendix: Publikationen I – XVII

Publikation I

Schmidt-Hieber M, Silling G, **Schalk E**, Heinz W, Panse J, Penack O, Christopeit M, Buchheidt D, Meyding-Lamadé U, Hähnel S, Wolf HH, Ruhnke M, Schwartz S, Maschmeyer G. CNS infections in patients with hematological disorders (including allogeneic stem cell transplantation) – Guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Medical Oncology (DGHO). **Ann Oncol 2016**;27(7):1207-1225

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CNS infections in patients with hematological disorders (including allogeneic stem-cell transplantation)—Guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Medical Oncology (DGHO)

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Infections of the central nervous system (CNS) are infrequently diagnosed in immunocompetent patients, but they do occur in a significant proportion of patients with hematological disorders. In particular, patients undergoing allogeneic hematopoietic stem-cell transplantation carry a high risk for CNS infections of up to 15%. Fungi and *Toxoplasma gondii* are the predominant causative agents. The diagnosis of CNS infections is based on neuroimaging, cerebrospinal fluid examination and biopsy of suspicious lesions in selected patients. However, identification of CNS infections in immunocompromised patients could represent a major challenge since metabolic disturbances, side-effects of antineoplastic or immunosuppressive drugs and CNS involvement of the underlying hematological disorder may mimic symptoms of a CNS infection. The prognosis of CNS infections is generally poor in these patients, albeit the introduction of novel substances (e.g. voriconazole) has improved the outcome in distinct patient subgroups. This guideline has been developed by the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Medical Oncology (DGHO) with the contribution of a panel of 14 experts certified in internal medicine, hematology/oncology, infectious diseases, intensive care, neurology and neuroradiology. Grades of recommendation and levels of evidence were categorized by using novel criteria, as recently published by the European Society of Clinical Microbiology and Infectious Diseases.

Key words: guideline, central nervous system infection, immunocompromised patient, diagnosis, treatment

introduction

Infections of the central nervous system (CNS) occur in a relevant proportion of immunocompromised patients and contribute significantly to morbidity and mortality. Only limited data are available on the clinical characteristics, optimal diagnostic procedures and treatment of CNS infections in these patients, and studies on CNS infections frequently focused on specific causative agents or distinct patient subgroups such as recipients of allogeneic hematopoietic stem-cell transplantation (allo-HSCT) [1, 2].

This guideline focuses on patients with hematological malignancies including allo-HSCT recipients defined as 'patients with hematological disorders' hereafter. Patients with nonmalignant hematological disorders (e.g. aplastic anemia) or solid tumors are not specifically excluded albeit CNS infections are very rare in these patients and larger analyses focusing on CNS infections in these subgroups are lacking. In the first part of this guideline, an overview on epidemiology, causative agents, risk factors,

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Table 1. Strength of recommendation (A) and quality of evidence (B) [3]

(A)	
Grade	Strength of recommendation
Grade A	AGIHO 'strongly' supports a recommendation for use
Grade B	AGIHO 'moderately' supports a recommendation for use
Grade C	AGIHO 'marginally' supports a recommendation for use
Grade D	AGIHO 'supports' a recommendation 'against' use
(B)	
Level	Quality of evidence
I	Evidence from at least one properly designed randomized, controlled trial
II*	Evidence from at least one well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time series; or from dramatic results of uncontrolled experiments
	*: Added index
	r: Meta-analysis or systematic review of randomized, controlled trials
	t: Transferred evidence, that is, results from different patients' cohorts, or similar immune-status situation
	h: Comparator group is a historical control
	u: Uncontrolled trial
	a: Published abstract (presented at an International Symposium or meeting)
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies

Quality of evidence is used for treatment recommendations only (and not for diagnostic procedures).

pathogenesis, prophylaxis in addition to general diagnostic strategies and management of CNS infections is given. The second part focuses on distinct infectious agents. For recommendations on diagnosis and treatment of bacterial CNS infections (including tuberculous meningitis), see supplementary Material, available at *Annals of Oncology* online. The strengths of recommendation and levels of evidence were categorized according to the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) criteria (Table 1) [3].

consensus process

See supplementary Material, available at *Annals of Oncology* online.

epidemiology and causative agents

Patients undergoing allo-HSCT are among those with the highest risk for CNS infections with an overall incidence of up to 15% [1, 4, 5]. *Aspergillus* and *Toxoplasma* spp. are frequently prevailing in these patients [4, 6]. Patients after an alemtuzumab-based conditioning before allo-HSCT carry a considerable risk for viral CNS infections [2, 7]. Mucormycosis is diagnosed in ∼0.1% of all patients with hematological disorders, but an increased incidence (1.0%–1.9%) has been reported among patients with acute myeloid leukemia [8]. The lungs are frequently infected in mucormycosis, but the CNS might be involved in 10%–20% of patients [9, 10]. Progressive multifocal leukencephalopathy (PML) is a rare (<1%), but frequently fatal CNS disease caused by the JC virus. It mainly affects allo-HSCT recipients, but also patients after rituximab-based treatment strategies or with multiple lines of immunosuppression [2, 11, 12]. Bacterial CNS infections are rarely diagnosed in patients with hematological disorders, and they occur more frequently in patients with intraventricular devices or after neurosurgical interventions [1, 13–15].

pathogenesis

See supplementary Material, available at *Annals of Oncology* online.

prophylaxis

Prophylactic strategies should follow recommendations for immunocompromised patients as published elsewhere [16, 17]. Patients with hematological disorders requiring intracerebral devices such as an external ventricular drainage could benefit from antimicrobial-impregnated catheters since they might be associated with a lower infection rate in comparison to standard catheters [15].

general strategies to diagnose and to treat CNS infections in patients with hematological disorders

Some principal aspects regarding the management of CNS infections in patients with hematological disorders should be considered:

(i) The management of CNS infections in patients with hematological disorders requires a high level of awareness, as neurological symptoms could be nonspecific and caused by noninfectious conditions related to the underlying disease and/or side-effects of antineoplastic or immunosuppressive treatment [1, 5, 14].

(ii) While clinical presentations of CNS infections in immunocompetent hosts are broadly categorized into meningitis, meningoencephalitis, cerebritis/abscess formation and infection of intracerebral devices, diminished inflammatory responses in immunocompromised patients can lead to only subtle symptoms. Mass lesions can be blurred by rather nonspecific cerebral dysfunctions such as confusion or altered consciousness [1, 14].

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(iii) Defined patient groups predispose for infections with certain pathogens based on their pattern of immunosuppression (defects in cell-mediated immunity versus defective humoral immunity) [18, 19]. Bacterial, fungal and viral CNS infections typically occur in neutropenic patients. Defects in T-cell immunity or in function of macrophages predispose for cerebral toxoplasmosis and cryptococcal meningitis [2, 18, 20].

(iv) Variations in the frequency of causative organisms (e.g. *Toxoplasma* spp. *Histoplasma capsulatum*, *Mycobacterium tuberculosis*) due to regional endemic differences should be taken into account [21–23].

diagnosis

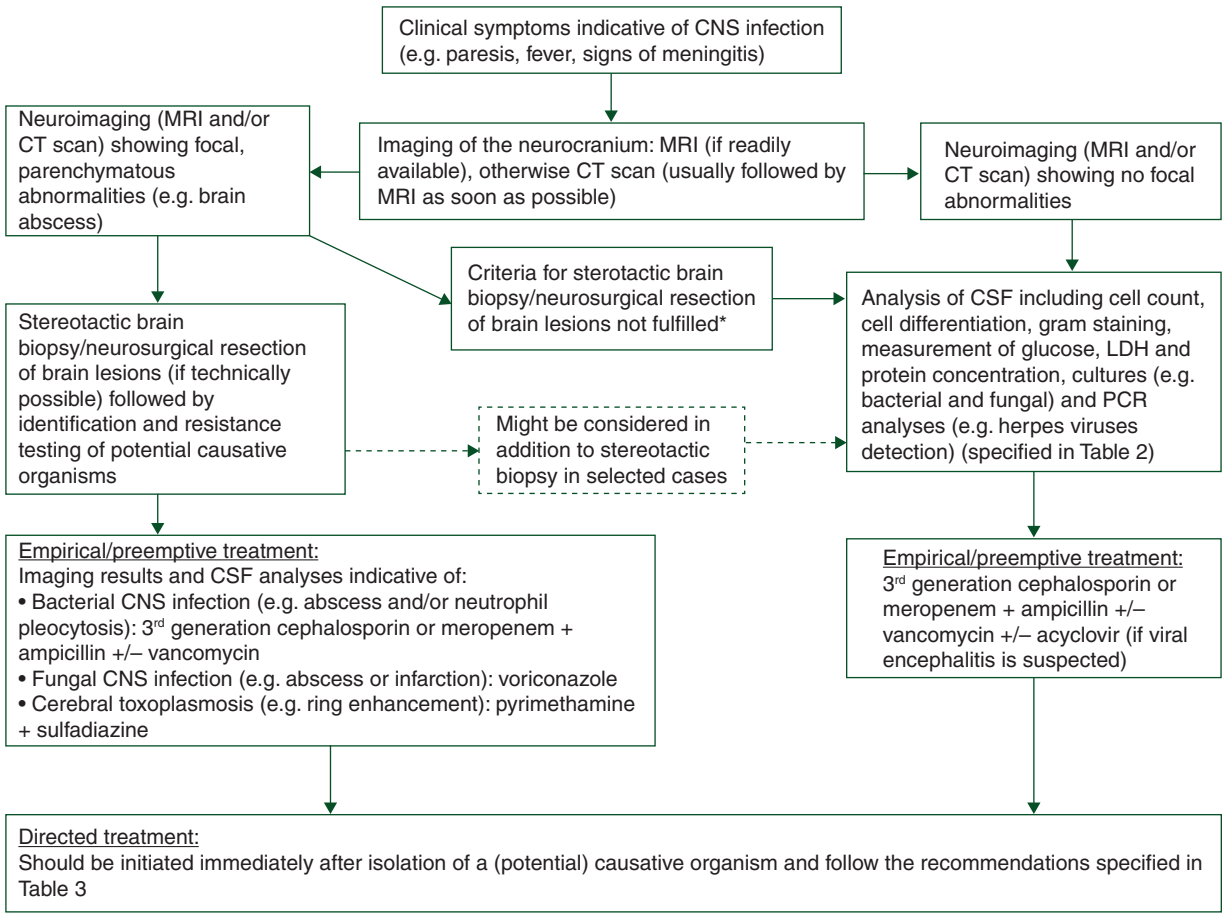
Any suspicion of CNS infection should immediately trigger adequate diagnostic procedures including neuroimaging, cerebrospinal fluid (CSF) examination and, in selected cases, biopsy of focal lesions (Figure 1). CSF analyses including various methods such as staining and microscopy, culturing, serological techniques and PCR assays are crucial to diagnose meningoencephalitis which is typically caused by viruses, *Candida* spp., bacteria or more rarely *Cryptococcus* spp. (Figure 1, Table 2). For these CNS infections, brain biopsy is required only in selected cases. Focal lesions, typically caused by *Toxoplasma* or *Aspergillus* spp. are commonly diagnosed by histopathology of suspicious lesions. Histopathological work-up should be done using adequate staining methods such as Calcofluor white. Routine parameters in the CSF are frequently nonspecifically altered in these patients.

Neuroimaging should commonly be based on magnetic resonance imaging (MRI) since it is more sensitive than computed tomography (CT) scan for diagnosis of the majority of CNS infections [102–105].

Further diagnostic methods such as positron emission tomography might help in selected patients to differentiate infectious from noninfectious CNS lesions [106].

antimicrobial treatment

Given the dismal outcome of delayed treatment in patients with hematological disorders and CNS infection, antimicrobial treatment should be initiated promptly once collection of CSF and blood cultures has been completed (Figure 1) [107–109]. After isolation and *in vitro* susceptibility testing of a (potentially) causative pathogen, antimicrobial treatment should be modified accordingly. Recommendations for empiric, pre-emptive and targeted treatment are specified in Figure 1, Table 3 and supplementary Table S1, available at *Annals of Oncology* online.



*The decision on brain biopsy/neurosurgical resection should always be made on the basis of the technical feasibility, the suspicious causative agent, and other factors (such as presence of thrombocytopenia). For example, brain biopsy might not be required to establish the diagnosis of PML in patients with typical neuroimaging findings together with a positive CSF JC virus PCR.

Figure 1. Diagnostic procedures and management in patients with hematological disorder and CNS infection.

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Table 2. Recommendations to diagnose CNS infections in patients with hematological disorders

Intention	Intervention	SoR	Comments	References
Toxoplasma spp.				
To diagnose cerebral toxoplasmosis	Demonstration of tachyzoites and/or cysts after Wright-Giemsa and/or immuno-peroxidase staining (CSF or biopsy material)	A	Can be combined with isolation of the parasite, e.g. after mouse inoculation or inoculation in tissue cell cultures	[24]
	PCR (CSF)	B	Sensitivity 50%–100%, specificity 90%–100%. Should be performed within the first week after initiation of antitoxoplasmic treatment	[25–28]
	IgG-ELISA/LAT (CSF)	C	IgG-ELISA is more sensitive than LAT (92% versus 48%)	[29]
	IgM-ELISA (CSF)	D	Negligible value	[29]
	LAMP assay (CSF)	D	Few data	[25]
Fungi				
To detect and specify a fungus obtained from CNS biopsy	Paraffin sections of CNS biopsies (e.g. using H&E, PAS, or Grocott/silver stains)	A	Might not always be possible (e.g. in patients with thrombocytopenia). Thus, biopsy of lesions from anatomic sites other than CNS might be considered sufficient to establish the diagnosis	[30, 31]
To diagnose CNS aspergillosis	Detection of galactomannan (CSF)	B	No validated cutoff (probably lower than for serum samples), reduced sensitivity under antifungal treatment	[32–36]
	PCR (CSF)	B	Sensitivity and specificity 90%–100% (in-house assays)	[33, 37–41]
	Fungal cultures (CSF)	B	Positive in ~30% of patients with *Aspergillus* meningitis	[32, 36]
	Detection of (1→3)-β-D-glucan (CSF)	C	Few data	[42, 43]
To diagnose *Candida* CNS infection	Microscopy/culture (CSF)	A	Sensitivity of microscopy ~40%, of culture 40%–80%	[44, 45]
	CNS biopsy (culture/histopathology)	B	If biopsy can be achieved (e.g. using Grocott/silver stains)	[44, 45]
	Detection of *Candida* mannan antigen (CSF)	C	Few data	[46–48]
	Detection of (1→3)-β-D-Glucan (CSF)	C		[43, 49]
	PCR (CSF)	C		[38, 50–52]
To diagnose mucormycosis	CNS/extracerebral tissue biopsy (culture/histopathology)	A	Useful stains: PAS, Grocott/silver stains, Calcofluor white	[53]
	PCR (tissue)	B	Few data	[54–56]
	PCR (blood)	C		[57]
	CSF-based diagnostics	D	No valid data	
To diagnose cryptococcal meningitis	Culture (CSF)	A	Sensitivity 60%–100%, specificity near 100%	[58–61]
	CSF microscopy (e.g. after India Ink staining)	A	Sensitivity 70%–95%, specificity near 100%; often operator-dependent	[58, 59, 61, 62]
	Detection of capsular antigen, e.g. by EIA, LAT or LFA (CSF)	A	Sensitivity and specificity 90%–100%	[58, 60, 61, 63]
	(Nested) PCR (CSF)	B	Sensitivity and specificity near 100%	[58–61]
	Biopsy (culture/histopathology), e.g. after Grocott/silver or Alcian blue staining	C	Required only in selected cases	[60]
Viruses				
To diagnose HSV encephalitis	PCR (CSF)	A	Sensitivity and specificity 95%–100%	[64, 65]
	Detection of HSV antigens and antibodies (CSF)	C	Sensitivity and specificity of HSV antigen detection ~90%, frequently nonspecific antibodies	[66, 67]
	Culture (CSF)	D	Low sensitivity of culture might be due to inhibiting HSV IgG antibodies	[66, 68, 69]
To diagnose CMV CNS disease	PCR (CSF)	A	Sensitivity nearly 100%	[70–72]
	Culture (CSF)	C	Might only be used as an adjunctive test (sensitivity ~20%)	[69, 72]
To diagnose EBV meningoencephalitis	PCR (CSF)	A	Might be false-negative in allo-HSCT recipients	[2, 73–76]

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To diagnose HHV-6 meningoencephalitis	PCR (CSF)	A	Might be positive in allo-HSCT recipients without associated symptoms	[77–79]
To diagnose VZV CNS disease	PCR (CSF)	A		[80–82]
	Detection of VZV IgG antibodies (CSF)	B	Might be more sensitive than CSF VZV PCR in the case of cerebral VZV vasculopathy	[83–85]
To diagnose JC virus-related PML	Biopsy of CNS lesions	A	Required for definitive diagnosis, demonstration of the typical triad including demyelination, bizarre astrocytes and enlarged oligodendroglial nuclei	[86, 87]
	PCR (CSF)	A	Sensitivity 75%–100%, repetitive CSF analyses might be useful, might also be false-positive (e.g. in healthy individuals with JC virus viremia)	[86, 88–90]
Bacteria				
To identify pathogen and perform resistance testing	Culture (CSF)	A	CSF culture yield might significantly be reduced in patients with delayed lumbar puncture (>4 h) after initiation of antibiotic treatment	[91–93]
	Culture (blood)	A	Positive in 50%–80% of patients, after initiation of antibiotic treatment in ~20%	[92, 94]
To identify bacteria in culture-negative CSF specimens	Gram stain (CSF)	A	Sensitivity 30%–93%, specificity 97% (frequently still positive after initiation of antibiotic treatment)	[91, 94, 95]
To document bacterial meningoencephalitis versus meningoencephalitis of other origin	Counting and differentiation of CSF cells	A	Might be of inferior value in neutropenia or after initiation of antibiotic treatment	[14, 92, 96, 97]
	Determination of CSF LDH concentration	B		[98]
	Determination of CSF protein and glucose concentration	C		[14, 92, 96, 97]
To identify causative bacterial agent in meningoencephalitis	CSF PCR	B		[99–101]

SoR, strength of recommendation; ELISA, enzyme-linked immunosorbent assay; LAT, latex agglutination test; LDH, lactate dehydrogenase; LAMP, loop-mediated isothermal amplification; H&E, hematoxylin and eosin; PAS, periodic acid-Schiff; EIA, enzyme immunoassay; LFA, lateral flow immunochromatographic assay.

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Table 3. Recommendations to treat CNS infections in patients with hematological disorders[a]

Causative agent	Intention	Intervention	SoR/QoE	Comments	References
Toxoplasma spp.					
Toxoplasma spp.	Primary anti-infective treatment and prevention of CNS relapse - to cure -	Pyrimethamine (orally, 100–200 mg load, then 50 mg/day) + sulfadiazine (orally, 1 g q6h)	AII_t	Anti-infective agents should be given for ~6 weeks in indicated dosages, then as maintenance therapy half of the original dosage for at least 3 months	[110]
		Pyrimethamine (orally, 100–200 mg load, then 50 mg/day) + clindamycin (orally or i.v., 600 mg q6h)	BII_t	Pyrimethamine should be combined with folinic acid	[111–113]
		Trimethoprim (10 mg/kg/day)—sulfamethoxazole (orally or i.v.)	BII_t		[114]
		Atovaquone (orally, e.g. 750 mg q6h)	$BII_{t,u}$	Might be used for maintenance in patients intolerant to conventional antitoxoplasmic agents, could be combined as primary treatment with pyrimethamine or sulfadiazine	[115, 116]
Fungi					
Aspergillus spp.	Primary anti-infective treatment[b] - to cure -	Voriconazole (i.v., 6 mg/kg q12h for the first 24 h, then 4 mg/kg q12h)	AII_u		[117, 118]
	-To obtain material for diagnosis	L-AmB (i.v., ≥5 mg/kg/day, optimal dose unclear) or ABLC[c] (i.v., 5 mg/kg/day)	BIII	Reserved for rare cases (e.g. severe intolerance to voriconazole, resistant isolates), might in particular be useful if mucormycosis cannot be excluded	[119–126]
	-To prevent serious neurological sequelae, decrease the burden of infected tissue and improve outcome	Itraconazole	DIII	Higher doses (800 mg/day) might be beneficial, low CNS penetration	[127–129]
		Caspofungin, micafungin	DIII	Few clinical data	[130, 131]
		Posaconazole	DIII		[132, 133]
		D-AmB	DII_u	Unfavorable toxicity profile, low efficacy	[134, 135]
		Stereotactic or open craniotomy for biopsy, abscess drainage or excision of lesions	BII_u	Resection might be effective in particular in patients with a focal lesion, a combined neuro- and rhinosurgical approach is recommended in selected cases	[117–119, 136–139]
Candida spp.	Primary anti-infective treatment[b] - to cure -	L-AmB (i.v., ≥5 mg/kg/day, optimal dose unclear) or ABLC[c] (i.v., 5 mg/kg/day) ± 5-FC (i.v., 25 mg/kg q6h)[d]	BIII	Mainly preclinical data, case reports or small patient series (and data from extracerebral systemic *Candida* infection)	[140–144]
		Voriconazole (i.v., 6 mg/kg q12h for the first 24 h, then 4 mg/kg q12h)	CIII		[145, 146]
		Fluconazole (i.v., loading dose 800 mg/day, then 400 mg/day)	CIII	If a susceptible *Candida* spp. has been isolated and the patient is clinically stable and not neutropenic and had no prior azole exposure	[44, 141, 147–149]
		D-AmB	DIII	Unfavorable toxicity profile	[44, 135, 147, 149, 150]
		Caspofungin, micafungin, anidulafungin	DIII	Mainly preclinical data and few case reports	[151–153]

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Mucorales	Primary treatment - to cure -	Surgery	$AII_{t,u}$	Should be considered whenever possible	[8, 9, 154, 155]
		L-AmB (i.v., ≥5 mg/kg/day, optimal dose unclear, up to 10 mg/kg/day has been used)	$AII_{t,u}$	Treatment delay may enhance mortality, response rate 80%–95%	[10, 155, 156]
		Reduction of immunosuppression	BIII	No comparative data, not always feasible	
		ABLC[c] (i.v., 5 mg/kg/day)	BIII	Around 70% response rate	[157]
		L-AmB (i.v., ≥5 mg/kg/day) + caspofungin (i.v., 50–70 mg/day)	CIII		[158–163]
		Posaconazole (preferable i.v., 300 mg q12h for the first 24 h, then 300 mg/day)	CIII	Low CNS penetration, dosages up to 3200 mg/day have been used	[156, 164]
		Posaconazole (preferable i.v., 300 mg q12h for the first 24 h, then 300 mg/day) + L-AmB (i.v., ≥5 mg/kg/day)	CIII	Might be used for extended cases or patients refractory to single-agent treatment	[156, 161, 164–166]
		Itraconazole (orally or i.v., higher dosages of up to 800 mg/day might be used)	CIII	Low CNS penetration	[9]
		D-AmB	DIII	Unfavorable toxicity profile	[9, 135]
	Salvage treatment - to cure/prolong survival -	Posaconazole (preferable i.v., 300 mg q12h for the first 24 h, then 300 mg/day)	BIII	Might be combined with caspofungin or L-AmB	[164, 167, 168]
		Isavuconazole (i.v. or orally, 200 mg q8h for the first 48 h, then 200 mg/day)	CIII		[169, 170]
Cryptococcus spp.	Primary treatment - to cure -	L-AmB (i.v., 3–4 mg/kg/day) or ABLC[c] (i.v., 5 mg/kg/day) + 5-FC (i.v., 25 mg/kg q6h)[d]	AII_t	• Induction therapy for at least 4 weeks, might be followed by consolidation with fluconazole (400 mg/d) at least 8 weeks • Consider unfavorable toxicity profile of D-AmB	[171–173]
		D-AmB (i.v., 0.7–1.0 mg/kg/day) + 5-FC (i.v., 25 mg/kg q6h)[d]	BII_t		[171–174]
		D-AmB (i.v., 0.7–1.0 mg/kg/day) + voriconazole (preferable i.v., 6 mg/kg q12h for the first 24 h, then 4 mg/kg q12h)	BII_t		[175]
		L-AmB (i.v., 3 mg/kg/day)	BII_t		[176–178]
		D-AmB (i.v., 0.7–1.0 mg/kg/day) + fluconazole (preferable i.v., 800–1200 mg/day)	CII_t		[171, 173, 175, 179]
		Voriconazole (preferable i.v., 6 mg/kg q12h for the first 24 h, then 4 mg/kg q12h)	CIII		[180]
		ABLC[c] (i.v., 5 mg/kg/day)	CIII		[181]
		Fluconazole (preferable i.v., loading dose 1200 mg/day, then 800 mg/day) + 5-FC (i.v., 25 mg/kg q6h)[d]	CII_t	Study performed in Malawi with limited economic resources	[182]
	Salvage treatment - to cure/prolong survival -	Voriconazole (preferable i.v., 6 mg/kg q12h for the first 24 h, then 4 mg/kg q12h)	CIII	Clinical efficacy rate ~40%	[183]
		Posaconazole (preferable i.v., 300 mg q12h for the first 24 h, then 300 mg/day)	CIII	Clinical efficacy rate ~50%	[132]
	Primary or salvage treatment	Caspofungin, micafungin, anidulafungin	DIII	No relevant activity	[184]
Viruses					

Continued

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Table 3. *Continued*

Causative agent	Intention	Intervention	SoR/QoE	Comments	References
HSV	Primary or salvage treatment - to cure -	Aciclovir (i.v., 10 mg/kg q8h)	AII_t	Treatment duration at least 2–3 weeks[e]	[2, 73, 185–189]
		Foscarnet (i.v., 60 mg/kg q8h or 90 mg/kg q12h)	CIII	Might be used in refractory cases	[190]
		Valaciclovir (orally, 1 g q8h)	CIII	Might be used as continuation therapy	[191–194]
CMV	Primary or salvage treatment - to cure -	Ganciclovir (i.v., 5 mg/kg q12h) or foscarnet (i.v., 60 mg/kg q8h or 90 mg/kg q12h) as single agent	AIII	Consider main side-effects (myelotoxicity versus nephrotoxicity) and the presence of CMV resistance mutations (e.g. UL97, UL54)	[188]
		Ganciclovir (i.v., 5 mg/kg q12h) + foscarnet (i.v., 60 mg/kg q8h or 90 mg/kg q12h)	BIII		[188, 195–197]
		Cidofovir (i.v., optimal dosage unclear, e.g. 5 mg/kg once weekly)	CIII		[198, 199]
		Ganciclovir (i.v., 5 mg/kg q12h) + cidofovir (i.v., e.g. 5 mg/kg once weekly)	CIII		[195, 200]
		Foscarnet (i.v., 60 mg q8h or 90 mg/kg q12h) + cidofovir (i.v., e.g. 5 mg/kg once weekly)	CIII		[195, 201]
EBV (meningoencephalitis)	Primary or salvage treatment - to cure -	Reduction of immunosuppression	AIII	Might not always be possible	[188, 202]
		Ganciclovir (i.v., 5 mg/kg q12h)	BIII	Valganciclovir (orally) has also been used	[202–207]
		Aciclovir (i.v., 10 mg/kg q8h)	CIII	Few reports with success published	[208, 209]
HHV-6	Primary or salvage treatment - to cure -	Foscarnet (i.v., 60 mg/kg q8h or 90 mg/kg q12h) or ganciclovir (i.v., 5 mg/kg q12h)	AIII	Variant A and B might respond similarly to antivirals	[7, 77, 78, 210–213]
		Foscarnet (i.v., 60 mg/kg q8h or 90 mg/kg q12h) + ganciclovir (i.v., 5 mg/kg q12h)	CIII		[78, 214]
		Cidofovir (i.v., e.g. 5 mg/kg once weekly)	CIII		[215]
VZV	Primary or salvage treatment - to cure -	Aciclovir (i.v., 10 mg/kg q8h)[f]	AIII	Inefficacy has been reported	[2, 73, 216–218]
		Aciclovir (i.v., 10 mg/kg q8h) + foscarnet (i.v., 60 mg/kg q8h or 90 mg/kg q12h)	CIII		[219]
		Ganciclovir (i.v., 5 mg/kg q12h)	CIII		[188, 220]
JC virus (PML)	Primary or salvage treatment - to cure -	Reduction of immunosuppression	AIII	Not always possible	[12]
		Cidofovir	$DII_{t,u}$		[221]
Bacteria	To reduce mortality	Empiric treatment	$AII_{t,u}$		[107, 222, 223]
	To reduce mortality and neurologic defects	Dexamethasone (e.g. 0.15 mg/kg q6h for the first 4 days)	$CII_{r,t}$	Should be started with first dose of antibiotics if it is used	[224, 225]

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To reduce mortality in first-line empirical treatment	Meropenem (2 g q8h) or ceftriaxone (2 g q12h) or cefotaxime (8–12 g/day in 4–6 daily dosages) + ampicillin (2 g q4h) ± vancomycin (30–60 mg/kg/day in 2–3 daily dosages)	AII_t	Add vancomycin if a high rate of penicillin-resistant *S. pneumoniae* strains is present	[92, 226]
To reduce mortality (Gram-negative strains)	Meropenem (2 g q8h)	BIII	Carbapenem of choice for *Enterobacteriaceae* (more potent than imipenem and ertapenem)	[227, 228]

The authors do not take any responsibility for dosages of antiinfectious agents.
[a]For detailed recommendations on treatment of different bacterial CNS infections in patients with hematological disorders, see supplementary Material, available at *Annals of Oncology* online.
[b]Antifungal drug therapy should be continued for at least 4 weeks after resolution of all signs and symptoms of the infection.
[c]Not distributed in some countries (e.g. Germany).
[d]Therapeutic drug monitoring recommended.
[e]Longer treatment periods might be advisable (e.g. determined by repeated CSF analyses).
[f]Usual pediatric dose (immunocompromised host): 10–20 mg/kg q8h.
QoE, quality of evidence; ABLC, amphotericin B lipid complex.

Due to the lack of systematic data, decisions about the duration of antimicrobial treatment should be assessed individually. Hereby, the strategy of treatment (such as antimicrobial drug therapy with or without surgery), resolution of symptoms and recovery of the individual immune-status, as defined by the presence of neutropenia, hypogammaglobulinemia and graft-versus-host disease should be taken in account. In patients with persisting complex immunodeficiencies, targeted antimicrobial treatment might be followed by maintenance treatment (e.g. for cerebral toxoplasmosis). To improve efficacy and minimize toxicity, therapeutic drug monitoring (TDM) might be useful for antimicrobial agents, such as 5-fluorocytosine (5-FC), voriconazole and posaconazole [**BII**] [229, 230]. TDM might be of particular relevance in patients with hematological disorders since impaired gastrointestinal resorption and interferences with co-medication are common in this population [230–232].

adjunctive treatment

Adjunctive treatment may include neurosurgery, platelet transfusion and administration of corticosteroids, anticonvulsants, sedatives or antipyretics (see supplementary Material, available at *Annals of Oncology* online).

CNS infections related to specific causative agents

parasitic CNS infections

Toxoplasma spp. belong to the most common causative agents in allo-HSCT recipients with CNS infections [1, 6]. However, other parasitic CNS infections such as malaria, microsporidiosis, leishmaniasis, trypanosomiasis or helminthic infections have also been described in immunocompromised hosts [233].

Toxoplasma spp. Mental abnormalities, fatigue and fever are frequent clinical symptoms in allo-HSCT recipients with cerebral toxoplasmosis [234]. Neuroimaging by MRI frequently shows typical hypo-/isointensities mainly in the basal ganglia and the frontal lobe (supplementary Figure S1, available at *Annals of Oncology* online) [105]. Higher sensitivity of MRI compared with CT scan has been demonstrated in a comparative retrospective analysis [104, 105]. However, typical nodular or ring enhancement surrounded by edema was visible by MRI in only 60% of allo-HSCT patients [235]. Besides neuroimaging, diagnosis of cerebral toxoplasmosis is based on demonstration of tachyzoites or cysts in the CSF [**A**], CSF PCR [**B**] and serological tests such as CSF enzyme-linked immunosorbent assay [**C**] [24, 25, 29].

Primary treatment of cerebral toxoplasmosis should comprise a combination of pyrimethamine and sulfadiazine [$\mathbf{AII_t}$] [110]. Pyrimethamine in combination with clindamycin [$\mathbf{BII_t}$] or single-agent trimethoprim-sulfamethoxazole [$\mathbf{BII_t}$] may alternatively be used [110, 111, 236]. Maintenance treatment should be conducted for at least 3 months [**BIII**]. Atovaquone could be administered in patients with intolerance/refractoriness to conventional antitoxoplasmic agents [$\mathbf{BII_{t,u}}$] [115, 116].

fungi

The predominant fungal pathogens causing CNS infections in patients with hematological disorders are *Aspergillus* spp., with

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A. fumigatus prevailing over other species such as *A. nidulans*, *A. terreus* and *A. flavus* [117]. *Mucorales*, *C. neoformans* and *Candida* spp. may also be detected in these patients [150].

Aspergillus *spp.* Most commonly, CNS *Aspergillosis* results in brain abscess formation, but fungal embolism can also cause cerebral infarction with or without hemorrhage. Rarely, CNS aspergillosis presents with overt meningitis or cause granuloma [32, 150, 237].

MRI may show ring-enhanced lesions, infarction and dural or vascular infiltration from adjacent regions (supplementary Figure S2, available at *Annals of Oncology* online) [238, 239]. A definitive diagnosis frequently requires biopsy of suspicious lesions and demonstration of typical septate hyphae [**A**] [30, 31]. Several studies indicate that detection of CSF galactomannan [**B**] or the PCR assay [**B**] might also be useful to diagnose CNS aspergillosis [32–35, 37]. In *Aspergillus* meningitis, CSF galactomannan might be detected in almost 90% of cases, whereas fungal cultures are positive in ∼30% [32]. CSF fungal cultures are usually negative in patients with *Aspergillus* CNS infection other than meningitis [32].

Voriconazole is the drug of choice in CNS aspergillosis, as this azole displays sufficient penetration into the CNS [$\mathbf{AII_u}$] [117, 118, 240]. Amphotericin B deoxycholate (D-AmB) should be avoided due to its poor tolerability and negligible efficacy [$\mathbf{DII_u}$], but the use of higher doses of liposomal AmB (L-AmB) resulted in successful outcomes in a limited number of patients [**BIII**] [119–123, 134]. Due to its limited CNS penetration and the limited number of successfully treated cases in the literature, the use of itraconazole does not appear justifiable in patients with CNS aspergillosis [**DIII**] [127–129]. Posaconazole has been used in a series of patients with CNS infections caused by various fungi, including three assessable patients with CNS aspergillosis [**DIII**] [132]. Caspofungin has demonstrated some activity in a mouse model exploring CNS aspergillosis, but clinical data on the use of echinocandins in CNS aspergillosis are scarce [130, 131]. Some animal model data suggest that combination therapy (e.g. voriconazole with L-AmB) might be beneficial, but meaningful clinical data are not available to recommend the use of combination therapies in CNS aspergillosis [**DIII**] [241, 242].

Intrathecal or intralesional administration of AmB has been repeatedly been applied to patients with CNS aspergillosis, but published data are limited to case reports [**DIII**] [243, 244]. In addition, intrathecal D-AmB could cause chemical arachnoiditis and it is unlikely that sufficient drug concentration is achieved in infected brain tissues [245]. Adjunctive corticosteroid therapy could reduce mass effects and brain edema, but should be avoided whenever possible due to its deleterious effects in invasive fungal infections [246]. If corticosteroid therapy is unavoidable, prednisolone should be preferred over dexamethasone, as dexamethasone is associated with low voriconazole levels (S. Schwartz, personal communication).

Neurosurgical interventions could facilitate diagnostic confirmation and contribute to a successful outcome, likely by removing infarcted areas with poor drug penetration [$\mathbf{BII_u}$] [117, 118, 136, 137].

Candida *spp.*. *Candida* CNS infections typically present as meningoencephalitis or as ventriculitis associated with foreign bodies such as shunts or, rarely, as brain abscesses. *Candida* microabscesses could be discovered at autopsy, while CT and CSF analysis not always show clearly pathological findings in this situation [44]. Neuroimaging might show hydrocephalus in *Candida* meningitis and MRI is considered to be more sensitive than CT scan [44, 147]. In the case of *Candida* meningitis, yeasts can be detected by CSF staining in ∼40% and in ∼40%–80% by fungal cultures [**A**] [44, 45]. The PCR technique as well as the detection of (1 → 3)-β-D-Glucan or the *Candida* mannan antigen might also be useful to diagnose *Candida* meningitis from CSF, but these methods are not yet considered as clinical routine procedures [**C**] [38, 46, 47, 49].

Most data on the treatment of *Candida* CNS infection are derived from pediatric patients. The use of D-AmB with 5-FC has been suggested as the optimal initial therapy for many years due to the excellent CSF penetration of 5-FC, the documented synergism of both compounds *in vitro* and *in vivo* and their documented clinical activity in *Candida* infections [44, 150]. The rationale for the use of L-AmB is mainly reasoned by studies in experimental *Candida* meningoencephalitis and clinical data from preterm newborns [140, 141, 247, 248]. Since L-AmB has an improved toxicity profile compared with D-AmB, the combination of L-AmB and 5-FC should be preferred to treat *Candida* CNS infections [**BIII**]. Fluconazole, alone or in combination with 5-FC, may be used as an oral consolidation therapy [**BIII**]. Voriconazole is a reasonable therapeutic option for *Candida* CNS infection [**CIII**] [145, 249]. Animal models suggest the potential usefulness of the echinocandins in *Candida* CNS infection, although higher doses might be required (as studied for micafungin) [151]. Clinical data are limited to case reports; thus this approach cannot be recommended for routine use yet [**DIII**] [152]. Any indwelling device such as a ventricular drain or a central venous line should be removed in invasive *Candida* infection [**BIII**] [250, 251].

mucorales. Mucormycosis is a rare opportunistic infection mainly caused by *Rhizopus* spp. and *Mucor* spp. [9, 156]. The brain might be involved in a disseminated infection or by infiltration from adjacent rhino-sinu-orbital regions [8–10, 154, 156]. Clinical symptoms such as facial pain or swelling may be nonspecific but are frequently present in patients with rhinocerebral mucormycosis [158]. The CT scan frequently reveals characteristic bone destruction of the paranasal sinuses, the hard palate or adjacent structures [252]. The diagnosis should always be confirmed by a histopathological examination and/or culturing of tissue specimens [**A**]. Histopathological examination of infected tissue typically shows the irregular fungal hyphae with wide-angle branching, in addition to tissue necrosis and fungal angioinvasion [53]. PCR assays using infected tissue specimens [**B**] or blood [**C**] have also been evaluated to diagnose mycormycosis [54, 55, 57]. However, these methods are not standardized yet.

Single-agent L-AmB is recommended to treat mucormycosis [$\mathbf{AII_{t,u}}$], but some experts suggest a primary polyene–caspofungin combination [**CIII**] [158–160]. Immediate surgical resection of necrotic tissue may be crucial in addition to antifungal treatment in invasive mucormycosis [$\mathbf{AII_{t,u}}$] [8, 9, 154, 155]. Besides reduction of immunosuppressive drugs conditions associated with the occurrence of mucormycosis such as hyperglycemia,

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lactic acidosis and iron overload should be corrected whenever possible [**BIII**]. However, a placebo-controlled trial exploring L-AmB together with the iron chelating agent deferasirox was terminated prematurely due to inefficacy, despite the crucial role of iron in the pathogenesis of mucormycosis [**DII$_t$**] [253]. Posaconazole [**BIII**] or isavuconazole [**CIII**] might be used as salvage treatment of mucormycosis [167–170]. Hyperbaric oxygen has been investigated as primary or salvage treatment of mucormycosis [254–256]. This approach is available only in some centers and there are no larger trials confirming its benefit [**CIII**].

Cryptococcus *spp.* Reports from human immunodeficiency virus (HIV)-negative patients with hematological disorders and infection with *Cryptococcus* spp. are limited [257, 258]. Neuroimaging by MRI may show dilated Virchow-Robin spaces, cyst-like structures and granuloma of the choroid plexus [259]. A definitive diagnosis of cryptococcal meningitis is made by CSF cultures [**A**] or CSF microscopy using India Ink staining [**A**] [58–60, 62]. The diagnosis might further be confirmed by detection of capsular antigen using different techniques such as enzyme immune assays, latex agglutination or the lateral flow assay [**A**] [58, 61]. Likewise, CSF (nested) PCR assays might be used to diagnose cryptococcal meningitis [**B**] [58, 61]. Biopsy of infected tissues followed by culturing and histopathological investigation is required only in selected cases [**C**] [60].

Primary treatment of cryptococcal meningitis should encompass a combination of L-AmB and 5-FC [**AII$_t$**] [171, 172, 181, 260]. Voriconazole or posaconazole may be used for salvage treatment [**CIII**] [132, 180, 183]. *Cryptococcus* spp. are *in vitro* resistant to echinocandines [184]. Thus, these agents do not play a role in the treatment of cryptococcal meningitis [**DIII**]. Reducing the CSF opening pressure (e.g. by repetitive lumbar punctures) is useful besides anti-infectious drug therapy in selected patients with cryptococcal meningitis [**BII**] [172, 261].

viruses

Herpes viruses, in particular herpes simplex virus (HSV), Epstein–Barr virus (EBV) and human herpes virus-6 (HHV-6) are prevailing in allo-HSCT recipients [2, 73]. Viral CNS infections typically present as meningoencephalitis, but strokes—e.g. caused by varicella zoster virus (VZV)—or leukoencephalopathy (e.g. JC virus-associated PML) might occur [18]. The diagnosis of viral CNS infections is usually made by CSF PCR together with neuroimaging, preferably MRI [2, 109, 262].

CSF viral PCR assays have an excellent sensitivity and specificity of 90%–100% for the majority of virus types [64, 65]. Thus, CSF PCR is regarded as a 'gold standard' for diagnosis of viral CNS infections [**A**]. However, studies comparing viral isolation from autopsy samples or brain-biopsy specimens—the former reference standard—with PCR are available only for few viruses such as HSV or cytomegalovirus (CMV) [64, 65, 70]. CSF virus PCR might initially be false-negative and the probability of a positive PCR increases when there is a time frame of 3–14 days between onset of symptoms and lumbar puncture [263].

herpes simplex virus. The incidence of HSV encephalitis is relatively low in patients with hematological disorders and there have been few cases published which mainly include allo-HSCT recipients [2, 73, 264].

CSF PCR is a rapid method to diagnose HSV encephalitis with high sensitivity and specificity (both >90%) [**A**] [64, 65]. Detection of CSF HSV antibodies is not a reliable diagnostic tool for HSV encephalitis since the sensitivity and specificity is only 75%–85% and 60%–90%, respectively [**C**] [66]. Detection of CSF HSV antigen has a sensitivity and a specificity of ∼90% and might be of value as an adjunctive test [**C**] [66, 67]. CSF viral cultures are frequently negative in HSV encephalitis [**D**] [68]. Cerebral MRI typically shows abnormalities in the medial and inferior temporal lobe, the insula and the cingulate (supplementary Figure S3, available at *Annals of Oncology* online) [265]. However, cerebral MRI might also be inconspicuous in allo-HSCT recipients with HSV encephalitis [2, 73].

HSV encephalitis should immediately be treated with aciclovir [**AII$_t$**] [73, 185–187].

In rare cases of aciclovir resistance, foscarnet may be administered [**CIII**] [190]. Patients with HSV encephalitis have a good overall prognosis, but a large proportion of patients (up to 70%) recover with neurological sequelae [2, 187].

cytomegalovirus. CMV CNS disease is typically characterized by ventriculo-encephalitis, retinitis and polyradiculopathy [195, 266, 267]. CSF CMV PCR has a high sensitivity (up to 100%) for the diagnosis of CMV CNS disease [**A**] [69–72]. Detection of CMV in CSF by viral cultures might only be used as an adjunctive test since it has a low sensitivity of ∼20% [**C**] [69, 72].

CMV CNS disease is commonly treated with ganciclovir or foscarnet [**AIII**] [188]. Some authors recommend a combination of both agents [**BIII**] [188, 195–197]. Cidofovir as single agent or in combination with foscarnet or ganciclovir might be used for salvage treatment [**CIII**] [195, 200, 201]. Some reports support the use of leflunomide to control CMV disease [**CIII**] [201, 268, 269]. There are no systematic data showing a benefit of the routine administration of CMV hyperimmunoglobulin in patients with hematological disorders and CMV disease.

Epstein–Barr virus. Except for patients with allo-HSCT, EBV disease other than infectious mononucleosis is a rare entity. Diagnosis of EBV meningoencephalitis is based on CSF PCR [**A**] [2, 73–75]. However, brain-biopsy-proven EBV meningoencephalitis in conjunction with a negative CSF EBV PCR has been reported [76].

A reduction of immunosuppression should be attempted whenever possible in patients with EBV disease or infection [**AIII**] [188]. The role of rituximab in EBV disease (i.e. presence of EBV organ involvement) remains to be elucidated despite the fact that first experiences suggest that pre-emptive treatment of EBV infections (i.e. EBV reactivation only) might reduce the incidence of post-transplant lymphoproliferative disorder [270]. Likewise, it remains unclear whether antivirals are beneficial in EBV disease [188]. Ganciclovir, valganciclovir or foscarnet might be used to treat EBV meningoencephalitis [**BIII**] and there are few case reports on the potential efficacy of aciclovir in this situation [**CIII**] [188, 202–209].

human herpes virus-6. HHV-6 CNS disease (mainly encephalitis) has rarely been described except in allo-HSCT recipients [2, 7, 77, 78, 210]. HHV-6 encephalitis typically

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affects allo-HSCT recipients with unrelated (mainly cord blood) donors and it frequently develops at the time of engraftment (or shortly thereafter) [2, 7]. Common clinical symptoms include alteration of consciousness, short-term memory loss and seizures [2, 7, 271]. The diagnostic method of choice for diagnosis of HHV-6 meningoencephalitis is quantitative CSF PCR [**A**] [77, 78]. However, it should be noted that HHV-6 DNA might be detected in CSF in a significant proportion of asymptomatic allo-HSCT recipients [79]. CSF analysis might show elevated protein levels and, more rarely pleocytosis [2, 77]. Imaging abnormalities which typically involve the temporal lobe are more likely visible in MRI than in CT scan (supplementary Figure S4, available at *Annals of Oncology* online) [2, 77]. Despite this, cerebral MRI might be normal in the early phase of HHV-6 meningoencephalitis in allo-HSCT recipients [2, 77, 78].

Ganciclovir or foscarnet could be used as first-line therapy for HHV-6 meningoencephalitis [**AIII**] [7, 8, 210–213]. Cidofovir can be administered as second-line treatment [**CIII**] [215].

varicella zoster virus. Primary VZV infection (chickenpox) occurs rarely in patients with hematological disorders, since VZV-seronegativity in adulthood is rare (~5%). In VZV-seropositive recipients, VZV disease after allo-HSCT most commonly manifests as dermatomal herpes zoster but a VZV meningoencephalitis may occur [2, 216, 217]. Small patient series indicate that CSF PCR has a similar good sensitivity and specificity for diagnosis of VZV meningoencephalitis as for other herpes viruses [**A**] [80–82]. The CSF VZV viral load determined by PCR might correlate with the severity and the duration of VZV meningoencephalitis [218]. Diagnosis of VZV meningoencephalitis may be confirmed by serological tests such as detection of intrathecal VZV glycoprotein E [272]. Rash and CSF pleocytosis might be absent in patients with cerebral VZV vasculopathy (such as strokes). In this situation, detection of CSF anti-VZV IgG antibodies might have a higher sensitivity than CSF VZV PCR [**B**] [83].

VZV CNS infections can be successfully treated with aciclovir [**AIII**] [2, 73, 218]. However, aciclovir resistance could occur and there are case reports on fatal CNS meningoencephalitis in allo-HSCT recipients despite early therapy with high-dose aciclovir [216]. These patients might benefit from a combination of aciclovir and foscarnet [**CIII**] [219].

JC virus. JC virus-related PML typically affects severely immunocompromised hosts such as Acquired Immune Deficiency Syndrome (AIDS) patients or allo-HSCT recipients [2, 273]. CNS biopsy of suspicious lesions is required for definitive diagnosis of PML [**A**]. The typical triad (demyelination, bizarre astrocytes and enlarged oligodendroglial nuclei) can frequently be demonstrated by histopathological work-up in biopsies which might be combined with tissue and CSF JC virus (dual qualitative-quantitative nested) PCR [**A**] [86, 88, 89]. MRI typically shows abnormalities in the posterior white matter without contrast enhancement (supplementary Figure S5, available at *Annals of Oncology* online) [274]. The diagnosis of PML could also be established without CNS biopsy in immunocompromised patients with typical clinical symptoms and characteristic findings by neuroimaging together with a positive CSF JC virus PCR [**A**] [86].

Immune reconstitution seems to be crucial for treatment of PML, as suggested by the observation that the incidence of PML could be markedly reduced in AIDS patients by the introduction of highly active antiretroviral therapy (HAART) [273, 275]. However, PML might develop or worsen (in the case of pre-existing PML) at the beginning of HAART (PML-immune reconstitution inflammatory syndrome, IRIS) [273, 275, 276]. PML-IRIS has also been described during withdrawal of agents which are associated with the occurrence of PML, such as natalizumab [277].

Immunosuppressives should be reduced in allo-HSCT recipients with PML whenever possible [**AIII**] [12]. Treatment with cidofovir may be beneficial in some patients with PML [2, 278, 279]. In contrast, other allo-HSCT recipients as well as a larger series of 370 AIDS patients with PML did not improve after treatment with cidofovir [$\mathbf{DII_{t,u}}$] [12, 221]. Several experimental approaches such as adoptive T-cell therapy or administration of interleukin-2, mefloquine or mirtazapine have been tested as a treatment option for PML [12, 278–280]. Since none of them has clearly shown to be effective in larger series of patients they are recommended within experimental protocols only [**DIII**].

conclusions

Diagnosis of CNS infections remains a great challenge in patients with hematological disorders since symptoms might both be masked and be mimicked by other conditions such as metabolic disturbances or consequences from antineoplastic treatment. Thus, awareness of this complication is crucial and any suspicion of a CNS infection should lead to timely and adequate diagnostics and treatment to improve the outcome in this population.

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patients suffering from neurological complications associated with chicken pox or herpes zoster. J Clin Microbiol 1991; 29(7): 1513–1516.
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ORIGINAL PAPER

Use of capillary blood count parameters in adults

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Vox Sanguinis

Background and Objectives Capillary samples can provide blood for cell counts in haematologic patients and blood donors. However, some accept only values from venous blood. This study compares capillary and venous blood counts to verify the hypothesis that they are equivalent.

Materials and Methods We analysed 463 capillary (fingerstick) and venous blood samples from 428 adults of both sexes (71% haematologic patients, 29% potential blood and apheresis donors). Both samples were taken at the same time from each subject. Haemoglobin (Hb), haematocrit (Hct), white blood cells (WBC), platelets, red blood cells (RBC), mean corpuscular volume (MCV), mean corpuscular Hb (MCH) and mean corpuscular Hb concentration (MCHC) were measured using a haematology analyser (Advia 120, Bayer).

Results Capillary Hb, Hct, WBC, RBC, MCV and MCH were all significantly higher than the venous values [+0·2 mmol/l (+0·3 g/dl), +0·02 l/l (+2%), $+0{\cdot}2 \times 10^9$/l, $+0{\cdot}1 \times 10^{12}$/l, +3·1 fl and +0·01 fmol, respectively], whereas the capillary MCHC was lower (–0·6 mmol/l). There was no difference in platelets (-1×10^9/l). Capillary Hb and Hct values were higher in patients with anaemia and polycythaemia, respectively. However, no significant differences occurred in severe thrombocytopenia.

Conclusion In adult haematologic patients, however, only the differences in Hb and Hct values may be of clinical relevance. For potential blood and apheresis donors, Hb and platelet screening are equivalent with either capillary and venous blood using a haematology analyser.

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Key words: blood counts, blood donors, capillary, haematologic disease, venous.

Introduction

Patients with haematologic diseases need regular, even daily blood counts. In haematology, capillary blood count analyses are established routines, long accepted by patients and medical personnel [1]. However, some physicians accept only venous values in clinical practice and in haemoglobin (Hb) and platelet screening for potential blood and apheresis donors. Does capillary blood give discrepant results in these measurements? If so, to what extent? Therapeutic decisions, for example, transfusion and blood donation, are based only on venous values. For patients, data so far are inadequate. Either studies involved only a few healthy adults [2,3] or the subjects were newborns and children [4–6] (Table 1). Therefore, our aim was (i) to compare capillary blood counts with venous to verify the hypothesis that they are equivalent, (ii) to include enough adult haematologic patients (with low and high values) and healthy adults, (iii) to be able to convert measured capillary values to the corresponding venous values, and (iv) to apply these findings to potential blood and apheresis donors.

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Materials and methods

Patients and healthy volunteers

This study (ClinicalTrials.gov no. NCT00390988) was conducted in the Division of Haematology/Oncology and in the Institute

Table 1 Blood count parameters (capillary vs. venous) in comparison with previous studies

Study	*n*	Age	Hb	Hct	WBC	Platelets	RBC	MCV	MCH	MCHC
Daae *et al.* [2]	40	22 years–62 years	↑	↑	↑	↓	↑	n.s.	n.s.	n.s.
Daae *et al.* [4]	16	3 months–14 years	↑	↑	↑	n.s.	↑	n.s.	n.s.	n.s.
Özbek *et al.* [5]	95	1 day	↑	↑	↑	↓	↑	n.s.	n.s.	↑
Yang *et al.* [3]	24	20 years–22 years	n.s.	n.s.	↑	n.s.	n.s.	n.a.	n.a.	n.a.
Kayiran *et al.* [6]	236[a]	1 day –28 days	↑	↑	↑	↓	↑	n.s.	n.s.	↑
Present study	463	18 years–82 years	↑	↑	↑	n.s.	↑	↑	↑	↓

n.a., not available; n.s., not significant; ↑ and ↓, capillary value is higher or lower, as applicable, compared to the venous value.
[a]Includes all data from Özbek *et al.* [5].

for Transfusion Medicine and Immunohaematology, University Hospital of Magdeburg, Germany, from July to September 2006. We enrolled haematologic patients (from our outpatient department and ward) and healthy volunteers of both sexes, aged 18 years or older. The volunteers were employees of our division or blood donors at our institution. We excluded those under the age of 18, or who had acute or chronic infections and autoimmune or malignant diseases. Age, sex and haematologic diagnoses were listed. The ethical committee of our institution endorsed the study protocol, and each subject gave informed written consent.

Blood sampling and measurement

We drew capillary blood from the lateral aspect of the tip of the third or fourth finger, using an automated lancet (BD Genie Lancet, BD, Plymouth, UK), without any procedures for stimulating blood circulation. The first drop of blood was discarded. The next drops were collected into a capillary blood collection tube (200 µl; Kabe Labortechnik, Nümbrecht-Elsenroth, Germany) with ethylenediaminetetraacetic acid (EDTA) for anticoagulation. Venous blood came from the cubital vein, a central venous catheter (CVC) or a venous port system (VPS) into a vacuum tube (4·5 ml; BD Vacutainer) with EDTA. For sampling venous blood by using a CVC or VPS, we discarded the first 5 ml of blood before using the tube for analysis. Capillary and venous blood samples were collected at the same time from each subject. Both samples were measured using the haematology analyser Advia 120 (Bayer, Fernwald, Germany) in our accredited haematology laboratory (DIN EN ISO 15189). The measurements were of Hb, haematocrit (Hct), white blood cells (leucocytes; WBC), platelets, red blood cells (erythrocytes; RBC), mean corpuscular volume (MCV), mean corpuscular Hb (MCH), and mean corpuscular Hb concentration (MCHC).

The values are in SI units. In the text only, Hb and Hct appear as conventional units too.

Statistical analysis

We used an Excel 2000 database (Microsoft Corporation) and the Statistical Package of Social Science (SPSS for Windows, version 12; SPSS GmbH Software, Munich, Germany) to create and analyse the data. Data are presented as mean ± standard deviation and ranges. Comparison between capillary and venous blood counts was by paired Student's *t*-test. Differences were considered statistically significant for two-sided P values ≤ 0·05. We indicate also the deviation value (d; defined as difference capillary to venous values), the Pearson's correlation coefficient (r), and the conversion factor (c; defined as ratio venous to capillary values), respectively. Sensitivity was defined as the ratio of number of capillary values above (or below) cut-off values to number of corresponding venous values, and specificity as the ratio of number of capillary values below (or above) cut-off values to number of corresponding venous values. The plus (+) and the minus (–) signs (text, Tables 2 and 3) indicate higher and lower capillary values, respectively, in comparison with the corresponding venous values. The Greek delta (Δ) (Tables 3, 4 and 5) indicates the change in the stated parameter (e.g. sensitivity) after correction of the measured capillary parameter by the d value or c factor.

Results

Patients, healthy volunteers, blood sampling and measurement

This study enrolled 428 subjects (mean age 51 years, range 18–82; 50% men, 50% women), and analysed 463 pairs of capillary and venous blood counts. Thirty-five patients were recruited twice, that is, at the beginning of chemotherapy and later in aplasia. Of the 303 (71%) patients (mean age 58 years, range 18–82), 54% were men and 46% women. The most frequent haematologic diagnoses were lymphoma (172; 57%), leukaemia (42; 14%) and myeloproliferative disease (41; 14%).

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Table 2 Blood count parameters: capillary vs. venous samples ($n = 463$)

	Venous[a]	Capillary[a]	d value[b]	c factor[c]	r value[d]	*P* value
Hb (mmol/l)	8·0 ± 1·5 (3·6–11·8)	8·2 ± 1·5 (3·7–12·4)	+0·2	0·98	0·98	< 0·0001
Hct (l/l)	0·38 ± 0·07 (0·17–0·55)	0·40 ± 0·07 (0·18–0·57)	+0·02	0·95	0·97	< 0·0001
WBC ($\times 10^9$/l)	8·9 ± 17·7 (0·1–299·5)	9·1 ± 18·3 (0·1–307·4)	+0·2	0·99	1·00	0·002
Platelets ($\times 10^9$/l)	205 ± 109 (3–801)	204 ± 110 (4–863)	−1	1·01	0·99	0·08
RBC ($\times 10^{12}$/l)	4·2 ± 0·9 (1·7–7·5)	4·3 ± 0·9 (1·7–7·4)	+0·1	0·98	0·98	< 0·0001
MCV (fl)	90·2 ± 8·5 (54·1–127·6)	93·3 ± 8·8 (57·8–133·8)	+3·1	0·97	0·97	< 0·0001
MCH (fmol)	1·91 ± 0·18 (0·99–2·61)	1·92 ± 0·18 (1·02–2·68)	+0·01	1·00	0·98	< 0·0001
MCHC (mmol/l)	21·2 ± 0·7 (17·8–23·5)	20·6 ± 0·8 (17·4–22·6)	−0·6	1·03	0·76	< 0·0001

[a]Mean, standard deviation and range are indicated.
[b]Deviation value.
[c]Conversion factor
[d]Correlation coefficient.
+ and −, capillary value is higher or lower, as applicable, compared with the venous value.

Table 3 Deviation of measured capillary values in comparison to venous values ($n = 463$)

	Deviation (%)	Δd value	Δc factor
Hb	+2·4	−0·2	+0·4
Hct	+5·2	−0·3	−0·1
WBC	+3·5	−2·4	+2·5
Platelets	+0·1	+1·3	+1·1
RBC	+2·2	−0·3	+0·1
MCV	+3·4	−0·1	+0·3
MCH	+0·5	±0·0	+0·5
MCHC	−2·6	+0·2	+0·3

For the d values and the c factors, see Table 2.
+ and −, capillary value is higher or lower, as applicable, compared with the venous value.

Of the 125 (29%) healthy volunteers (mean age 36 years, range 19–67), 43% were men and 57% women. Of these, 70 (56%) were potential blood donors (mean age 38 years, range 19–66; 50% men and 50% women).

No local infectious complications were seen in neutropenic patients after fingerstick sampling.

The variation coefficient (CV) was 1·4% for capillary measurements (Hb 0·8%, Hct 1·1%, WBC 2·6%, platelets 3·0%, RBC 0·9%, MCV 0·4%, MCH 0·9% and MCHC 1·1%) and 1·2% for venous (Hb 0·6%, Hct 0·8%, WBC 2·4%, platelets 3·4%, RBC 0·8%, MCV 0·2%, MCH 0·7% and MCHC 0·8%).

Blood counts

Table 2 summarizes the main results of the study.

Red cell counts

We found increased values for capillary Hb [+0·2 mmol/l (+0·3 g/dl); $P < 0·0001$, $r = 0·98$], Hct [+0·02 l/l (+2%); $P < 0·0001$, $r = 0·97$] compared to venous. In anaemia [Hb ≤ 6·0 mmol/l (9·6 g/dl), $n = 55$], we also noted significantly higher Hb values [+0·2 mmol/l (+0·3 g/dl); $P < 0·0001$, $r = 0·93$] in the capillary samples. Likewise, higher capillary Hct values occurred in polycythaemia [Hct ≥ 0·48 l/l (48%), $n = 34$; +0·04 l/l (+4%); $P < 0·0001$, $r = 0·66$].

Table 4 Reliability of measured capillary values in patients (thresholds for clinical decisions)

	Sensitivity			Specificity		
	%	Δd value	Δc factor	%	Δd value	Δc factor
Anaemia[a]	89·1	94·5	92·7	99·3	98·5	98·8
Polycythaemia[b]	100·0	100·0	76·9	95·3	98·9	99·3
Thrombocytopenia[c]	90·5	85·7	85·7	99·5	99·8	99·8

[a]Hb ≤ 6·0 mmol/l (9·6 g/dl), $n = 55$.
[b]Hct ≥ 0·48 l/l (48%), $n = 34$.
[c]Platelets ≤ 20×10^9/l, $n = 21$.
For d values and c factors, see Table 2.

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Table 5 Reliability of measured capillary values in potential blood and apheresis donors

	Sensitivity			Specificity		
	%	Δd value	Δc factor	%	Δd value	Δc factor
Hb screening						
All	98·3	90·0	90·0	60·0	100·0	100·0
Men[a]	100·0	97·0	97·0	100·0	100·0	100·0
Women[b]	96·3	81·5	81·5	50·0	100·0	100·0
Platelet screening						
All[c]	100·0	100·0	100·0	100·0	100·0	100·0

Cut-off values according to the German guidelines for blood donation: [a]Hb ≥ 8·4 mmol/l (13·5 g/dl) for men ($n = 35$); [b]Hb ≥ 7·8 mmol/l (12·5 g/dl) for women ($n = 35$); and [c]Platelets ≥ 150×10^9/l for all apheresis donors ($n = 70$).
For d values and c factors see Table 2.

Leucocyte counts

We noted increased values for capillary WBC (+0·2 × 10^9/l; $P = 0{\cdot}002$, $r = 1{\cdot}00$) compared to venous. For patients with severe leucocytopenia (WBC ≤ 1·0 × 10^9/l, $n = 18$) no statistically significant differences were found between capillary and venous samples (+0·1 × 10^9/l; $P = 0{\cdot}06$, $r = 0{\cdot}87$). High WBC values from capillary samples (WBC ≥ 11·5 × 10^9/l, $n = 44$) were significantly higher (+1·4 × 10^9/l; $P = 0{\cdot}02$, $r = 1{\cdot}00$) than the venous values.

Platelet counts

No significant difference was seen for platelet values (–1 × 10^9/l; $P = 0{\cdot}08$, $r = 0{\cdot}99$), whether with very low capillary platelet values (platelets ≤ 20 × 10^9/l, $n = 21$; +1 × 10^9/l; $P = 0{\cdot}06$, $r = 0{\cdot}88$) or high (platelets ≤ 367 × 10^9/l, $n = 25$; +1 × 10^9/l; $P = 0{\cdot}86$, $r = 0{\cdot}98$), when compared to venous values.

Red cell indices

The capillary values for RBC (+0·1 × 10^{12}/l; $P < 0{\cdot}0001$, $r = 0{\cdot}98$), for MCV (+3·1 fl; $P < 0{\cdot}0001$, $r = 0{\cdot}97$) and for MCH values (+0·01 fmol; $P < 0{\cdot}0001$, $r = 0{\cdot}98$) were significantly higher than venous. The capillary MCHC value was significantly lower than venous (–0·6 mmol/l; $P < 0{\cdot}0001$, $r = 0{\cdot}76$).

Subgroups: patients, healthy subjects and blood donors

The subgroup analyses for 334 patients and for 129 healthy subjects were mostly comparable with the data for all 463 samples (see Table 2). Differences were only seen for platelet and RBC values in healthy subjects: The capillary platelet values are lower than venous (–4 × 10^9/l; $P = 0{\cdot}0007$, $r = 0{\cdot}96$) and there was no measurable difference between capillary and venous RBC values (± 0 × 10^{12}/l; $P = 0{\cdot}30$, $r = 0{\cdot}93$). No differences existed between capillary and venous Hb values in potential blood donors (± 0·0 mmol/l; $P = 0{\cdot}28$, $r = 0{\cdot}95$; $n = 70$), but for apheresis candidates the capillary platelet values are significantly lower than venous (–5 × 10^9/l; $P = 0{\cdot}004$, $r = 0{\cdot}95$; $n = 70$).

Accuracy and reliability of capillary measured values

The deviation between measured capillary and venous values averages +1·8%. After correction of the measured capillary values by addition or subtraction of the contrary or opposite d values [e.g. –0·2 mmol/l (–0·3 g/dl) for Hb values] and multiplication, respectively, of the stated c factors (Table 2), the mean deviation of capillary and venous values amounts to only –0·2% and +0·6%, respectively (Table 3).

By capillary measurements we can detect anaemia [Hb ≤ 6·0 mmol/l (9·6 g/dl)], polycythaemia [Hct ≥ 0·48 l/l (48%)] and thrombocytopenia (platelets ≤ 20 × 10^9/l) with a mean sensitivity of 93·2% and with a mean specificity of 98·0%. In some cases the conversion of measured capillary values to the corresponding venous values using the d value or the c factor results in a higher sensitivity or specificity (Table 4).

In potential blood and apheresis donors, the mean sensitivity to detect all subjects with capillary measured Hb and platelet above cut-off values is 99·2%, that is, we detected nearly all potential donors with Hb or platelets above the cut-off values. All potential apheresis donors with capillary platelets below the cut-off values were detected, that is, the rejection rate (corresponding specificity) is 100·0%. Capillary Hb alone detected only 60·0% of those with Hb below the cut-off. But, by conversion of the measured capillary value to the corresponding venous value the rejection rate increased to 100·0% of those with low Hb (Table 5).

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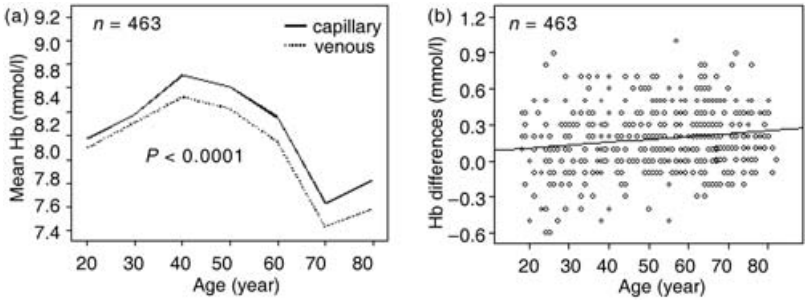

Fig. 1 Relation between capillary and venous Hb values and the age of the subjects (a). However, the age does not influence the differences between capillary and venous Hb values: there are no statistical differences between younger (< 50 years) and older (> 50 years) patients ($P = 0{\cdot}11$) and between younger (< 50 years) and older (> 50 years) healthy subjects ($P = 0{\cdot}12$) (b).

Discussion

In this study we found differences between capillary (fingerstick) and venous blood counts that averaged approximately +1·8%. Except for platelet values, the differences were statistically significant (Table 2). However, the correlation between the capillary and venous values was very high for the most of the eight parameters (on average, $r = 0{\cdot}95$), so capillary and venous values are equally good. Also, according to the laboratory directive of the German Federal Medical Council, the relative (+1·8%) and the absolute (4·8%) differences as well as the CV are within the allowed error of measurement of the haematology analyser. For the present, these findings do not suggest any clinically relevant differences between capillary and venous blood counts.

We found differences to be less than the +3·3% level reported previously for adults [2]. Yang and co-workers found relative differences between capillary and venous counts of +6·8 to +9·2% for WBC-related parameters and +0·2 to +1·2% for others [3]. In children, greater differences exist between capillary and venous blood samples (+5·4%) [4]. This is particularly so in the neonatal period (+12% on postnatal Day 1 and +5 to +7% on Days 7–28). These higher capillary values reflect peripheral haemoconcentration [4,6]. As shown in Fig. 1, the age of subjects has no influence on the differences between capillary and venous Hb values in patients or healthy subjects. So we can rule out the effects of haemoconcentration in younger and older adults on the clinically important measurement of Hb. Incorrect capillary sample collection techniques may result in haemodilution, but not haemoconcentration [7].

Results of previous studies (Table 1) and our data suggest statistically higher values for capillary measured Hb, Hct, WBC and RBC compared to venous. However, conflicting findings were obtained for platelets, MCV, MCH and MCHC. The studies cited were based on different age ranges – healthy adults [2,3] or newborns and children [4–6] – and in part paucity of samples or subjects (on an average, $n = 27$) [2–4]. Unlike our study, they enrolled few patients with pathologic values. For platelets, for example, three studies reported significantly lower capillary than venous values [2,5,6]. We found no statistically significant differences between capillary and venous platelet values. However, analysing the subgroup of normal platelet values (range 150–375 $\times$ 10^9/l, $n = 316$), we noted significantly lower capillary values compared to venous (–3 $\times$ 10^9/l; $P = 0{\cdot}003$, $r = 0{\cdot}96$), but such a difference is of no clinical relevance. This finding suggests that more normal and pathologic values will be needed to enable conclusions to be drawn.

The differences between capillary and venous Hb levels exceeded the limit of ± 0·6 mmol/l (± 1·0 g/dl) in +6·7% and +2·9% for all subjects and blood donors, respectively. This suggests greater accuracy of the haematology analyser, especially for Hb screening in potential blood donors. The differences are greater using portable photometers with microcuvettes (+8·8%, HemoCue, Großostheim, Germany; 20·4%, Biotest Medizintechnik, Alzenau, Germany), which are often used in blood banks [8].

Capillary blood counts have enough sensitivity to detect patients with anaemia, polycythaemia and severe thrombocytopenia as well as potential blood and apheresis donors with Hb and platelets at or above cut-off values. Also, in the above-mentioned important clinical situations and in potential apheresis donors the specificity is very high (Tables 4 and 5). The rejection rate of potential blood donors according to the Hb cut-off values for capillary samples is 60·0%. By conversion of the measured capillary Hb to venous values, the rejection rate increases to 100·0%, that is, this method detects all potential blood donors with capillary Hb less than venous cut-off Hb values (Table 5). These results suggest the d values and the c factors as helpful tools for the accuracy and reliability of capillary measurements. Thus, capillary measurements can defer from blood or platelet donation those with unacceptable Hb and platelets values.

In the clinical setting, we found significantly higher capillary than venous Hb values in anaemia. Therefore, recommendations for RBC transfusion would be earlier with capillary Hb measurements, leading to more transfusions. In our division the threshold for RBC transfusion for patients with cancer and non-symptomatic anaemia is 5·0 mmol/l (8·0 g/dl) [9]. The new threshold for capillary Hb should then be 5·2 mmol/l (8·3 g/dl). Only 18 of 26 patients with venous Hb at or below 5·0 mmol/l (8·0 g/dl) also had a capillary Hb at or below 5·0 mmol/l (8·0 g/dl). This finding may suggest

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undertransfusion of patients with severe anaemia and capillary-measured Hb in about 30% (eight of 26 patients) in the past – if clinicians are guided only by thresholds or cut-off values.

For high Hct values the differences between capillary and venous samples are statistically significant, but the *r* value is low. This may suggest a clinically significant difference and needs to be considered in patients with polycythaemia vera. Surprisingly and importantly, we found no statistically significant differences for capillary and venous values in patients with severe leucocytopenia and thrombocytopenia. Prophylactic transfusion of platelets is recommended in patients with cancer for platelets between 10 and 20×10^9/l [9,10]. No threshold adjustment is required for platelet counts from capillary samples.

Capillary blood count analyses are advantageous compared to venous analyses. For example, their material costs are about half that of venous (€0·50 vs. €1·00 per analysis). This should to be considered if many analyses are provided, for example, in haematology divisions or blood banks. Furthermore, capillary blood count analyses lead to lower blood loss. In our study group (East German Haematology and Oncology Group, OSHO), the mean duration of neutropenia (absolute neutrophil count $< 1{\cdot}0 \times 10^9$/l) after myelosuppressive chemotherapy in acute myeloid leukaemia is 21 days [11], and about 31 blood counts are necessary per cycle (about 92 per whole course of therapy). With capillary blood counts, we could save about 130 ml whole blood per cycle (about 400 ml per whole course of therapy). In patients with poor peripheral venous access, capillary blood samples spare the veins, thus saving them for temporary peripheral venous catheters, for example, for transfusions. In appropriate conditions, capillary sampling provides valid and useful values.

In conclusion, for clinical use in patients, and for Hb and platelet screening in potential blood and apheresis donors, most capillary and venous blood count measurements using a haematology analyser are equivalent. The capillary approach provides simple and reliable blood counts. After conversion, capillary blood counts can be used for clinical decisions and Hb screening of potential blood donors. However, the differences between Hb and Hct may be of clinical relevance in adult haematologic patients. If Hb and Hct are determined by capillary measurement, the regime of RBC transfusion or phlebotomy could change, that is, earlier RBC transfusion and later phlebotomy.

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Publikation III

Schalk E, Scheinpflug K, Mohren M. Correlation of capillary and venous absolute neutrophil counts in adult hematological patients and normal controls. **Am J Hematol 2008**;83(7):605

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Correlation of capillary and venous absolute neutrophil counts in adult hematological patients and normal controls

To the Editor: Absolute neutrophil counts (ANC) are being used to define neutropenia or agranulocytosis. ANC are essential for therapeutic strategies, e.g., antibiotic prophylaxis after aggressive chemotherapy. Capillary blood samples are easily obtained making results quickly available, but venous values are generally accepted as references.

We compared 447 pairs of capillary (fingerstick) and venous (cubital vein) ANC of 421 adult hematological patients (70%) and healthy subjects (30%) using a hematology analyzer (Advia 120, Bayer, Fernwald, Germany). Mean age of all subjects was 51 years, range 18–81 years; the ratio of male to female was 1:1. The most frequent diseases were malignant lymphoma (43%), multiple myeloma (17%), myeloproliferative diseases (14%), and acute leukemia (11%). Both blood samples were collected at the same time from each subject.

ANC were calculated on the basis of measured white blood cell counts and relative neutrophil counts. For statistical analyses, Student's *t*-test and Pearson's correlation coefficient (*r* value) were used; $P < 0.05$ was considered statistically significant.

No statistically significant differences were seen in the ANC, regardless whether capillary or venous sampling was done; capillary and venous ANC correlate very well. Likewise, no statistically significant differences were seen in capillary and venous ANC for patients with neutropenia (ANC $< 1.50 \times 10^9$/l) and agranulocytosis (ANC $< 0.50 \times 10^9$/l) (Table I). Importantly for routine clinical use, no local infectious complications were seen in patients with neutropenia or agranulocytosis after capillary fingerstick sampling. Also, no statistically significant differences between capillary and venous ANC were seen in comparison to both patients and healthy subjects ($P = 0.15$). Sensitivity to detect patients with neutropenia or agranulocytosis is high using capillary blood samples (95%). Furthermore, specificity is even higher (100%). The variation coefficient, defined as ratio of standard deviation to mean, of repeated capillary and venous measurements was 3.2% for capillary ANC and 2.4% for venous ANC.

In contrast to our results, in previously published studies capillary were found to be higher than venous ANC. For adults, data are lacking so far, because the cohort size up to $n = 40$ is not sufficient [1]. Furthermore, data for adult hematological patients are not available. In children, much higher capillary than venous ANC were found (17.2%; $n = 9$, aged 3 months to 14 years) in comparison to young adults (12.6%; $n = 24$, aged 20–22 years) and older adults (8.2%; $n = 40$, aged 22–62 years) [1–3]. Thus, it seems that there is an age-dependant tendency for higher capillary ANC that decreases with older age. Our different results may be explained by the fact that we have included a large cohort size and ~60% of subjects were above 50 years, most likely representing the age cohort of hematological patients.

Capillary ANC may be preferable in patients with poor or difficult peripheral access, especially because only small blood samples are used.

In conclusion, capillary and venous ANC correlate very well in adults. The capillary approach provides simple and reliable ANC in patients and normal subjects, and allows to detect true-positive and true-negative adult patients with neutropenia or agranulocytosis.

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Complications of -thalassemia intermedia: A 12-year Lebanese experience

To the Editor: Thalassemia is an inherited disease that affects α- or β-chain molecules of hemoglobin [1,2]. The Middle East has one of the highest rates of incidence worldwide, and the Lebanese population specifically has 3% carrier prevalence with approximately one-third of the patients suffering from thalassemia intermedia (TI).

By definition, TI includes a wide clinical spectrum as follows: mildly affected patients are completely asymptomatic until adult life, experiencing only mild anemia and maintaining hemoglobin levels between 7 and 10 g/dl. These patients require only occasional blood transfusions, if any; patients with more severe TI generally present between the ages of 2 and 6 years, and although they are able to survive without regular transfusion therapy, their growth and development can be retarded.

The purpose of this study is to shed light on the complications for the Lebanese TI population. The TI patients are being followed up at the Chronic

TABLE I. Comparison of Capillary and Venous Absolute Neutrophil Counts (ANC)

	Capillary ANC ($\times 10^9$/l)[a]	Venous ANC ($\times 10^9$/l)[a]	Δ value ($\times 10^9$/l)	*r* value	*P* value
ANC (total, $n = 447$)	4.21 ± 3.85 (0.02–51.83)	4.28 ± 3.63 (0.02–41.61)	−0.07 (−1.0%)	0.98	0.05
Neutropenia ($n = 43$)[b]	0.66 ± 0.50 (0.02–1.71)	0.63 ± 0.48 (0.02–1.44)	+0.03 (+5.5%)	0.98	0.07
Agranulocytosis ($n = 19$)[c]	0.18 ± 0.18 (0.02–0.51)	0.16 ± 0.15 (0.02–0.46)	+0.02 (+6.7%)	0.97	0.15

[a]Mean, standard deviation, and range are indicated.
[b]ANC $< 1.50 \times 10^9$/l.
[c]ANC $< 0.50 \times 10^9$/l.
+ and −, capillary value is higher or lower, respectively, when compared with venous value; Δ value, capillary/venous difference.

Publikation IV

Schalk E, Scheinpflug K, Mohren M. Capillary blood count analyses in the clinical practice: a safe, reliable and valid method. **J Lab Med 2009**;33(5):303-309

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Originalarbeit

Kapilläre Blutbildanalysen in der klinischen Praxis: eine sichere, zuverlässige und valide Methode

Capillary blood count analyses in clinical practice: a safe, reliable and valid method

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Zusammenfassung

In der Hämatologie erfolgen Blutbildbestimmungen teilweise durch kapilläre Punktion. Akzeptiert sind jedoch nur venöse Werte. Ziel dieser Arbeit war es daher, die Problematik der kapillären Blutbildbestimmung aus labormedizinischer und klinischer Sicht zu beleuchten. Dazu führten wir eine selektive Literaturrecherche durch. Ergänzend wurden eigene Daten dargestellt. Bei Erwachsenen lagen die kapillär-venösen Differenzen im Mittel für Hämoglobin bei +0,3 g/dL bzw. +0,2 mmol/L (+2,1%), für Hämatokrit bei +1,5% bzw. +0,02 L/L (+3,6%), für Leukozyten bei $+0{,}2\times10^3/\mu L$ (+2,7%), für neutrophile Granulozyten (absolut) bei $+0{,}22\times10^3/\mu L$ (+4,7%), für Thrombozyten bei $-19\times10^3/\mu L$ (–8,3%) und für Erythrozyten bei $+0{,}1\times10^6/\mu L$ (+1,8%). Bei Kindern waren die Differenzen größer als bei Erwachsenen: Hämoglobin +1,1 g/dL bzw. +0,7 mmol/L (+6,3%), Hämatokrit +3,1% bzw. +0,03 L/L (+6,0%), Leukozyten $+2{,}0\times10^3/\mu L$ (+14,6%), neutrophile Granulozyten (absolut) $+0{,}91\times10^3/\mu L$ (+11,0%), Thrombozyten $-33\times10^3/\mu L$ (–14,1%) und Erythrozyten $+0{,}3\times10^6/\mu L$ (+6,0%). Die kapillären Werte korrelierten sehr gut mit den entsprechenden venösen Werten. Die kapilläre Blutbildbestimmung ist risikoarm, zuverlässig, gegenüber einer venösen Bestimmung durchaus vorteilhaft und erbringt mit hoher Wahrscheinlichkeit *richtig*-positive bzw. *richtig*-negative Werte für Patienten mit Anämie, Polyglobulie, Thrombo- oder Neutrozytopenie im Vergleich zur venösen Blutbildbestimmung. Die kapilläre Blutbildbestimmung kann damit zumindest bei Erwachsenen in der klinischen Praxis eingesetzt werden.

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Schlüsselwörter: Blutbildparameter; kapillär; venös.

Abstract

In haematology, blood count analyses are often performed on samples obtained by capillary puncture. However, only venous values are well accepted. This paper reviews the data available and highlights this topic from the viewpoint of laboratory medicine and clinical practice. We also present our own data. Mean capillary-venous differences were +0.3 g/dL or +0.2 mmol/L (+2.1%) for haemoglobin, +1.5% or +0.02 L/L (+3.6%) for haematocrit, $+0.2\times10^3/\mu L$ (+2.7%) for white blood cells, $+0.22\times10^3/\mu L$ (+4.7%) for absolute neutrophil counts, $-19\times10^3/\mu L$ (–8.3%) for platelets and $+0.1\times10^6/\mu L$ (+1.8%) for red blood cells. Differences were greater in children than in adults: +1.1 g/dL or +0.7 mmol/L (+6.3%) for haemoglobin, +3.1% or +0.03 L/L (+6.0%) for haematocrit, $+2.0\times10^3/\mu L$ (+14.6%) for white blood cells, $+0.91\times10^3/\mu L$ (+11.0%) for absolute neutrophil counts, $-33\times10^3/\mu L$ (–14.1%) for platelets and $+0.3\times10^6/\mu L$ (+6.0%) for red blood cells. The capillary values correlated very well with the venous values. Capillary blood count analysis is safe, reliable and advantageous compared to venous analysis and has high probability for *true*-positive and *true*-negative values for patients with anaemia, polyglobulia, thrombocytopenia and neutrocytopenia in comparison to venous blood count analysis. Therefore, at least in adults, capillary blood count analysis can be used as a substitute for venous blood count analysis in clinical practice.

Keywords: blood count parameters; capillary; venous.

Einleitung

Die kapilläre Blutentnahme hat sich zu einer Alternative zur Venenpunktion entwickelt [1]. Die Durchführung ist einfach und kann durch medizinisch-technische Assistenten erfolgen. Da nur ein geringes Blutvolumen benötigt wird, hat die kapilläre die venöse Blutentnahme in der Pädiatrie bei vielen Untersuchungen abgelöst [2, 3]. Für die Bestimmung der Glukose- [4–6], der Cyclosporin-

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Konzentration [3], der Blutgasanalyse [7, 8] und der Überwachung der oralen Antikoagulation [9] gibt es Erfahrungen mit der kapillären Analyse. In der Hämatologie wird die kapilläre Blutbildanalyse teilweise praktiziert. Die Blutbildbestimmung aus einem venös abgenommenen Röhrchen gilt als Standardmethode [10]. Nur wenige Labore haben eine Standardisierung kapillärer Blutbildanalysen vorgenommen. Abweichungen zwischen kapillären und venösen Parametern sind zu vermuten. Diese sind jedoch im klinischen Alltag, v. a. bei hämatologischen Patienten, inakzeptabel. Es wird sogar gefordert, dass der Begriff „peripheres Blut“ nicht verwendet werden sollte. Er sollte vielmehr durch „kapilläres“ oder „venöses“ Blut ersetzt werden, damit eine genaue Bewertung erfolgen kann [11].

In unserem hämatologischen Labor ist die kapilläre Blutbildbestimmung seit jeher etabliert und wird in der klinischen Routine angewandt. Erst durch die Akkreditierung des Speziallabors wurden wir auf eine Validierung aufmerksam gemacht.

Die vorliegende Arbeit gibt einen Überblick über die aktuelle Literatur und beleuchtet die Thematik der kapillären Blutbildbestimmung aus labormedizinischer und klinischer Sicht.

Material und Methoden

Wir führten eine Literaturrecherche (PubMed) zu Studien durch, in denen kapilläre und venöse Blutbildparameter verglichen wurden. Schlüsselwörter waren „capillary“, „venous“ und „blood counts“. Wir fanden 14 Publikationen aus den Jahren 1979–2008 (Tabelle 1). Studien, die nicht zwischen Kindern und Erwachsenen unterschieden, wurden nicht mit in die Analyse aufgenommen.

Die Analyse der kapillär-venösen Differenzen erfolgte für Hämoglobin, Hämatokrit, Leuko-, neutrophile Granulo-, Thrombo- und Erythrozyten. Die Angaben der Differenzen erfolgte als Absolut- und als Relativwert. Weiterhin erfolgte die Angabe des Korrelationskoeffizienten *r* nach Pearson.

Ergebnisse

Aus den zitierten Studien wurden insgesamt 6.475 kapillär-venöse Messungen zusammengefasst. Die einzelnen Studiendaten sind in Tabelle 1 dargestellt. Zwölf Studien erhielten Angaben zu Kindern, 11 zu Erwachsenen. Es handelte sich im Mittel pro Studie um 79 Vergleiche von kapillären und venösen Parametern (Spanne 10–463). Die Studienpopulationen waren bei Kindern kleiner (49, Spanne 16–95) als bei Erwachsenen (112, Spanne 10–463). Einige Studien untersuchten Gesunde und Kranke (z.B. Infektionen, Anämien und andere benigne und maligne hämatologische Erkrankungen) gemeinsam. In den meisten Studien wurde jedoch zwischen beiden Gruppen differenziert. Nur wenige Studien wiesen die für verschiedene pathologische Werte (z.B. Thrombozytopenie) entsprechende Daten auf. Als kapilläre Quelle diente entweder die Fingerbeere oder die Ferse, letztere nur bei Kindern. Es kamen verschiedene Blutbildautomaten zum Einsatz (Tabelle 1).

Vergleich kapillärer und venöser Blutbildparameter (Tabelle 1)

Hämoglobin (Hb) Die kapillären Hb-Werte liegen 0,8 g/dL bzw. 0,5 mmol/L (4,8%) über den entsprechenden venösen Werten. Bei Kindern liegen die kapillär-venösen Differenzen höher [1,1 g/dL bzw. 0,7 mmol/L (6,3%)] als bei Erwachsenen [0,3 g/dL bzw. 0,2 mmol/L (2,1%)]. Die Korrelationswerte liegen zwischen $r = 0{,}85–0{,}98$ [13, 21, 22].

Bei Patienten mit Anämie (Hb $< 9{,}6$ g/dL bzw. $< 6{,}0$ mmol/L) sind die kapillär-venösen Differenzen für den Hb-Wert ebenfalls gering: die kapillären Werte liegen 0,3 g/dL bzw. 0,2 mmol/L höher als die venösen Werte ($r = 0{,}93$) [22].

Hämatokrit (Hct) Die kapillären Hct-Werte liegen 2,4% bzw. 0,02 L/L (5,0%) höher als die entsprechenden venösen Werten. Bei Kindern sind die kapillär-venösen Differenzen größer [3,1% bzw. 0,03 L/L (6,0%)] als bei Erwachsenen [1,5% bzw. 0,02 L/L (3,6%)]. Die Korrelationswerte liegen zwischen $r = 0{,}96–0{,}97$ [14, 22].

Bei Patienten mit Polyglobulie (Hct $> 48{,}0\%$ bzw. $> 0{,}48$ L/L) liegen die kapillären Werte 4,0% bzw. 0,04 L/L höher als die venösen Werte ($r = 0{,}66$) [22].

Leukozyten (WBC) Die kapillären WBC-Werte liegen im Mittel um $1{,}2 \times 10^3/\mu L$ (9,5%) über den entsprechenden venösen Werten. Bei Kindern liegen die kapillär-venösen Differenzen höher [$2{,}0 \times 10^3/\mu L$ (14,6%)] als bei Erwachsenen [$0{,}2 \times 10^3/\mu L$ (2,7%)]. Die Korrelationswerte liegen zwischen $r = 0{,}98–1{,}0$ [14, 22].

Die kapillären WBC-Werte bei Patienten mit Leukozytopenie (WBC $< 1{,}0 \times 10^3/\mu L$) liegen mit $0{,}1 \times 10^3/\mu L$ über den entsprechenden venösen Werten ($r = 0{,}87$). Bei Patienten mit Leukozytose (WBC $> 11{,}5 \times 10^3/\mu L$) sind die kapillären Werte $1{,}4 \times 10^3/\mu L$ höher als die venösen ($r = 1{,}0$) [22].

Neutrophile Granulozyten, absolut (ANC) Die kapillären ANC-Werte liegen im Mittel um $0{,}68 \times 10^3/\mu L$ (8,9%) über den entsprechenden venösen Werten. Bei Kindern sind diese Differenzen größer [$0{,}91 \times 10^3/\mu L$ (11,0%)] als bei Erwachsenen [$0{,}22 \times 10^3/\mu L$ (4,7%)]. Die Korrelationswerte liegen zwischen $r = 0{,}81–0{,}98$ [13, 14, 23].

Bei Patienten mit Neutrozytopenie (ANC $< 1{,}5 \times 10^3/\mu L$) oder mit Agranulozytose (ANC $< 0{,}5 \times 10^3/\mu L$) liegen die kapillären ANC-Werte $0{,}03 \times 10^3/\mu L$ bzw. $0{,}02 \times 10^3/\mu L$ über den venösen ($r = 0{,}98$ bzw. $r = 0{,}97$) [23].

Thrombozyten (Plt) Die kapillären Plt-Werte sind im Mittel niedriger als die entsprechenden venösen Werte

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Tabelle 1 Vergleich von kapillären und venösen Blutbildparametern (n = 6.475)

Studie	n	Alter	Ges./Pat.	Hb, g/dL	Hct, %	WBC, $10^3/\mu L$	ANC, $10^3/\mu L$	Plt, $10^3/\mu L$	RBC, $10^6/\mu L$	Kapilläre Quelle	Gerät (Hersteller)
[12]	29	Erw.	Ges.	k. A.	+1,0 (+2,4%)	k. A.	k. A.	–33 (–15,2%)	k. A.	Finger	Coulter ZBI (Coulter Electronics)
[12]	40	Kinder	Pat.	k. A.	k. A.	k. A.	k. A.	–7 (–10,9%)	k. A.	Finger	Coulter ZBI (Coulter Electronics)
[13]	30	1 T.	Ges.	+1,6 (+8,3%)	k. A.	k. A.	+2,20 (+21,2%)	k. A.	k. A.	Ferse	Coulter S+ (k. A.)
[13]	30	2 T.	Ges.	+0,8 (+4,4%)	k. A.	k. A.	+1,10 (+11,2%)	k. A.	k. A.	Ferse	Coulter S+ (k. A.)
[14]	40	22-62 J.	Ges.	+0,3 (+2,4%)	+1,2 (+3,1)	+0,6 (+8,2%)	+0,37 (+8,2%)	–22 (–8,8%)	+0,1 (+2,3%)	Finger	Ortho-ELT 800 WS (Ortho Diagnostic Systems)
[15]	10	Erw.	Ges.	+0,5 (+3,4%)	+0,9 (+2,0%)	+0,2 (+3,4%)	+0,30 (+8,8%)	–12 (–5,4%)	+0,1 (+2,1%)	Finger	Cell-Dyn 900 (Sequoia-Turner)
[15]	70	6 Mo.–14 J.	Pat.	+0,4 (+3,5%)	+1,4 (+4,0%)	+0,5 (+10,6%)	+0,20 (+9,1%)	–7 (–2,5%)	+0,2 (+4,0%)	Finger	Cell-Dyn 900 (Sequoia-Turner)
[16]	50	Erw.	k. A.	+0,3 (+2,1%)	+3,4 (+7,7%)	–0,1 (–1,3%)	k. A.	–108* (–58,9%*)	+0,1 (+2,1%)	k. A.	Coulter S7, ULTRA FLO 100* (k. A.)
[10]	16	3 Mo.–14 J.	Pat.	+0,3 (+2,7%)	+1,0 (+2,4%)	+1,6 (+19,2%)	+0,70 (+17,2%)	–3 (–0,6%)	+0,1 (+1,9%)	Finger	Ortho-ELT 800/WS (Ortho Diagnostic Systems)
[17]	60	Erw.	Ges., Pat.	k. A.	k. A.	–0,4 (–5,8%)	–0,10 (–3,6%)	k. A.	k. A.	k. A.	Technicon H1 (Miles Diagnostics)
[18]	18	28 J.	Ges.	k. A.	k. A.	k. A.	k. A.	–19 (–8,1%)	k. A.	Finger	Baker 810 Platelet Analyzer (Baker)
[18]	17	30 J.	Pat.	k. A.	k. A.	k. A.	k. A.	–9 (–14,8%)	k. A.	Finger	Baker 810 Platelet Analyzer (Baker)
[19]	95	1 T.	Ges.	+2,1 (+10,9%)	+6,7 (+9,4%)	+3,4 (+14,7%)	+1,90 (+17,9%)	–34 (–19,0%)	+0,5 (+9,1%)	k. A.	Coulter (STKS)
[20]	24	20–22 J.	Ges.	–0,1 (–0,7%)	+0,4 (+1,0%)	+0,6 (+8,0%)	+0,58 (+11,2%)	–2 (–0,9%)	+0,1 (+0,2%)	Finger	Sysmex F-820 (Sysmex)
[21]	72	6 Mo.–15 J	Pat.	+0,6 (+4,4%)	k. A.	k. A.	k. A.	k. A.	k. A.	Finger	Celldyn (k. A.)
[21]	72	17–73 J.	Ges.	+0,4 (+3,0%)	k. A.	k. A.	k. A.	k. A.	k. A.	Finger	Celldyn (k. A.)
[11]	95	1 T.	Ges.	+2,3 (+11,8%)	+6,6 (+10,7%)	+3,1 (+13,4%)	+2,70 (+23,5%)	–39 (–23,4%)	+0,6 (+10,7%)	k. A.	Coulter (STKS)

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Tabelle 1 (Fortsetzung)

Studie	n	Alter	Ges./Pat.	Hb, g/dL	Hct, %	WBC, $10^3/\mu L$	ANC, $10^3/\mu L$	Plt, $10^3/\mu L$	RBC, $10^6/\mu L$	Kapilläre Quelle	Gerät (Hersteller)
[11]	38	7 T.	Ges.	+1,0 (+5,4%)	+1,7 (+3,5%)	+1,1 (+8,7%)	+0,10 (+2,7%)	–55 (–22,1%)	+0,2 (+3,7%)	k. A.	Coulter (STKS)
[11]	35	14 T.	Ges.	+1,1 (+6,3%)	+2,7 (+5,7%)	+2,6 (+18,6%)	+0,03 (+0,9%)	–58 (–16,9%)	+0,3 (+5,8%)	k. A.	Coulter (STKS)
[11]	32	21 T.	Ges.	+0,7 (+4,8%)	+1,9 (+4,7%)	+1,7 (+15,2%)	+0,11 (+3,9%)	–61 (–19,1%)	+0,2 (+4,8%)	k. A.	Coulter (STKS)
[11]	36	28 T.	Ges.	+1,0 (+7,2%)	+3,0 (+7,7%)	+1,9 (+16,7%)	+0,04 (+1,9%)	–31 (–12,1%)	+0,3 (+7,9%)	k. A.	Coulter (STKS)
[22]	463	18–82 J.	Ges., Pat.	+0,3 (+2,4%)	+2,0 (+5,2%)	+0,2 (+3,5%)	k. A.	–1 (–0,1%)	+0,1 (+2,2%)	Finger	Advia 120 (Bayer)
[23]	447	18–81 J.	Ges., Pat.	k. A.	k. A.	k. A.	–0,07 (–1,0%)	k. A.	k. A.	Finger	Advia 120 (Bayer)

Ges., Gesunde; Pat., Patienten; Erw., Erwachsene; + und –, kapillärer Wert ist höher oder niedriger im Vergleich mit dem venösen Wert; k. A., keine Angaben. Zum Teil gerundete Daten.
*Plt gemessen mit ULTRA FLO 100.

[$26\times10^3/\mu L$ (11,4%)]. Nur in einer Studie lagen die kapillären Werte über den venösen [18]. Auch bei den Plt-Werten waren die kapillär-venösen Differenzen bei Kindern größer als bei Erwachsenen [$33\times10^3/\mu L$ (14,1%) bzw. $19\times10^3/\mu L$ (8,3%)]. Die Korrelationswerte liegen zwischen r = 0,96–0,99 [14, 22].

Bei Patienten mit schwerer Thrombozytopenie (Plt $<20\times10^3/\mu L$) oder mit Thrombozytose (Plt $>367\times10^3/\mu L$) liegen die kapillären Plt-Werte jeweils um $1\times10^3/\mu L$ über den venösen (r = 0,88 bzw. r = 0,98) [22].

Erythrozyten (RBC) Die kapillären RBC-Werte sind im Mittel um $0,2\times10^6/\mu L$ (4,4%) höher als die entsprechenden venösen Werte. Bei Kindern sind die kapillär-venösen Differenzen größer als bei Erwachsenen [$0,3\times10^6/\mu L$ (6,0%) bzw. $0,1\times10^6/\mu L$ (1,8%)]. Die Korrelationswerte liegen zwischen r = 0,96–0,98 [14, 22].

Kapilläre Blutbildanalysen in der klinischen Praxis

Zulässigkeit Bei Qualitätskontrollen gemäß der Laborrichtlinie der Bundesärztekammer (RiLiBÄK) erfolgt die Analyse einer Kontrollprobe. Für die Messung einer Kontrollprobe ist, z.B. beim Hb-Wert, eine relative Abweichung von 4,0% zulässig [24]. Zur Frage der Zulässigkeit der kapillären Blutbildbestimmung wurden eigene Daten [22] erneut ausgewertet. Es wurde dabei angenommen, dass der durch venöse Punktion ermittelte Wert quasi dem einer Kontrollprobe entsprach. Für den Hb-Wert z.B. sollte dann die kapilläre Messung innerhalb einer relativen Abweichung von 4,0% zur entsprechenden venösen Messung liegen (Beispiel: venöser Hb = 10,0 mmol/L, zulässiger kapillärer Hb zwischen 9,6 und 10,4 mmol/L).

Wir fanden dabei, dass fast zwei Drittel (63,7% der kapillär-venösen Differenzen für Hb, Hct, WBC, Plt und RBC innerhalb der zulässigen relativen Messabweichungen lagen. In Anlehnung an die RiLiBÄK sind Abweichungen für Hb-Werte von 4,0% „gestattet“: 69,3% (321/463) der kapillär-venösen Differenzen für Hb-Werte waren kleiner als die maximal zulässigen 4,0%. Für Hct-Werte (maximal 5,0% Abweichung) waren es 54,9% (254/463), für WBC-Werte (maximal 6,5% Abweichung) 43,3% (180/416), für Plt-Werte (7,5%, 8,5% bzw. 13,5% Abweichung – für Plt >300 bis $700\times10^3/\mu L$, >150 bis $\leq300\times10^3/\mu L$ bzw. 40 bis $\leq150\times10^3/\mu L$) 81,0% (345/427) und für RBC-Werte (maximal 4,0% Abweichung) 69,5% (321/462).

Komplikationen Bei Patienten mit Neutrozytopenie bzw. Agranulozytose waren keine lokalen Infektionen nach Blutbildbestimmung durch Punktion der Fingerbeere nachweisbar [23]. Patienten mit schwerer Thrombozytopenie zeigten keine vermehrte Blutung aus der punktierten Fingerbeere [22].

Präzision Als ein Maß der Zuverlässigkeit, d.h. Reproduzierbarkeit einer Methode kann der Variationskoeffi-

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zient (VK) herangezogen werden. Der VK für wiederholte kapilläre Messungen ist höher als der entsprechende venöse Wert: VK_{Hb} = 0,8–4,5% vs. 0,6–4,4% [20–22], VK_{Hct} = 1,1–3,2% vs. 0,8–2,8% [20, 22], VK_{WBC} = 2,6–6,1% vs. 2,4–3,7% [20, 22], VK_{ANC} = 1,9–3,2% vs. 2,4–2,8% [20, 23], VK_{Plt} = 2,5–9,8% vs. 2,3–8,1% [18, 20, 22] und VK_{RBC} = 0,9–3,2% vs. 0,8–2,6% [20, 22].

Validität Mittels der kapillären Blutbildanalyse können Patienten mit Anämie (Hb <12,0 g/dL bzw. <7,5 mmol/L) mit einer Sensitivität von 86% und mit einer Spezifität von 100% im Vergleich zur Standardmethode der venösen Blutentnahme korrekt detektiert werden. Für Patienten mit schwerer Anämie (Hb <9,6 g/dL bzw. <6,0 mmol/L) gelingt dieses durch die kapilläre Messung mit einer Sensitivität von 89% und mit einer Spezifität von 99%. Für Patienten mit Polyglobulie (Hct >48,0% bzw. 0,48 L/L) konnte für die kapilläre Analyse eine Sensitivität von 100% und eine Spezifität von 95% ermittelt werden. Eine Sensitivität von 91% und Spezifität von 100% wiesen die kapillären Messungen für Plt-Werte bei schwerer Thrombozytopenie (Plt $<20\times10^3/\mu L$) auf. Für neutrozytopenische Patienten (ANC $<1{,}5\times10^3/\mu L$) bzw. Patienten mit Agranulozytose (ANC $<0{,}5\times10^3/\mu L$) lagen die Werte für die kapilläre Messung für die Sensitivität bei jeweils 95% und die für die Spezifität bei jeweils 100% [21–23].

Die Adjustierung der kapillär gemessenen Werte durch Addition bzw. Subtraktion der entgegengesetzten Differenzen (siehe Tabelle 1; z.B. bei Hb-Werten: –0,3 g/dL bzw. –0,2 mmol/L) bringt zum Teil eine leichte Verbesserung der Sensitivitäten und Spezifitäten im Sinne einer verbesserten Güte der kapillären Methode [21, 22].

(Anmerkung: Die angegebenen Grenzwerte wurden für die Berechnungen willkürlich festgelegt).

Überbewertung Die kapillär-venösen Differenzen für die Hb-Bestimmung sind bei Messung mit einem Blutbildautomaten geringer als bei Messung mit einem portablen Photometer. In einer aktuellen Studie waren 6,7% aller kapillär-venösen Differenzen für Hb-Werte größer als 1,0 g/dL bzw. 0,6 mmol/L (Patienten und Gesunde bzw. Blutspender; Blutbildautomat). Bei Blutspendern lagen hingegen nur 2,9% der kapillär-venösen Hb-Differenzen (Blutbildautomat) über den o.g. Grenzwerten [22]. Bei der Verwendung von zwei verschiedenen portablen Photometern lagen bei Blutspendern 8,8% bzw. 20,4% der Werte über den o.g. Grenzwerten [25]. Ähnliche Ergebnisse finden sich auch in anderen Studien [21, 26].

Die kapilläre Punktionsstelle – Fingerbeere oder Ohrläppchen – hat einen Einfluss auf die kapillär-venösen Differenzen [25]. So konnte auch anhand eigener Daten gezeigt werden, dass bei Gesunden der kapilläre Hb-Wert aus der Fingerbeere um 0,2 g/dL bzw. 0,1 mmol/L und der Wert aus dem Ohrläppchen um 1,0 g/dL bzw. 0,6 mmol/L höher als der entsprechende venöse Hb-Wert lagen (Jentsch-Ullrich *et al.* 2006; unveröffentlichte Daten).

Diskussion

Kapilläres Blut ist hauptsächlich aus Blut aus Arteriolen zusammengesetzt, weniger aus Kapillaren und kleinen Venen [10]. Durch die kapilläre Blutentnahme tritt in den Arteriolen ein laminarer Blutfluss mit einem zentral schnelleren Strom auf, in dem sich konzentriert Erythrozyten und Leukozyten befinden. Thrombozyten und Plasma befinden sich dagegen mehr am Rand der Blutgefäße – große Zellen werden also bei der kapillären Blutentnahme „bevorzugt“. Das führt zu erhöhten kapillären WBC- und RBC- sowie zu niedrigeren Plt-Werten. Verstärkt wird dieses Phänomen bei Kälteexposition, wahrscheinlich wegen der Blutung aus kontrahierten Arteriolen. Dieses zeigt sich dann z.B. an höheren WBC-Werten aus einem kalten Ohrläppchen [10, 14]. Eine andere Ursache für die höheren kapillären Werte könnte die Hämokonzentration aufgrund der kapillären Flüssigkeitstranssudation sein [10, 11]. Bei Neugeboren wird auch eine Makrozytose diskutiert [10, 13].

Durch den Stich der Lanzette kommt es bei der kapillären Blutentnahme zu einem Gewebeschaden und damit zur Freisetzung von Thromboplastin, hauptsächlich im ersten Blutstropfen. Durch die Thrombozytenaggregation bleiben die Thrombozyten am Stichkanal „hängen“ und die Plt-Werte werden *falsch*-niedrig gemessen. Das, sowie das oben geschilderte Phänomen der kapillären Blutströmung, kann erklären, warum die kapillär gemessen Plt-Werte unter denen der venösen Werte liegen [10, 12, 14, 27, 28]. Der erste Blutstropfen muss daher verworfen werden [27]. Bei den Plt-Werten spielt also die Entnahmetechnik eine besondere Rolle [18], was möglicherweise die unterschiedlich großen Schwankungen der kapillär-venösen Differenzen in den einzelnen Studien erklärt. Die Differenzen lagen zwischen $-1\times10^3/\mu L$ (–0,1%) [22] und $-108\times10^3/\mu L$ (–58,9%) [16]. Thrombozyten-Werte zählen zu den instabilsten hämatologischen Parametern [20]. Die im Vergleich zu anderen hämatologischen Parametern relativ großen Variationskoeffizienten für die Thrombozyten [18, 20, 22] spiegeln möglicherweise einen relativ instabilen Status der Antikoagulation von Blut *in vitro* wider, für den die Thrombozyten am empfindlichsten sind [20]. Das könnte ebenso die unterschiedlich großen Differenzen für Plt-Werte erklären.

Die kapilläre Punktion mittels Lanzette, insbesondere mit einem automatischen System, ist sicher für den Anwender [29]. Der Durchmesser der verwendeten Lanzetten scheint für den Patienten weniger von Bedeutung zu sein, wohingegen jedoch mit dickeren Lanzetten und tieferer Penetration größere Blutvolumina gewonnen werden können [30]. Schmerzfrei ist die Prozedur an der Fingerbeere allerdings nicht [29]. Weniger schmerzhaft sind Punktionen an alternativen Stellen, z.B. am Unterarm [31].

Die kapilläre Blutentnahme wird vom Patienten als weniger traumatisch bzw. schmerzhaft und zudem bequemer als die venöse Abnahme empfunden. Weiter-

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hin bedarf sie keiner aktiven Mitarbeit durch den Patienten (z.B. Hand zur Faust ballen, Arm strecken). Die kapilläre Blutentnahme wird daher von Patienten bevorzugt [2, 9, 32]. Ein weiterer Vorteil der kapillären Punktion ist die problemlose Gewinnung von Blut bei Patienten mit schwierigen peripheren Venenverhältnissen [22, 33].

Unter wirtschaftlichen Gesichtspunkten erweist sich die kapilläre Blutbildbestimmung günstiger als die venöse. So liegen die Materialkosten für die kapilläre Analyse mit Lanzette und Röhrchen 50% unter denen für die venöse Analyse mittels Nadel und Vakutainersystem (0,50 € vs. 1,00 €) [22]. Ein Faktor, der bei einer großen Anzahl an Analysen, wie z.B. in einem hämatologischen Speziallabor, nicht unerheblich ist.

Da für die kapilläre Blutbildanalyse nur wenige Mikroliter Blut benötigt werden, kann so bei Patienten mit multiplen Blutbildanalysen Vollblut im Gegensatz zur venösen Abnahme „eingespart" werden. Bei Patienten mit akuter myeloischer Leukämie sind fast tägliche Blutbildanalysen erforderlich. Der Unterschied im Blutvolumen zwischen kapillärer und venöser Abnahme beträgt für die gesamte Leukämietherapie (Induktions- und Konsolidierungstherapien) ca. 400 mL [22]. Ob durch kapilläre Blutbildanalysen auch Erythrozytenkonzentrate eingespart werden könnten, bleibt unklar.

Bei der Analyse von kapillären Blutbildparametern muss bedacht werden, dass es Unterschiede zwischen den kapillären Quellen (Fingerbeere vs. Ohrläppchen) gibt [25]. Hinsichtlich der Blutbildparameter ist kapilläres Blut nicht gleich kapilläres Blut (siehe auch oben), wohingegen z.B. für die Bestimmung der Blutglukose keine Unterschiede zwischen Blut aus der Fingerbeere und dem Ohrläppchen bestehen [34]. Die kapilläre Blutbildanalyse ist von der Entnahmetechnik [2, 21, 27], von der Haut- bzw. Umgebungstemperatur [10, 14] und wahrscheinlich vom kapillären Blutfluss [12, 28] abhängig. Da nicht alle kapillaren Punktionen unter gleichen, standardisierten Bedingungen erfolgten, sind so womöglich auch die Diskrepanzen der kapillär-venösen Differenzen zwischen den hier zitierten Studien zu erklären.

Die hier vorgestellte Analyse kapillär-venöser Differenzen zeigte, dass die kapillären Blutbildparameter in der Gesamtheit im Mittel um 2,8% über denen der entsprechenden venösen Messungen liegen. Bei Kindern sind die Differenzen zum Teil deutlich größer als bei Erwachsenen. Mit Ausnahme der Plt-Werte waren die kapillär gemessenen Werte höher als die venösen. Die größten kapillär-venösen Differenzen gibt es bei den Plt-, gefolgt von den WBC- und ANC- sowie den Hct-Werten. Die Abweichungen für RBC- und Hb-Werte sind am geringsten (Tabelle 1).

Die kapillären Werte korrelieren sehr gut mit den entsprechenden venösen Werten (mittleres $r = 0{,}98$; eine hohe Korrelation wurde für $0{,}7 < r < 0{,}9$ angenommen). Zumindest bei Erwachsenen ist daher keine Unterscheidung zwischen „kapillärem" und „venösem" Blut erforderlich, wenn von peripherem Blut gesprochen wird. Bei Kindern hingegen sollten auch für kapillär gemessene Werte entsprechende Referenzwerte erstellt werden. Alternativ sollte in der Befunddarstellung zwischen kapillären und venösen Werten differenziert werden, insbesondere vor dem Hintergrund, dass in der Klinik abwechselnd beide Entnahme-/Analysetechniken zum Einsatz kommen [11].

Die kapilläre Blutbildbestimmung ist risikoarm, zuverlässig (mittlerer $VK_{kapillär} = 3{,}5\%$), tlw. gegenüber einer venösen Bestimmung vorteilhafter und erbringt mit hoher Wahrscheinlichkeit *richtig*-positive (mittlere Sensitivität = 92%) sowie *richtig*-negative (mittlere Spezifität = 99%) Werte für Patienten mit Anämie, Polyglobulie, Thrombo- oder Neutrozytopenie im Vergleich zur venösen Blutbildbestimmung.

Es muss allerdings kritisch hinterfragt werden, inwieweit die hier zusammengetragenen Studien vergleichbar sind. Wie bereits dargestellt, sollte zwischen Kindern und Erwachsenen differenziert werden, da sich für beide Gruppen die kapillär-venösen Differenzen zum Teil erheblich unterscheiden. Da unterschiedliche Geräte verwendet wurden und die Spannen der Variationskoeffizienten teilweise relativ groß waren, liegt die Vermutung nahe, dass technisch bedingte Abweichungen bei der Interpretation der Studien zu berücksichtigen sind. In einer Studie [16] wurde für die Messung der Thrombozyten ein anderes Gerät als für alle anderen Parameter verwendet, so dass hier selbst die Analyse der Studiendaten aus dieser separaten Studie schwierig ist. Da der Ort der kapillären Punktion offensichtlich eine Rolle bei der Größe der kapillär-venösen Differenzen spielt, stellt sich die Frage, inwieweit kapilläre Messwerte von Punktionen aus dem Finger und der Ferse verglichen werden können, da diese beiden kapillären Quellen in verschiedenen Studien verwendet wurden. Bislang sind zu dieser Problematik keine Daten verfügbar. In einigen Studien wurden nur Gesunde und in anderen wurden nur Patienten analysiert. Da es Unterschiede in den kapillär-venösen Differenzen zwischen normalen und pathologischen Werten gibt, könnte das bei der Interpretation der zusammengefassten Daten ebenfalls problematisch sein [22]. Nur wenige Studien fassten Gesunde und Patienten zusammen, was die klinische Praxis besser widerspiegelt. Bedacht werden muss ebenfalls, dass die meisten Studien nur wenige Dutzend Messungen analysierten. Die statistische Aussagekraft ist dann eher gering.

Wünschenswert wären daher größere Studien mit einheitlichen Bedingungen bzw. Multicenterstudien, damit die Frage der Wertigkeit der kapillären Blutbildbestimmung in der klinischen Praxis noch genauer beantwortet werden kann.

Wir können jedoch schlussfolgern, dass die kapilläre Blutbildbestimmung in der klinischen Praxis, zumindest bei Erwachsenen, eingesetzt und auch bei Fragen nach Erythrozyten-, Thrombozytentransfusionen, Aderlässen und Neutrozytopenie als gleichwertig zur venösen Analyse angesehen werden kann.

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Interessenkonflikt

Alle Autoren erklären, dass kein Interessenkonflikt besteht.

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Publikation V

Scheinpflug K*, **Schalk E***, Grabert E, Achenbach HJ. Procalcitonin is not useful to discriminate between infectious and non-infectious CRP elevation in patients with non-small cell lung cancer. **Infect Control Hosp Epidemiol 2015**;36(9):1117-1118
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Procalcitonin Is Not Useful to Discriminate Between Infectious and Noninfectious CRP Elevation in Patients with Non–Small Cell Lung Cancer

To the Editor—Lung cancer is a leading cause of cancer-related mortality worldwide. These patients frequently encounter infection during the course of their disease. C-reactive protein (CRP) already achieves high levels in cases with lung cancer without underlying infection, so its diagnostic specificity is limited.[1,2–4] Procalcitonin (PCT) has been demonstrated to discriminate between infectious and noninfectious inflammatory reactions in critically ill patients.[1,5–9] However, clinical data regarding to the utility of PCT in cancer patients with elevated CRP are inconsistent.

Between January and October 2013, PCT and CRP values were measured simultaneously in 100 cases of 63 patients admitted to our department. All of these patients were suffering from non-small cell lung cancer (NSCLC) and presented with CRP elevation. They were evaluated by medical history and physical examination. Patient characteristics were analyzed from medical records. Written informed consent was not acquired due to the retrospective nature of this noninterventional study. All patients underwent chest X-ray and/or thoracic computed tomography as well as laboratory and lung function tests. If necessary, abdominal and/or pleural sonography was performed. A clinically defined infection was diagnosed with a clinically evident source of infection. Microbiological analyses were performed on blood samples, urine specimens, stool samples, sputum samples, bronchoscopy aspirates, or specimens from other body regions suggestive of infection (eg, paracentesis or thoracocentesis). Peripheral venous blood was obtained from all patients. PCT concentrations were measured with an enzyme-linked fluorescent assay (VIDAS B.R.A.H.M.S PCT; Brahms Diagnostica GmbH, Germany). PCT concentrations <0.5 ng/mL were considered normal. CRP concentrations were determined using the CRP latex agglutination test and turbidimetry (COBAS INTEGRA System; Roche Diagnostics, Germany). CRP concentrations <5.0 mg/L were considered normal. Student t test and Fisher's exact test were used for univariate analysis. Correlation between PCT and CRP levels was evaluated using Pearson correlation coefficients (positive correlation with $r > 0$). Receiver operating characteristic [ROC] curve analysis was used to determine the accuracy of discrimination between infectious and noninfectious patients (area under the curve [AUC] <0.5, no diagnostic accuracy; AUC = 0.5, low diagnostic accuracy; AUC = 0.7, moderate diagnostic accuracy; AUC = 0.9, high diagnostic accuracy). Two-sided p-values <0.05 were considered statistically significant.

The mean patient age was 65.6 years, and 69.8% of patients were male. Of the total cohort, 76.2% had NSCLC stage IV and 57.1% had adenocarcinoma. Infections were observed in 79% of cases (infectious group, $n = 79$); none of these patients had sepsis or febrile neutropenia. Among the infectious group of 79 patients, the majority of infections (47 of 79, 59.5%) were caused by pneumonia; 14 (17.8%) were caused by acute exacerbation of chronic obstructive lung disease, 12 (15.2%) were caused by empyema; and 4 (5.0%) were caused by urinary tract infection, and 2 had other causes. The simultaneous elevation of PCT and CRP was not associated with higher risk for infection (odds ratio, 0.8; 95% confidence interval [CI], 0.26–2.55; $P = .93$). The mean CRP value was not significantly higher in the infectious group compared with the noninfectious group (144.6 vs 108.8 mg/L; $P = .09$), whereas the mean PCT value was not significantly higher in the noninfectious group (0.37 vs 0.50 ng/mL; $P = .47$). However, correlation between PCT and CRP values was positive in both the infectious group and the noninfectious group ($r = 0.48$ and $r = 0.80$, respectively). Regarding prediction of infection in NSCLC patients, the areas under the ROC curve for PCT and CRP were 0.46 and 0.59, respectively. Thus, especially PCT was not a discriminator between having and not having infection in this patient cohort.

In clinical practice, CRP and PCT are used for the diagnosis and follow-up of infectious diseases. For the diagnosis and follow-up of sepsis, PCT is superior to CRP[5–7]; however, only few reports are available on lung cancer patients. Tulek et al[2] evaluated CRP and PCT levels in 79 histopathologically proven NSCLC patients and 20 healthy controls. High CRP levels in noninfectious NSCLC patients were mainly related to performance status and were weakly related to tumor size. These investigators concluded that adding serum PCT measurement may contribute to exclude infections in patients with NSCLC.[2] Katsuhiro et al[9] investigated a total of 121 patients with advanced lung cancer treated with chemotherapy. Blood samples were obtained on the first day of fever. CRP and PCT were measured; sputum and blood cultures were collected. PCT-positive patients showed poor outcomes on antibiotic therapy. Furthermore, PCT was able to discriminate infective fever from fever due to inflammation.[9]

The overall aim of this study was to determine the diagnostic utility of PCT to discriminate between infectious and noninfectious CRP elevation in patients with NSCLC.

The simultaneous elevation of PCT and CRP was not associated with infection. Correlation between PCT and CRP values was positive in both the infectious group and the noninfectious group. Thus, PCT was not a discriminator between having and not having infection.

In conclusion, the diagnostic utility of PCT to discriminate between infectious and noninfectious CRP elevation in patients with NSCLC could not be shown. Therefore, not every PCT elevation in NSCLC patients with elevated CRP is associated with infection. This knowledge could be an important factor in antimicrobial stewardship.

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The Slippery Slope of Mandatory Quarantine for Healthcare Workers with Exposure to Ebola—Let's Do the Math

To the Editor—Recently in the United States, attempts have been made to place into quarantine for 21 days asymptomatic healthcare workers with exposure either to patients infected with Ebola virus or to their laboratory specimens. These actions have been taken despite the absence of scientific evidence that asymptomatic persons who may be incubating Ebola virus pose any risk of transmitting the virus to others. The selection of persons for this unwarranted isolation has been seemingly arbitrary, with policies differing from state to state. This procedure is reminiscent of some of the irrational early responses to the HIV epidemic, driven by fear, in which patients with AIDS were kept in strict isolation and were sometimes shunned in the community.[1,2]

Fortunately, the majority of healthcare workers in the United States who are or who have been providing care or other services for Ebola patients have not been placed into quarantine. But what if some state governors or other authorities decided to actually enforce a policy in which all healthcare workers who have cared for Ebola patients either in West Africa or in the United States were quarantined for 21 days?

Imagine the following scenario. If 10 hospital workers were involved each day with a single patient with Ebola in the United States (a conservative estimate), after 2 consecutive days of care, these individuals would have to be sent into a 21-day quarantine, because the incubation period extends from 2 to 21 days. Of course, as a consequence, other hospital workers would need to take their places. If we assume that the patient with Ebola would be hospitalized for 14 days (also a conservative estimate), then 60 additional hospital workers would eventually be needed to provide care for this 1 patient—a total of 70 healthcare workers. The 70 healthcare workers would eventually spend a total of 1,470 days in quarantine, more than 4 years in total days.

Publikation VI

Penack O, Becker C, Buchheidt B, Christopeit M, Kiehl M, von Lilienfeld-Toal M, Hentrich M, Reinwald M, Salwender H, **Schalk E**, Schmidt-Hieber M, Weber T, Ostermann H. Management of sepsis in neutropenic patients: 2014 updated guidelines from the Infectious Diseases Working Party of the German Society of Hematology and Medical Oncology (AGIHO). **Ann Hematol 2014**;93(7):1083-1095

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REVIEW ARTICLE

Management of sepsis in neutropenic patients: 2014 updated guidelines from the Infectious Diseases Working Party of the German Society of Hematology and Medical Oncology (AGIHO)

Olaf Penack · Carolin Becker · Dieter Buchheidt · Maximilian Christopeit · Michael Kiehl · Marie von Lilienfeld-Toal · Marcus Hentrich · Marc Reinwald · Hans Salwender · Enrico Schalk · Martin Schmidt-Hieber · Thomas Weber · Helmut Ostermann

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Abstract Sepsis is a major cause of mortality during the neutropenic phase after intensive cytotoxic therapies for malignancies. Improved management of sepsis during neutropenia may reduce the mortality of cancer therapies. Clinical guidelines on sepsis treatment have been published by others. However, optimal management may differ between neutropenic and non-neutropenic patients. Our aim is to give evidence-based recommendations for haematologist, oncologists and intensive care physicians on how to manage adult patients with neutropenia and sepsis.

Keywords Guideline · Sepsis · Neutropenia · Management

Clinical significance and methods

Sepsis is a leading cause of mortality in patients with haematologic malignancies or solid tumours undergoing intensive cytotoxic chemotherapy [29, 168]. Therefore, optimization of diagnosis and management of sepsis could improve outcome of intensive cytotoxic therapies. A number of prior

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guidelines on the management of sepsis have been published [15, 41, 43, 60, 96, 106, 132, 137]; however, none of these guidelines specifically address diagnosis and management of sepsis in neutropenic patients.

These updated guidelines were written to provide guidance on diagnosis and management of sepsis in the neutropenic host. First, a panel of 13 experts in the field of infectious diseases in haematology and oncology agreed to participate in preparing the guidelines. Second, the guidelines were thematically divided into six subtopics. Then, subcommittees of two to four authors were created, being responsible for literature search in one of the subtopics. We systematically searched Medline for English language publications up to June 2013 using the key terms: sepsis and one of the following: neutropenia, bacteraemia, bloodstream infection (bacteraemia), definition, epidemiology, incidence, risk factors, prognosis, treatment, antibiotic, antifungal, cardiovascular, pulmonary failure, ventilation, renal dysfunction, renal failure, dialysis, haemofiltration, nutrition, hyperglycaemia, steroid, coagulation, growth factor, immunoglobulin and transfusion. Meeting abstracts were not included; however, references generated from published guidelines and reviews were also investigated. The consensus process was performed as an email- and meeting-based discussion group. In a second step, the manuscript draft was peer reviewed by the review committee of the Infectious Diseases Working Party of the German Society of Hematology and Medical Oncology (AGIHO) on October 1st, 2013. In a third step, the guidelines were approved by the assembly of the members on October 20th, 2013. Criteria used to quote levels and grades of evidence are as outlined in Table 1 [88]. The first draft of the manuscript was written by the subcommittees. The final version of the manuscript was prepared by the corresponding author and has been approved by all authors.

Table 1 Categories of evidence used in this guideline [88]

Category, grade	Definition
Strength of recommendation	
A	Good evidence to support a recommendation for use
B	Moderate evidence to support a recommendation for use
C	Poor evidence to support a recommendation
D	Moderate evidence to support a recommendation against use
E	Good evidence to support a recommendation against use
Quality of evidence	
I	Evidence from ≥1 properly randomized, controlled trial
II	Evidence from ≥1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 centre); from multiple time-series; or from dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees

Definitions

A formal definition of sepsis has long been tried by several researchers and must lack specificity given the broad spectrum of reactions to pathogens.

We suggest using the diagnostic consensus criteria for sepsis adapted to neutropenic patients (Table 2) [97, 98]. In neutropenic patients, the white blood cell count cannot be used as a criterion to define sepsis. The definitions of severe sepsis and septic shock remain unchanged and refer to sepsis-induced organ dysfunction (Table 3).

Table 2 Diagnostic criteria for sepsis during neutropenia [97, 98]. In neutropenic patients, cytopenia cannot be used as a criterion to define sepsis

General parameters
Fever (core temperature >38.3 °C)
Hypothermia (core temperature <36.0 °C)
Heart rate (>90 bpm or >2 SD above the normal value for age)
Tachypnoea (>30 bpm)
Altered mental status
Significant edema or positive fluid balance (>20 mL/kg over 24 h)
Hyperglycaemia (plasma glucose >110 mg/dL or >7.7 mmol/L) in the absence of diabetes
Inflammatory parameters
Plasma C reactive protein or plasma procalcitonin (>2 SD above the normal value)
Haemodynamic parameters
Arterial hypotension (systolic blood pressure <90 mmHg, mean arterial pressure <70 mmHg, or a systolic blood pressure decrease >40 mmHg in or <2 SD below normal for age)
Mixed venous oxygen saturation (>70 %)
Cardiac index (>3.5 L/min/m^2)
Organ dysfunction parameters
Arterial hypoxaemia (PaO2/FIO2 <300)
Acute oliguria (urine output <0.5 mL/kg/h for ≥2 h)
Creatinine increase (≥0.5 mg/dL)
Coagulation abnormalities (international normalized ratio >1.5 or activated partial thromboplastin time >60 s)
Ileus (absent bowel sounds)
Hyperbilirubinemia (plasma total bilirubin >4 mg/dL or 70 mmol/L)
Tissue perfusion parameters
Hyperlactataemia (>3 mmol/L)
Decreased capillary refill or mottling

Table 3 Definitions of severe sepsis and septic shock

Severe sepsis	Sepsis with new signs of organ dysfunction or a decrease in organ perfusion (lactate acidosis, oliguria (<30 mL/h or <0.5 mL/kg/h), hypotension (<90 mmHg or decrease of >40 mmHg), mental alteration)
Septic shock	Severe sepsis and hypotension persistent despite adequate fluid substitution and exclusion for other reasons for hypotension

Incidence

Systematic data evaluating the overall incidence of neutropenic sepsis in cancer patients are lacking. The incidence of febrile neutropenia and bacteraemia has been studied more in detail, albeit the majority of studies did not use uniform definitions, include at least partly non-neutropenic patients and focus on distinct patient subgroups. Patients with solid tumours develop febrile neutropenia in around 10–40 %, but this complication might occur in more than 80 % of patients with haematological malignancies [1, 54]. In patients with indwelling central venous catheters (CVC), febrile neutropenia is frequently caused by catheter-related or catheter-associated bacteraemia with an incidence of around 10–20/1,000 neutropenic days [16, 34]. Likewise, translocation of gut organisms, such as vancomycin-resistant enterococci (VRE), may cause bacteraemia and, ultimately, sepsis in neutropenic cancer patients in up to 40 % of colonized patients [30, 101, 154].

It can be assumed that >50 % of patients with febrile neutropenia or bacteraemia develop sepsis using the consensus definition. Severe sepsis and septic shock, which have been investigated in a few prospective and retrospective analyses, might occur in up to 20–30 and 5–10 % of patients with febrile neutropenia, respectively [6, 78, 81, 95, 109, 112].

The increasing numbers of elderly patients undergoing intensive treatment modalities and patients infected with treatment-resistant organisms led to the assumption that the frequency of neutropenic sepsis will increase [11].

Risk factors and prognosis

Prospective data of risk factors and prognosis for sepsis in adult neutropenic patients are rare [6, 63, 78].

Risk factors for bacteraemia

There are few data on risk factors for bacteraemia during neutropenia. Apostolopoulou et al. observed a significant higher rate of bacteraemia, potentially resulting in sepsis, in patients with neutropenia <0.5 g/L. Additionally, acute myeloid leukaemia, a prolonged hospital stay, a Hickman catheter, or pre-treatment with antibiotics, chemotherapy or surgery were significantly associated with BSI in haematological and oncological patients [16].

Risk factors for development of severe sepsis

The presence of hypophosphataemia (<0.8 mmol/L) and hypoproteinaemia (<62 g/L) have been identified as risk factors for severe sepsis in febrile neutropenia [78]. The development of septic shock in febrile neutropenia is independently predicted by the presence of pulmonary infection, tachypnoea, increased serum levels of procalcitonin (≥1.5 ng/mL), high lactate levels [6, 109], decreased serum levels of bicarbonate (<17 mmol/L), antithrombin (<70 %) or factor VIIa (<0.8 ng/mL) [63, 78, 109, 135]. A low Multinational Association for Supportive Care in Cancer (MASCC) risk index score of <21 is associated with an increased risk for septic shock in febrile neutropenic patients [6].

Prognosis

Prolonged neutropenia <0.5 g/L or the delayed initiation of antibiotics is associated with poor clinical outcome in neutropenic patients with sepsis [5, 103]. Severe sepsis and septic shock negatively influence outcome [64, 95, 162]. A recent prospective study demonstrated mortality rates of 35 % in severe sepsis, 47 % in septic shock and 85 % in multi-organ failure in patients with haematological malignancies [19]. Factors that were significantly associated with hospital survival included remission of malignant tumour and time to intensive care unit (ICU) admission <24 h. Negative predictive factors for hospital survival were as follows: allogeneic haemopoietic stem cell transplantation (HSCT), poor performance status, invasive pulmonary aspergillosis, malignant organ infiltration and acute respiratory failure. In another study, Legrand et al. identified prognostic factors for neutropenic patients with severe sepsis or septic shock: The appearance of acute non-infectious complications, of neurological, respiratory or hepatic dysfunction, the need for vasopressor therapy, or older age increased the mortality. On the other hand, the early removal of a CVC and combined antibiotic therapy were associated with higher survival [95].

Microbiology

Blood cultures as part of the usual microbiological work-up as per local protocol (including urine cultures, stool cultures etc.) remain the gold standard for the diagnosis of bacteraemia and fungaemia. Blood cultures should be standardized in terms of volume, culture sets, frequency, processing, interpretation and reporting.

However, although most episodes of febrile neutropenia are assumed to be caused by an infection, blood cultures are positive in less than 30 % of febrile neutropenic episodes [48]. Typical organisms causing sepsis during neutropenia are summarized in Table 4.

The epidemiology of gram-positive versus gram-negative bacteraemia varies in different countries [115]. In contrast to other countries, Germany has a predominance (>50 %) of gram-positive bacteria as the cause for febrile neutropenia [45]. Knowledge about the local epidemiology is essential for a rational choice of empirical antibiotic therapy as already pointed out by others. This is particularly true for colonization with resistant bacteria, since these have been associated with an increased risk of bacteraemia with these pathogens [101].

PCR-based methods to detect bacterial and fungal DNA have yet to be validated in larger cohorts [8, 93, 105, 120, 164]. In contrast, PCR-based methods play a definitive role in the diagnosis of viral infections, which may cause sepsis in severely immunocompromised patients [71, 102, 129].

Treatment

Antimicrobial treatment

Empirical antimicrobial treatment using broad-spectrum antibiotics must be started immediately in neutropenic patients with sepsis (AII). A large retrospective study including more than 2,000 patients showed that during severe sepsis, effective antimicrobial administration within the first hour of documented hypotension is associated with increased survival [95]. In this study, each hour of delay in antimicrobial administration over the ensuing 6 h was associated with an average decrease in survival of 7.6 % [95].

Table 4 Typical pathogens during bacterial sepsis in neutropenic patients

Origin	Frequent pathogens
Unknown	Coagulase-negative *Staphylococci*, *Escherichia coli*, *Enterococcus* species
Lung	*Pseudomonas aeruginosa*, *Streptococcus pneumoniae* (pneumococci), *Viridans* (alpha-haemolytic) *streptococci*, *Acinetobacter species*
Abdomen	*Escherichia coli*, *P. aeruginosa*, *Clostridium spp.*, *Enterococcus spp.*, *Klebsiella* species
Urogenital	*Escherichia coli*, *Klebsiella* species, *Pseudomonas aeruginosa*
Soft tissue	*Staphylococcus aureus*, alpha-haemolytic *streptococci*
CVC	Coagulase-negative *Staphylococci*, *Coryneform bacteria*, *Propionibacterium* species, *Candida albicans*, *Candida tropicalis*, *Candida parapsilosis*, *Stenotrophomonas maltophilia*

CVC central venous catheter

In neutropenic patients with sepsis, results from randomized controlled trials are lacking, and recommendations are based on study results from non-neutropenic patients as well as on expert opinions. We recommend initial treatment with meropenem or with imipenem/cilastatin or with piperacillin/tazobactam (AIII).

Meta-analyses show that a combination treatment with aminoglycosides increased renal toxicity without improving efficacy in neutropenic patients with bacteraemia [125–127]. However, in a retrospective study, the use of β-lactam antibiotic/aminoglycoside combinations were associated with superior outcome, as compared with single-agent antimicrobial treatment, in neutropenic patients with severe sepsis and septic shock [95]. Another retrospective study showed reduced hospital mortality in non-neutropenic patients with severe bacterial sepsis after combination therapy comprising at least two antibiotics of different mechanisms versus antibiotic monotherapy [92]. Taken together, a combination treatment with an aminoglycoside may be considered in neutropenic patients with septic shock and severe sepsis (BIII).

Knowledge of local microbiology data is crucial for the choice of antimicrobial agents. Importantly, local resistance patterns as well as colonization with resistant bacteria have to be considered [101]. If infection due to bacteria with frequent resistance to carbapenems or piperacillin/tazobactam is suspected, a specific antibiotic should be added (BIII). If a specific organ infection is suspected, antibiotic therapy should be adapted accordingly. Recommendations on antifungal therapy during neutropenia were recently published by our group and by others [55, 104, 118, 157].

Treatment of cardiovascular insufficiency

Aggressive and early goal-directed treatment aiming at restoration of cardiovascular function is crucial [42, 140]. To restore adequate cardiac filling pressures and to maintain adequate organ perfusion (goal, mean arterial pressure 65 mmHg, central venous pressure 8–12 mmHg, pulmonary wedge pressure 12–15 mmHg, urinary output 0.5 mL/kg/h and central venous or mixed venous oxygen saturation 70 %), crystalloid fluids are recommended as the initial fluid of choice in severe sepsis and septic shock. Compared to crystalloids, randomized controlled trials did not show beneficial effects of colloids, especially hydroxyethyl starches for fluid resuscitation in sepsis [32, 62, 128]. However, the risk of acute kidney injury requiring renal replacement therapy is substantially increased by the use of hydroxyethyl starch (EI) [128].

While a large randomized study indicated that albumin administration was safe and equally effective as 0.9 % saline [50], a meta-analysis of data from 17 randomized trials found that the use of albumin-containing solutions for fluid resuscitation of patients with sepsis was associated with lower mortality compared with crystalloids [40]. However, in a

multicenter randomized trial (n=794) in patients with septic shock, the use of albumin therapy did not significantly reduce 28-day mortality compared to saline solution [50]. Thus, albumin-containing solutions may be used for fluid resuscitation of patients with sepsis and septic shock (CII).

If a sufficient mean arterial pressure (>65 mmHg) cannot be achieved by volume substitution in a reasonable time frame, treatment with vasopressors is indicated. The drug of choice to elevate the vasotonus is norepinephrine in a dose of 0.1–1.3 μg/kg/min (BII) [48].

In retrospective and small prospective studies, vasopressin (0.01–0.04 U/min) increased urinary output and creatinine clearance compared to norepinephrine [51–53]. However, in the large VASST trial, no reduction in 28-day mortality was found in the vasopressin group, and there is currently poor evidence to support the use of vasopressin in septic shock (CI) [54]. In case of sepsis-related myocardial depression leading to low cardiac output despite adequate volume substitution, vasopressor treatment with dobutamine should be instituted (AII) [140]. Of note, results from an observational study suggest that dopamine administration may be associated with increased mortality rates in septic patients [142].

Bicarbonate therapy is not recommended for the purpose of improving haemodynamics or reducing vasopressor requirements in the presence of lactic acidosis and pH >7.15 (DII) [38, 108].

Treatment of pulmonary failure

Pneumonia leading to acute respiratory failure is a major cause of sepsis in neutropenic cancer patients [19, 20]. On the other hand, severe sepsis may lead to acute lung injury/acute respiratory distress syndrome (ARDS) [145].

In cooperative and awake patients with mild to moderate pulmonary failure, non-invasive positive pressure ventilation should be preferred (AII) [19, 37, 69, 70, 145]. Both non-invasive treatment options led to a significant reduction of intubation compared to the control group in neutropenic cancer patients [19, 73]. An early start of non-invasive ventilation, prior to development of severe hypoxaemia, is favourable (BII) [21]. Failure of non-invasive ventilation occurs in half of the critically ill haematologic patients and is associated with an increased mortality [21]. Predictors of non-invasive ventilation failure are as follows: high respiratory rate, short time between admission and non-invasive ventilation [21], vasopressor use, renal replacement therapy and the development of ARDS [3].

In moderate to severe respiratory insufficiency, endotracheal intubation and mechanical ventilation are necessary. Survival is positively correlated to the experience of the ICU with haematologic and oncologic patients [171]. In a retrospective multicenter study of allogeneic HSCT recipients admitted to the ICU, mechanical ventilation was associated with low survival rates [107]. These data were confirmed in a prospective study [19].

Percutaneous extracorporeal membrane oxygenation showed to be a rescue therapy to bridge hypoxemia due to ARDS in patients with oncological or malignant haematological diseases [59, 99, 111]. Further studies are needed in this field, before a recommendation can be given.

Management of renal dysfunction

Acute kidney injury (AKI) develops in approximately 20 % of patients with severe sepsis and 50 % with septic shock. The combination of acute renal failure and sepsis is associated with a 70 % mortality [144]. Specific data for neutropenic patients are lacking, and recommended management of renal dysfunction is not different from non-neutropenic patients.

In short, no clear guidelines on the timing of the initiation of renal replacement therapy (RRT) can be given. Regarding the mode of replacement therapy, intermittent haemodialysis and continuous renal replacement therapies (CRRT) are equivalent in patients with sepsis and AKI (BI) [57, 58, 84, 100, 134, 155]. In haemodynamically unstable patients, control of fluid balance may be facilitated by the use of CRRT (BII) [42, 79].

Increasing the frequency of RRT is thought to reduce the rate of uremic complications and improve outcome in patients with AKI. However, randomized controlled studies showed conflicting results [42, 79, 138]. A recent meta-analysis indicates that high-dose RRT in critically ill patients with AKI does not improve patient survival or recovery of renal function as compared with less-intensive regimes [75, 122, 160]. Thus, no firm recommendations can be given for the increased frequency of RRT (CI).

In patients undergoing renal replacement therapy, the dosage of antimicrobial substances should be carefully checked and adjusted [86]. The use of low-dose dopamine for protection of renal function is not recommended (EI) [26, 85].

Nutrition and control of metabolic functions

Caloric intake

Most recommendations reported are extrapolated from analyses in critically ill and well-nourished patients without neutropenia. Enteral nutrition is preferred over parenteral nutrition unless contraindicated or impossible, as it is associated with a lower rate of infections (BII) [67]. Enteral caloric intake should be calculated according to the phase of sepsis: during the initial phase of sepsis, the supply of >20–25 kcal/kg ideal bodyweight (IBW) has been associated with inferior outcome in one observational study (DIII) [91]. During recovery, 25–30 kcal/kg IBW should be provided (BIII) [89, 149].

Supplements

As reproducible mortality benefits for supplementation of arginine [31, 56], omega-3 fatty acids [24, 130, 131] and combined formulations [27, 56, 68] in patients with severe sepsis and septic shock are lacking, we do not recommend general use of either of these supplements (DII). Substitution of glutamine did not positively affect the primary survival endpoint in two randomized trials including together over 1,000 patients with sepsis [9, 66] and significantly increased in-hospital and 6-month mortality in the REDOXS study [66]. Therefore, glutamine substitution cannot be recommended (EI).

Two recent large randomized two-factorial trials compared the influence of lower doses of selenium substitution to placebo in critically ill patients [9, 66]. In these trials including 282 and 826 septic patients, respectively, selenium substitution had no effect on mortality [9, 66]. In a smaller trial, higher dose selenium substitution (1,000 μg daily) was associated with mortality reduction only in the per protocol analysis [10]. In a meta-analysis including nine trials with septic patients, selenium substitution was associated with lower mortality, especially in patients receiving selenium in higher doses (≥1,000 mg daily) and for ≥6 days [74]. Thus, further clinical trials regarding the adequate dosing and treatment duration are needed before treatment with selenium can be recommended (DI).

Hyperglycaemia

Hyperglycaemia in patients requiring intensive care is associated with an inferior outcome [23, 47]. Results of clinical trials in patients with severe sepsis and septic shock [13, 32] as well as clinical trials [51, 133, 158] including patients with underlying malignant disease [158] and a meta-analysis [61] in mixed populations of critically ill patients failed to show a benefit of intensified insulin therapy. These results are in contrast to the results of the initial trial by van den Berghe et al. [159] which had suggested a benefit of a tight blood glucose control (blood glucose level of 4.4–6.6 mmol/L (80–120 mg/dL)). Thus, we do not recommend intensive insulin therapy aiming at a blood glucose level of 4.4–6.6 mmol/L (80–120 mg/dL; EI). Based on these data and international guidelines [44, 76, 137], we recommend to maintain blood glucose levels at least ≤9.9 mmol/L (≤180 mg/dL; BIII). A high variability of blood glucose levels in septic patients should be avoided, as this is associated with increased mortality (BIII) [7, 22, 46].

Treatment with corticosteroids

Replacement of an impaired adrenal reserve and anti-inflammatory properties is a rationale for studying corticosteroids as an adjunctive to sepsis therapy. The use of corticosteroids in sepsis has not been studied in a prospective fashion for neutropenic patients. In the CORTICUS trial, 84 cancer patients were included; however, no subgroup analysis of these patients has been published [35].

High-dose corticosteroid treatment (>300 mg hydrocortisone per day)

Randomized controlled trials and meta-analyses reported on increased overall mortality and increased mortality from secondary infections in non-neutropenic patients with sepsis receiving high-dose steroids [28, 39, 113, 153, 163]. Thus, high-dose corticosteroids are not recommended as treatment of sepsis (EI).

Low-dose corticosteroid treatment (≤300 mg hydrocortisone per day)

Substitutive doses of hydrocortisone during sepsis remain controversial. Annane et al. identified a benefit in 28-day mortality for the treatment group [14]. The CORTICUS trial did not reveal a difference in 28-day mortality between treatment and placebo and found a higher incidence of hyperglycaemia, hypernatraemia and secondary infections in the treatment group [152]. The results of meta-analyses have been similarly contradictory. Some meta-analyses support the use of low doses of hydrocortisone [12, 114, 150], while others do not support the use of low doses of hydrocortisone [80, 116, 146]. Newer data from three observational studies with a total of over 25,000 patients from sepsis registries showed no mortality benefit for low-doses steroids [25, 33, 49]. Thus, we do not recommend the routine use of substitutive doses of hydrocortisone in neutropenic patients with sepsis (DI). However, low-dose corticoid treatment may be considered in patients with insufficient restoration of blood pressure levels despite adequate fluid resuscitation and vasopressor treatment (BII) [124]. The results of three ongoing large randomized controlled trials will hopefully further clarify the role of low-dose steroids in severe sepsis.

Treatment with coagulation inhibitors

In sepsis, the coagulation cascade is frequently activated at early time points. As thrombocytopenia and an increased risk of bleeding are frequently present in patients with cancer and chemotherapy, attempts to positively influence coagulation in patients with neutropenia have to be exerted carefully.

Heparin

Retrospective trials in patients with sepsis have shown a reduction in mortality using unfractionated heparin [170].

The prospective randomized controlled HETRASE study has investigated treatment with low-dose heparin (500 IU/h during 7 days) in 319 patients with sepsis [77]. No influence on 28-day all-cause mortality was found. This trial was characterized by low mortality, perhaps explained by liberal inclusion criteria. Treatment was discontinued when the partial thromboplastin time exceeded 60 s. Under these conditions, the administration of low-dose heparin was safe. Further trials including more patients and defined subgroups are needed before recommendations for the use of heparin in neutropenic sepsis can be made (CI).

Antithrombin

Antithrombin has anti-thrombotic and anti-inflammatory properties. Based on the negative data from the KyberSept trial [165], a Cochrane analysis [4], and subgroup analyses of several trials [72, 87, 167], we do not recommend the routine use of antithrombin as treatment of neutropenic sepsis in the absence of disseminated intravascular coagulation (DIC; DI). However, in patients with DIC and sepsis, the administration of antithrombin may be considered (BII) [87].

Activated protein C (APC)

In response to the results of the PROWESS-SHOCK trial [136], APC is no longer in use.

Thrombomodulin

Thrombomodulin decreases thrombus formation, activates protein C and has anti-inflammatory properties [2, 119, 148, 161]. Results from a phase IIb study suggested efficacy in patients with sepsis and suspected DIC [161]. However, safety and efficacy is not known in cytopenic patients, and no evidence-based recommendation can be made.

Cytokines and haematopoietic growth factors (G-CSF, GM-CSF)

The central role of cytokines during the hyper- and anti-inflammatory phases of sepsis prompted clinical studies on the use of cytokines and cytokine inhibitors as therapeutic agents. However, studies on the therapeutic efficacy of IL-1 receptor antagonist, TNF-inhibitors, TLR-4 inhibitors and interferon gamma did not show a clinical benefit (EI) [52, 53, 117, 121, 139].

The known effect of G-CSF and GM-CSF in increasing the number of circulating granulocytes was the rationale for clinical studies assessing their role as additional therapy to antibiotics in febrile patients with chemotherapy-induced neutropenia. A meta-analysis of 13 randomized controlled trials including a total of 1,518 patients showed that G-CSF/GM-

Table 5 Summary of treatment recommendations given by the Infectious Diseases Working Party of the German Society of Hematology and Medical Oncology (AGIHO)

Recommendation	Evidence level
Antimicrobial treatment	
Initial treatment with meropenem or with imipenem/cilastatin or with piperacillin/tazobactam	AIII
A combination treatment with an aminoglycoside in neutropenic patients with septic shock and severe sepsis may be considered	BIII
Cardiovascular insufficiency	
Albumin-containing solutions may be used in patients with sepsis and septic shock	CII
The drug of choice to elevate the vasotonus is norepinephrine	BII
In case of sepsis-related myocardial depression leading to low cardiac output despite adequate volume substitution, vasopressor treatment with dobutamine should be instituted	AII
Treatment of pulmonary failure	
Non-invasive positive pressure ventilation (CPAP or bilevel positive airway pressure) should be preferred if possible in patients without hypotension or altered mental status	AII
An early start of non-invasive ventilation, prior to development of severe hypoxaemia, is favourable	BII
Management of renal dysfunction	
Intermittent haemodialysis and continuous renal replacement therapies are equivalent	BI
No firm recommendations can be given for the use of increased doses of renal replacement therapy	CI
Low-dose dopamine for protection of renal function is not recommended	EI
Nutrition and control of metabolic functions	
Enteral nutrition is preferred over parenteral nutrition	BII
During initial phase of sepsis, energy supply should not exceed 20–25 kcal/kg ideal bodyweight (IBW)	DIII
During recovery, 25–30 kcal/kg IBW should be provided	BIII
We do not recommend general use of arginine, omega-3 fatty acids and combined formulations in patients with severe sepsis and septic shock	DII
Glutamine substitution cannot be recommended in patients with severe sepsis and septic shock	EI
Further clinical trials regarding the adequate dosing and treatment duration are needed before treatment with selenium can be recommended	DI
Aiming at strictly normal blood glucose level of 4.4–6.6 mmol/L (80–120 mg/dL) is not recommended	EI
Blood glucose levels should be kept ≤9.9 mmol/L (≤180 mg/dL) in septic neutropenic patients	BIII
A high variability of blood glucose levels in septic patients should be avoided, as this is associated with increased mortality	BIII
Corticosteroids	
High-dose corticosteroids should not be used in neutropenic or non-neutropenic septic patients	EI
The routine use of substitutive doses of hydrocortisone in neutropenic patients with sepsis is not recommended	DI
Low-dose corticoid treatment may be considered in patients with insufficient restoration of blood pressure levels despite adequate fluid resuscitation and vasopressor treatment	BII

Table 5 (continued)

Recommendation	Evidence level
Treatment with coagulation inhibitors	
Further trials on the use of low-dose heparin (500 IU/h for 7 days) are needed before recommendations can be made	CI
Routine use of antithrombin is not recommended as treatment of sepsis in neutropenic patients antithrombin may be considered during DIC and sepsis	DI BII
Growth factors and immunoglobulins	
The routine additional use of G-CSF or GM-CSF as standard treatment of sepsis in neutropenia is not recommended	DI
There is moderate degree of evidence to support the use of i.v. immunoglobulins in sepsis	BII
Transfusion management	
The cut-off for substitution of platelets is often set to a higher value (platelets 20,000/μL instead of 10,000/μL during sepsis)	BIII
A transfusion trigger of <9 g/dL haemoglobin during neutropenic sepsis is recommended	BIII

CSF effectively reduces the time to neutrophil recovery and the length of hospitalization [36]. However, despite a marginally significant benefit for the use of G-CSF/GM-CSF in reducing infection-related mortality, overall mortality appeared not to be influenced. Even though this meta-analysis reported only mild side effects associated with G-CSF/GM-CSF treatment (bone pain, joint pain and flue-like symptoms), there is an accumulating number of publications on respiratory deterioration with ARDS during G-CSF/GM-CSF-induced neutropenia recovery [17, 18, 83, 147]. In non-neutropenic patients with pneumonia or sepsis, G-CSF/GM-CSF appeared to be safe but ineffective in reducing mortality rates or complications from infection [141, 169]. On the basis of the current studies and reports, we do not recommend the routine additional use of G-CSF or GM-CSF to standard treatment of sepsis in neutropenia (DI). Although GM-CSF seems to be able to reverse sepsis-induced immune paralysis, it is currently not available for treatment in the EU [110, 143].

Immunoglobulins

The treatment of sepsis in neutropenia with i.v. immunoglobulin's (IVIG) did not show a significant difference in survival in a randomized controlled trial [65]. A meta-analysis on trials of IVIG in patients with sepsis identified 20 trials eligible for evaluation [156]. Compared with placebo or no intervention, the use of polyclonal IVIG was associated with a survival benefit (relative risk 0.74). The number needed to treat to save one life was nine. Interestingly, more severely ill patients, those receiving treatment for more than 2 days and those receiving ≥1 g/kg, seemed to benefit most. As most of the individual trials analyzed had flaws in design, were rather small or performed during a time when the standard of care for septic patients was different from today; the authors conclude that a large randomized controlled trial should be performed [156]. Three additional meta-analyses investigated the use of IVIG during sepsis and had similar outcomes [90, 94, 151]. In conclusion, there is moderate degree of evidence to support the use of IVIG in sepsis (BII).

Granulocyte transfusions

Several case reports and phase I/II studies have shown some efficacy of granulocyte transfusions in patients with infections during severe neutropenia including patients with invasive fungal infections. However, complications have been reported as well, e.g. fatal CMV infection, allo-immunization and the transfusion-related acute lung injury syndrome. Recently, a randomized controlled trial has been published [101]. It failed to show any beneficial effect, but it was small, and the authors discussed several problems associated with the design of the trial. A meta-analysis of the use of granulocyte transfusion in neutropenic neonates yielded equivocal results [123]. Taken together, at this time, no recommendation can be given on the use of granulocyte transfusions outside of clinical trials.

Transfusion management in sepsis

The recommendations for substituting platelets or packed red blood cell in neutropenic patients can be applied to those patients developing sepsis as well. However, the cutoff for substitution is often set to higher values (platelets 20,000/μL instead of 10,000/μL; BIII). A randomized trial in children with sepsis showed no difference in outcome between a liberal (<9.5 g/dL) and a restrictive (<7 g/dL) trigger for erythrocyte transfusion [82]. Although there are no prospective randomized studies available, we recommend a transfusion trigger of <9 g/dL haemoglobin level to optimize tissue oxygenation (there was no consensus inside the panel of experts regarding the strength of recommendation) [166].

Summary of recommendations

Table 5 summarizes treatment recommendations given by the AGIHO.

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Publikation VII

Schalk E, Tammer I, Heidel FH. Germ and hematology: underlying disease influences diversity of germ spectra and antibiotic therapy. **Infect Control Hosp Epidemiol 2014**; 35(2):208-210

components. For MRSA, the 2 most common IPC interventions were hand hygiene campaigns (100 [49%] of 204) and contact isolation (84 [41.2%] of 204); 18 (8.8%) of 204 reported use of IPC bundle C, and 10 (4.9%) of 204 reported use of IPC bundle D. Compliance ranged from 20% to 94% for all IPC components. By multivariate analysis, no significant reduction in MDR *A. baumannii* or MRSA infection was evident among hospitals with less than 60% IPC compliance. Over the 1-year period, there were significant reductions in MDR *A. baumannii* among hospitals with 60%–80% compliance to IPC bundles A and B and significant reduction in MRSA among hospitals with 60%–80% compliance to IPC bundle D (Table 1). Having greater than 80% compliance with hand hygiene, contact isolation, ASP, and IPC bundles were associated with reduction in MDR *A. baumannii* and MRSA infection.

Our study findings emphasize the need for multifaceted interventions featuring a "horizontal" approach to control the spread of MDR *A. baumannii* and MRSA.[4,5] We acknowledge that the report of these survey findings includes limitations of sample size and recall biases related to survey design, execution, and analysis. Despite such limitations, we have identified modifiable gaps and opportunities for implementation of IPC bundles to limit transmission of MDR *A. baumannii* and MRSA in resource-limited settings.

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Germ and Hematology: Underlying Disease Influences Diversity of Germ Spectra and Antibiotic Therapy

To the Editor—Knowledge of microbiological germ spectra is a crucial prerequisite for calculated and empirical antibiotic therapy, especially for immunocompromised patients. The microbiological spectra of hematology patients, irrespective of the isolation site, may differ from that of other patients, and taking this into consideration may substantially influence the choice of antibiotics at admission, especially in an outpatient setting or in emergency departments. To elucidate the potential variability of microbiological spectra, we analyzed all consecutive admissions of patients with infectious complications at the Medical Center of the Otto-von-Guericke University in Magdeburg, Germany, over an 18-year period from January 1992 through December 2009. In this retrospective, single-center study, the microbiological isolates obtained from collected patient samples from the Department of Hematology and Oncology (hematology department patients [HP], who were mostly patients with acute leukemia and lymphoma) were compared with those obtained from all other departments (non–hematology department patients [NHP], who were treated in the medical and surgical departments).

Within the relevant period, 603,944 pathogens were isolated, of which 21,431 (3.5%) were obtained from HP. When comparing HP with NHP, the most frequent isolates were derived from blood cultures (43.2% vs 15.8%; $P < .001$) with an overall predominance of gram-positive bacteria. In HP specimens, the proportion of gram-positive bacteria was significantly higher than in NHP specimens (67.4% vs 58.4%; $P < .001$). Anaerobic bacteria were found less frequently in HP samples than in NHP samples (0.6% vs 1.0%; $P = .02$). No difference was detectable between the groups with respect to yeasts. *Staphylococcus aureus, Enterobacteriaceae,* and *Pseudomonadaceae* were significantly less frequent among HP than among NHP, whereas the prevalence of coagulase-negative

TABLE 1. Frequency of Isolated Pathogens, 1992–2009 (n = 603,944)

Pathogen	No. (%) of hematology patients (n = 21,431)	No. (%) of nonhematology patients (n = 582,513)	P
Aerobic bacteria	19,374 (90.4)	521,349 (89.5)	.50
Staphylococcus aureus	1,050 (4.9)	55,921 (9.6)	<.001
Coagulase-negative *Staphylococcus* species	6,772 (31.6)	114,173 (19.6)	<.001
Streptococcus species	3,472 (16.2)	69,902 (12.0)	.01
Enterococcus species	2,207 (10.3)	61,746 (10.6)	.61
Gram-negative cocci	1,136 (5.3)	16,893 (2.9)	.10
Enterobacteriaceae	2,657 (12.4)	112,425 (19.3)	<.001
Non-*Enterobacteriaceae*	407 (1.9)	7,573 (1.3)	.17
Gram-negative rods	193 (0.9)	12,233 (2.1)	<.001
Pseudomonadaceae	557 (2.6)	32,621 (5.6)	<.001
Gram-positive rods	986 (4.6)	37,281 (6.4)	.001
Gram-positive bacteria	14,444 (67.4)	340,188 (58.4)	<.001
Gram-negative bacteria	6,987 (32.6)	242,325 (41.6)	<.001
Anaerobic bacteria	129 (0.6)	5,825 (1.0)	.02
Yeasts	1,929 (9.0)	55,339 (9.5)	.70

NOTE. The frequency of isolates obtained from hematology patients was compared with that of isolates obtained from nonhematology patients using Student t test. Two-sided P values < .05 were considered to be statistically significant.

Staphylococcus species (CNS) and *Streptococcus* species appeared to be significantly increased (Table 1).

Analyzing the 2,226 aerobe isolates grown in blood cultures obtained from all consecutive febrile HP, we found that isolates were predominantly CNS (46.3%) followed by *Enterobacteriaceae* (19.0%), *Streptococcus* species (9.4%), *S. aureus* (6.2%), *Enterococcus* species (5.8%), and *Pseudomonadaceae* (4.5%).

Analyzing potential changes in germ spectra over time, we compared specimens obtained during the period 1992–2000 with those obtained during 2001–2009. Here, an increase in gram-positive bacteria could be observed in both HP (+9.0%; P = .002) and NHP (+2.7%; P = .002), with no change detectable for either gram-negative bacteria or anaerobes. The frequency of yeasts was significantly reduced over time in HP (−6.0%; P = .006), which may be attributed to antifungal prophylaxis, whereas it remained stable in NHP. Of note, significant increase was evident for *S. aureus* in HP (+2.7%; P = .03) and NHP (3.1%; P < .0001).

Microbiological spectra vary between general internal medicine and HP populations.[1,2] In our study, in the HP group, the most pronounced differences were seen for CNS (probably related to contaminated blood culture specimens) and *Enterobacteriaceae*. Over time, the frequency of gram-positive isolates was increasing in both of the cohorts that we compared. For the HP group, this increasing predominance of gram-positive bacteria during the past several decades may be attributed to the generous use of antibiotic prophylaxis, especially fluoroquinolones, as well as the more frequent use of central venous catheters and the increase in cases of oral mucositis.[3]

Taken together, our data provide evidence that calculated and empirical antibiotic regimens for patients with hematologic diseases should provide sufficient activity against gram-positive bacteria. Knowledge of the local bacterial spectrum and their susceptibility patterns as well as prompt initiation of effective antibiotic therapy are essential for patients with hematological malignancies, because inadequate initial antibiotic therapy is a significant predictor of mortality.[4] This information may be of special interest for primary care providers who initiate antibiotic therapy for HP at admission.

Because resistance rates among HP have increased to 25%–63% of tested antibiotics against CNS, methicillin-susceptible *S. aureus, Enterobacteriaceae, Pseudomonadaceae, Streptococcus* species, and *Enterococcus* species,[5] antimicrobial stewardship is clearly warranted to restrict use of prophylactic antibiotics. This is of special importance, because invention of new antibiotic drugs is not keeping pace with the development of resistance.[6]

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Publikation VIII

Schalk E, Färber J, Fischer T. Multidrug-resistant Gram-negative bacteria (MRGN) in hematology and oncology. **Infect Control Hosp Epidemiol 2014**;35(9):1203-1204

posure vs superficial cuts with an apparently clean sharp) and the presence of appropriate personal protective equipment help in optimizing management and reducing infection risks.[1,3,4] Knowledge about this condition and education of healthcare workers about the "dos and don'ts" is essential.

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Multidrug-Resistant Gram-Negative Bacteria in Hematology and Oncology

To the Editor—Reports on the current spectrum of infections among patients with cancer with chemotherapy-related neutropenia provide information of major importance for clinicians.[1] However, in sections of such articles regarding gram-negative bacteria (GN), authors deal with many pathogens (eg, extended spectrum β-lactamase [ESBL] producers, carbapenem-resistant Enterobacteriaceae, carbapenemase-producing GN, and nonfermentative GN). Therapy for such infections is becoming ever more difficult because of increasing rates of antibiotic resistance. Over the past several years, the prevalence of multidrug-resistant gram-negative bacteria (MRGN) has increased steadily.[2] In 2012, in Germany, the terms 3MRGN and 4MRGN were introduced to describe gram-negative aerobic rods with in vitro resistance to 3 and 4 groups, respectively, of bactericidal antibiotics.[3] Screening for carriage and the classification of GN as MRGN or non-MRGN are important tools for infection control measures aimed at reducing pathogen transmission among hospitalized patients,[2,3] both because of the major ongoing problem of antibiotic resistance per se and because of the lack of new antibiotics today and in future.[4]

Thus far, epidemiological data on 3/4MRGN in hematology and oncology are lacking. Therefore, we have retrospectively analyzed all consecutive inpatients admitted to our hematology and oncology 26-bed ward from July 1, 2012, through December 31, 2013. Altogether, 493 different patients were admitted (16,525 inpatient-days). Among these, 118 patients (3,411 patient-days; mean age, 61.8 years; male sex, 52.5%; acute leukemia, 32.2%) with colonization or infection due to GN were identified. The 3/4MRGN prevalence among all inpatients seems to be as low as 3.7% (18 of 493 different patients). However, in light of other "bad bugs," such as ESBL producers, vancomycin-resistant *Enterococcus faecium* (VRE), and methicillin-resistant *Staphylococcus aureus* (MRSA)—which had a prevalence of 2.0%, 0.6%, and 1.6%, respectively, in the same time period—the 3/4MRGN prevalence should not be neglected. Among all first isolates of GN ($n = 173$), 12.7% were 3/4MRGN; these were mostly *Escherichia coli* (36.4%), *Pseudomonas aeruginosa* (31.8%), and *Klebsiella pneumoniae* (9.1%), which were mainly associated with urinary tract infections. This high frequency, the high 3/4MRGN incidence of 6.4 cases per 1,000 inpatient-days (among all first isolates of GN), and the limited therapeutic options reflect the importance of hygiene and infection control measures, such as contact precautions or isolation and antibiotic stewardship programs.

Many patients with 3/4MRGN colonization or infection will be readmitted to the hospital for additional chemotherapy courses or complications, and therefore, the prevalence and incidence of 3/4MRGN will increase in the future. Especially among hematology patients, the overall 3/4MRGN incidence seems to be much higher (eg, 1.09 cases per 1,000 inpatient-days found in our department) compared with the overall inpatient population of a university hospital (0.43 cases per 1,000 inpatient-days).[5]

In our experience, the MRGN term is well established in our institution and is used by both clinicians and microbiologists to describe infectious high-risk patients. Because of the major, challenging problem regarding consumption of resources associated with MRGN (eg, contact precautions, cohorting patients or providing single rooms, and administration of antibiotics), we emphasize the use of an "MRGN

alert," similar to an "ESBL alert," "VRE alert," or "MRSA alert," to deal with antibiotic resistance, antibiotic stewardship, and hygiene measures, rather than describing single strains of resistant GN.[1]

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Port-Related *Aeromonas* Bacteremia

To the Editor—Aeromonas species are gram-negative, rod-shaped bacteria that are prevalent in the aquatic environment, including in fresh or brackish water, sewage, soil, and tap water, in temperate or subtropical countries.[1,2] Although the gastrointestinal tract is the most common site of infection caused by *Aeromonas* species,[1,2] extraintestinal *Aeromonas*-associated diseases, such as empyema, urinary tract infections, biliary tract infections, peritonitis, and skin and soft-tissue infections, have also been reported.[3-7] Herein, we report a study undertaken to find cases with unusual presentation of *Aeromonas* infection associated with subcutaneously implanted port reservoir (eg, port-related infection) and further investigate the associated clinical and microbiological characteristics.

This study was conducted at a single institution, a 900-bed hospital located in southern Taiwan. From the computerized database of the bacteriology laboratory, patients whose cultures yielded *Aeromonas* species were identified. The medical records of all patients with port-related infection caused by *Aeromonas* species were retrospectively reviewed and included in this study.

Blood specimens were inoculated into BACTEC culture bottles using the BACTEC 9240 system (Becton Dickinson). Gram-negative isolates that tested positive for cytochrome oxidase, glucose fermentation, citrate usage, indole production, and ornithine decarboxylase were classified as *Aeromonas* species, as in earlier studies.[6,7] Susceptibilities of these isolates to a battery of antimicrobial agents were determined using the disk diffusion method as described by the Clinical and Laboratory Standards Institute.[8]

The diagnosis of port-related *Aeromonas* bacteremia was defined as primary laboratory-confirmed *Aeromonas* bacteremia in a patient with a port at the time of or within 48 hours before the onset of symptoms for whom infection was not related to an infection at another site. Standard definitions for healthcare-associated infection (HAI) were used.[9,10] Shock was diagnosed in patients with a systolic blood pressure less than 90 mmHg or in patients who required inotropic agents to maintain blood pressure. Infections were classified as polymicrobial infections if non-*Aeromonas* pathogens also grew from the blood sample. Inappropriate use of antibiotics was defined as use of antimicrobial agents to which the clinical isolates were resistant in vitro.

During the study period, a total of 5 patients were identified as having port-related *Aeromonas* bacteremia. Two infections were caused by *Aeromonas veronii* biovar sobria, 2 by *Aeromonas caviae*, and 1 by *A. veronii* biovar veronii. All of the clinical isolates were resistant to ampicillin, amoxicillin-clavulanate, and cefazolin, but they were susceptible to amikacin and gentamicin. Additionally, third- or fourth-generation cephalosporins, piperacillin-tazobactam, and ciprofloxacin showed in vitro activity against 4 (80.0%) of 5 isolates.

The clinical characteristics of 5 patients with port-related *Aeromonas* bacteremia are summarized in Table 1. Men comprised 4 of 5 patients, and the age ranged from 57 to 82 years. All of them had various cancers, and 4 had received chemotherapy. Four of the patients had initial presentations of fever, and 2 had shock. Two of the patients had white blood cell counts greater than 11,000 cells/mL, and none had neutropenia. In addition, 3 patients had hemoglobin levels less than 10 g/dL, and 3 patients had an elevated C-reactive pro-

Publikation IX

Vehreschild MJGT, Vehreschild JJ, Hübel K, Hentrich M, Schmidt-Hieber M, Christopeit M, Maschmeyer G, **Schalk E**, Cornely OA, Neumann S. Diagnosis and management of gastrointestinal complications in adult cancer patients: evidence-based guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO). **Ann Oncol 2013**; 24(5):1189-1202

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Diagnosis and management of gastrointestinal complications in adult cancer patients: evidence-based guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO)

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Background: Cancer patients frequently suffer from gastrointestinal complications. However, a comprehensive, practical and evidence-based guideline on this issue is not yet available.
Patients and methods: An expert group was put together by the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO) to develop a guideline on gastrointestinal complications in

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cancer patients. For each subtopic, a literature search was carried out in PubMed, Medline and Cochrane databases and the strength of recommendation and the quality of the published evidence for major therapeutic strategies were categorized using a modification of the 'Infectious Diseases Society of America' criteria. Consensus discussions were held on each of the topics.

Results: Recommendations were made with respect to non-infectious and infectious gastrointestinal complications. For all recommendations, the strength of the recommendation and the level of evidence are presented.

Conclusion: This guideline is an evidence-based approach to the diagnosis and management of gastrointestinal complications in cancer patients.

Key words: diarrhea, enterocolitis, fever, gastrointestinal, neutropenia

introduction

Abdominal complications are a frequent matter of concern in patients with hematological or oncological malignancies. Even though several existing guidelines cover selected abdominal pathologies, a comprehensive, practical and evidence-based guideline on gastrointestinal complications in cancer patients is not yet available. The present guideline intends to close this gap, covering the epidemiology, pathophysiology, diagnosis and treatment of most non-infectious and infectious complications as well as the corresponding hygiene measures. Whenever possible, pre-existent recommendations were incorporated into this overview.

methods

Subtopics of this guideline were assigned to members of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO) and a literature search was carried out in PubMed, Medline and Cochrane databases. The strength of recommendation and the quality of evidence for major therapeutic strategies were categorized using a modification of the 'Infectious Diseases Society of America' criteria (IDSA, Table 1) [1]. To increase transparency in the evaluation of the evidence, we added an index to the level II recommendations and to all transferred evidence, where appropriate.

Consensus discussions were held on each of the topics. After ratification of all topics by this expert group, recommendations were discussed and ratified by the AGIHO during the 2011 guideline meeting.

Treatment-associated anorexia, nausea and emesis were not included in the guideline. While they involve the gastrointestinal tract, a complete overview of their management would go beyond the scope of this guideline and has already been provided elsewhere.

guideline

diarrhea

Independent of its cause, diarrhea should always be treated with adequate oral or intravenous fluid and electrolyte replacement (**AIII**). Patients should be observed for signs of malnutrition and/or catabolic state. If indicated, enteral or parenteral electrolytes, carbohydrates, lipids, amino acids, protein and vitamins should be supplemented (**AIII**). Figure 1 provides important facts on the diagnostic workup of diarrhea in cancer patients. As a general rule, repeat testing for the same pathogen should not be carried out to avoid false-positive results.

non-infection-related diarrhea

paraneoplastic diarrhea. Paraneoplastic diarrhea is a rare phenomenon which may be triggered by a variety of pathophysiological mechanisms. Secretion of vasoactive intestinal polypeptides (VIPs), as typically observed in patients with non-β islet cell tumors of the pancreas, may cause watery diarrhea, hypokalemia and hypochlorhydria [2]. Flush and diarrhea are the typical symptoms of serotonin-producing carcinoid tumors [3]. Other hormones that may cause paraneoplastic diarrhea include glucagon (glucagonoma), gastrin (gastrinoma or hepatocellular carcinoma), somatostatin (somatostatinoma or pheochromocytoma) and the prostaglandins (hepatocellular carcinoma) [4–8]. In association with small-cell lung carcinoma, antibodies directed against neuronal proteins

Table 1. Categories of evidence

Category, grade	Definition
Strength of recommendation	
A	Good evidence to support a recommendation for use
B	Moderate evidence to support a recommendation for use
C	Poor evidence to support a recommendation
D	Moderate evidence to support a recommendation against use
E	Good evidence to support a recommendation against use
Quality of evidence	
I	Evidence from one or more properly randomized, controlled trial
II	Evidence from one or more well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from more than one center); from multiple time-series; from meta-analyses or from dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees
Index	
r	Meta-analysis or systematic review of randomized, controlled trials
t	Transferred evidence, i.e. results from different patient cohorts, or similar immune-status situation
h	Comparator group is a historical control
u	Uncontrolled trial
a	Abstract published at an international meeting

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Box 1: Diagnostic workup of diarrhea (≥3 unformed bowel movements/24h)	
Hospital-acquired diarrhea (≥72h of hospitalization)	**Initial workup:** - *Clostridium difficile* - Norovirus **Extended workup:** - SSYC - Adenovirus, astrovirus, CMV, rotavirus - Parasites - Lactose breath test - Consider alternative causes (treatment-associated, paraneoplastic)
Community-acquired diarrhea (<72h of hospitalization)	**Initial workup:** - If recent chemotherapy or antibiotic treatment: *Clostridium difficile* - SSYC - Obtain travel history **Extended workup:** - *Clostridium difficile* (if not yet analyzed) - Adenovirus, astrovirus, CMV, norovirus, rotavirus - Parasites - Lactose breath test - Consider alternative causes (treatment-associated, paraneoplastic)
All cases	Consider local infectious diarrhea outbreaks

Figure 1. Diagnostic workup of diarrhea in cancer patients. SSYC, nontyphoidal *Salmonella*, *Shigella*, *Yersinia* or *Campylobacter* spp.; allo-SCT, allogeneic stem cell transplantation; CMV, cytomegalovirus; EBV, ebstein barr virus; HSV, herpes simplex virus; HHV6; human herpesvirus 6; GvHD, graft versus host disease; PCR, polymerase chain reaction.

may cause autonomic neuropathy and consequent diarrhea [9]. In patients with thymoma, diarrhea as part of a graft-versus-host-disease-like reaction has been described [10, 11].

In most cases of paraneoplastic diarrhea, diagnosis and treatment of the underlying disease are considered the only effective measure to reduce diarrhea. Carcinoid and some other neuroendocrine tumors might, however, respond to blockage of somatostatin receptors with octreotide or lanreotide (Table 2). Depot octreotide may be initiated at a dose of 20–30 mg im every 4 weeks. In case of severe initial or refractory symptoms, supplementation with short-acting octreotide at 150–250 μg tid sc is suggested. If clinical response is achieved, continuous therapy might be considered [12–14] (**AII**). Lanreotide may initially be administered at 60 mg qd im every 4 weeks [15] (**AII**).

therapy-associated diarrhea. In cancer patients, the factors related to toxic effects of chemotherapy are the most common cause of abdominal complications. 5-Fluorouracil, irinotecan, capecitabine, anthracyclines and a number of small molecules and monoclonal antibodies have been associated with an increased frequency of therapy-associated diarrhea [16–24]. Recent studies have reported incidence rates of diarrhea in 27%–76% of neutropenic patients. In only 5%–17% of these cases, an infectious agent was identified as the cause of diarrhea, suggesting primarily toxicity-related symptoms [16, 25–27]. Disruption of the gastrointestinal microflora after administration of antibiotics may result in osmotic diarrhea due to alterations in carbohydrate metabolism and impaired absorption of short-chain fatty acids in 5%–62% of patients [28–30]. In 7%–50% of these cases, overgrowth with *Clostridium difficile* may ensue, leading to *C. difficile*-associated diarrhea (see *Clostridium difficile* infection) [31, 32].

Chemotherapy-associated lactose intolerance presenting as diarrhea, bloating and malabsorption has also been discussed as a cause of non-infectious diarrhea in cancer patients. While up to 35% of patients have been shown to present with an abnormal lactose breath hydrogen test during chemotherapy, only up to 11% became symptomatic. Generally, test results returned to normal after completion of chemotherapy [33, 34].

Radiation therapy involving the gastrointestinal tract may cause severe mucosal bowel damage resulting in acute or chronic diarrhea. Symptoms usually peak about 7–14 days after initiation of radiation and may be intensified by combination treatment with chemotherapy. In some patients, surgical resection may result in impairment of physiological gastrointestinal function with diarrhea developing as a consequence of shortened gastric and intestinal transit times, bacterial overgrowth and altered secretion and absorption of bile acids.

Once an infectious cause of diarrhea has been discarded (see Figure 1), loperamide (2 mg po every 2 h and 4 mg po every 4 h at night) is recommended for first-line treatment of non-infectious diarrhea [35–38] (**AII$_u$**). In patients failing to respond to loperamide, octreotide at a dosage of 500 μg tid sc may be considered [39–41] (**BII**). In patients not responding to the initial dosage, dose increase until symptom control is recommended [39–43] (**AIII**). An alternative might be the administration of psyllium seeds, although this approach has not been evaluated in patients with chemotherapy-associated

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Table 2. Treatment of paraneoplastic and therapy-associated non-infection-related diarrhea

Clinical situation	Intervention	SoR	QoE	Reference	Comments
Paraneoplastic diarrhea in carcinoid tumors	Depot octreotide 20–30 mg im every 4 weeks	A	II	[12–14]	During first two weeks of treatment overlap with short acting octreotide at 150–250 μg tid sc In case of refractory symptoms, supplement with short acting octreotide at 150–250 μg tid sc In case of response, consider continuous therapy
	Depot lanreotide 60 mg im every 4 weeks	A	II	[15]	In case of response, consider continuous therapy
Therapy-associated diarrhea	Loperamide 2 mg po every 2 h and 4 mg po every 4 h at night	A	II_u	[36–38]	Only in persisting and severe cases of diarrhea and after exclusion of infectious diarrhea Careful risk-benefit assessment in neutropenic patients
Loperamide-refractory therapy-associated diarrhea	Octreotide 500 μg tid sc	B	II	[39–41]	Only in cases of persisting and severe diarrhea and after exclusion of infectious diarrhea Titration to higher dosages may be considered if no response to 500 μg tid sc Careful risk-benefit assessment in neutropenic patients
	Psyllium seeds	B	II_t	[44,45]	Only in persisting and severe cases of diarrhea and after exclusion of infectious diarrhea
	Alternatives: diphenoxylate plus atropine, paregoric tincture of opium, codeine or morphine	B	III		Only in cases of persisting and severe diarrhea and after exclusion of infectious diarrhea Careful risk-benefit assessment in neutropenic patients
Late-onset diarrhea after irinotecan therapy	Prophylaxis with budesonide 3 mg tid po *or* Neomycin 500 mg bid po	C B	II III	[46] [47,48]	Neomycin was only assessed as secondary prophylaxis in patients with grade II-IV diarrhea during the first chemotherapy cycle.
Late-onset diarrhea after irinotecan therapy	Treatment with loperamide *plus* Budesonide 3 mg tid po until resolution of symptoms *or* Acetorphan 100 mg tid po for 48 h	B B	II_u II	[23] [24]	Stop treatment, if no response after 72 h
Chemotherapy-associated lactose intolerance	Dietary restriction of milk products	B	II_u	[33,34]	Only if clinical signs and symptoms present
Antibiotic-associated diarrhea	Probiotic prophylaxis	C	III	[31,49,50]	No safety data in immunocompromised patients available

SoR, strength of recommendation; QoE, quality of evidence.

diarrhea [44, 45] (**BII_t**). Further options include diphenoxylate plus atropine and opiates such as paregoric tincture of opium, codeine and morphine [35] **(BIII)**.

While data on budesonide prophylaxis for late-onset diarrhea after treatment with irinotecan showed no significant advantage for preventive treatment [46] (**CII**), addition of budesonide [23] (**BII_u**) or acetorphan [24] (**BII**) to loperamide treatment was effective in two small clinical trials. In a small patient population, neomycin was assessed as secondary prophylaxis for irinotecan-induced diarrhea [47, 48] **(BIII)**.

Patients with severe diarrhea persisting for >48 h despite administration of antimotility agents should be hospitalized [35] **(AIII)**. Of note, in long-term neutropenic patients, overdosage of antimotility agents may lead to iatrogenic ileus with an increased risk of bacteremia.

Regarding chemotherapy-associated lactose intolerance, we do not recommend dietary restriction of milk products, unless clinical symptoms of lactose intolerance are observed after ingestion of milk products [33, 34] (**BII_u**).

A large number of trials assessing the protective effect of prophylactic probiotic treatment to avoid antibiotic-associated diarrhea have been conducted. Studies in immunocompetent patients suggest a protective effect for *Saccharomyces boulardii, Lactobacillus rhamnosus* and a combination of *L. casei, L. bulgaricus* and *S. thermophiles* [31, 49, 50]. However, the safety of probiotics in neutropenic patients has not been

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sufficiently assessed to recommend their prophylactic use in this population (**CIII**). In association with the yeast *S. boulardii*, bloodstream infections have been reported [51]. Recommendations on therapy-associated diarrhea have been summarized in Table 2.

infection-related diarrhea

The diagnosis of infection-related diarrhea should trigger adequate hygiene measures (**BI**) [52, 53]. The regular practice of appropriate hand hygiene is considered a cornerstone in the prevention of hospital-acquired infections [52, 53] and has been discussed in detail elsewhere [54]. Table 3 shows recommended hygiene procedures for most common infectious causes of gastroenteritis. Of note, hygiene measures can be subjected to local or national legislation which may differ from these recommendations.

clostridium difficile *infection.* *Clostridium difficile* is the most common cause of health-care associated infectious diarrhea and colitis, accounting for up to 50% of all cases of antibiotic-associated diarrhea [31, 32]. In adult patients with cancer, infections due to *C. difficile* (CDI) occur in 5%–9% of chemotherapy courses and 5%–20% of patients, respectively [26, 27, 55–60].

Binding of *C. difficile* toxins A and B to epithelial cells and subsequent internalization lead to diarrhea by induction of apoptosis [61]. An increase in the frequency of CDI has been reported and attributed to the emergence of a new and hypervirulent strain of *C. difficile*, named NAP1 (synonymous terms are BI, ribotype 027 and toxinotype III) [62–64]. In NAP1 strains, single-base deletion mutations at position 117 of the *tcdC* gene, a downregulator of toxin transcription, lead to disinhibition of toxins A and B production, thus contributing to increased intracolonic toxin levels [65]. Major risk factors for CDI include age, chemotherapy, antibiotic agents, antimotility drugs, ventilation, proton pump inhibitors, H_2 antagonists and hypalbuminemia [60, 64, 66–70].

Clinical signs and symptoms of CDI are diarrhea, fever, abdominal pain and distension. The severity of the disease ranges from mild diarrhea to fulminant pseudomembranous colitis with paralytic ileus, toxic megacolon or perforation [56, 59, 71]. The onset of diarrhea may occur at any time during and up to 2 weeks after the end of antibiotic treatment [71].

In accordance with ESCMID (European Society of Clinical Microbiology and Infectious Diseases) guidelines, CDI is defined as (i) >3 unformed stools within 24 h, (ii) ileus or toxic megacolon in combination with evidence of toxin-producing *C. difficile* in stools and absence of another cause of symptoms or (iii) pseudomembranous colitis diagnosed by endoscopy, colectomy or histopathological examination [72]. The proper laboratory specimen is an unformed stool promptly submitted to the laboratory [63, 73]. Processing a single specimen from a patient at onset of a symptomatic episode is sufficient and should not be repeated to avoid false-positive results through multiple testing [74].

Given the slow turnaround of highly sensitive (94%–100%) cytotoxin assays [63], stool samples should be tested for the presence of toxin-producing strains by enzyme immunoassays for cytotoxins A and B (sensitivity 50%–80%, specificity 98%–99%) [75] or for *C. difficile* common antigen (GDH; sensitivity 85%–95%, specificity 89%–99%) [76], or alternatively by real-time PCR assays for the gene-encoding toxin B (sensitivity 97%, specificity 93%) [77]. Samples with negative test results can be reported as negative, while samples with a positive first test result should be re-tested with a different method [73]. To avoid treatment delays in the setting of high-risk patients, we recommend early therapeutic intervention before confirmatory test results are available. In neutropenic patients, as well as in

Table 3. Isolation procedures for the most common causes of infectious diarrhea

Pathogen	SR	GG	M	Infectious Material	Stop	SoR	QoE	Comment
Clostridium difficile	•	○		Feces	Normalization of clinical symptoms (diarrhea or colitis)	B	III	Use warm water and plain soap for hand hygiene after patient contact No precautions for asymptomatically colonized patients Do not re-test for *C. difficile* toxin to evaluate further necessity of isolation Gloves and gown only if contact with infectious material or contaminated surfaces
Salmonella, Shigella, Yersinia, Campylobacter spp.	•	○		Feces, vomitus, possibly urine	Three negative stool samples	B	III	Gloves and gown only if contact with infectious material or contaminated surfaces
Norovirus and other causes of viral gastroenteritis	•	•	•	Feces, vomitus	Three negative stool samples	B	III	

•, always required; ○, only required under certain circumstances specified in the comment box; SR, single room; GG, gloves and gown; M, mask; SoR, strength of recommendation; QoE, quality of evidence.

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patients with severe colitis, diagnostic endoscopy is contraindicated because of the risk of colon perforation or hemorrhage [64].

Recently updated ESCMID and SHEA/IDSA guidelines differentiate between severe and non-severe cases of CDI [63, 72]. Leukocytosis, used as a crucial criterion for categorization in both the guidelines, is not a useful parameter in neutropenic patients. Neutropenic patients presenting with chemotherapy-associated bowel syndrome (CABS; $T \geq 37.8$°C and abdominal pain and/or lack of bowel movement for ≥72 h) have been shown to be more likely to suffer complications and death and should be categorized as having severe disease [26].

Three large controlled, randomized trials including predominantly immunocompetent patients reported CDI cure rates between 76% and 97% and recurrence rates between 7% and 27% [78–80]. CDI-associated mortality is estimated at 2%–7% in immunocompetent and -compromised patients [27, 60, 81, 82].

To minimize the risk of developing CDI, antibiotics should cover a spectrum no broader than necessary, and should be adapted with respect to results of cultures and/or susceptibility test data (**BIII**). If possible, other antibiotics should be discontinued after diagnosis of CDI [83–85] (**AII**); however, in febrile neutropenia, this may not always be possible.

There is no evidence to support prophylactic antibiotic treatment to prevent CDI (**CIII**). While there may be a protective effect by probiotic prophylaxis [86, 87], the safety of probiotics in neutropenic patients has not been sufficiently assessed to recommend their use (**CIII**). The results from one small, monocentric observational study in a mixed patient population do not suffice to generally recommend empirical therapy of diarrhea with metronidazole [88] (**CII**). However, in severe or complicated clinical disease with suspected CDI, empirical metronidazole treatment may be considered (**BIII**). Antiperistaltic agents, including opiates, are discouraged [89] (**DII**).

For non-severe CDI, a randomized, controlled trial showed similar cure rates for oral metronidazole and oral vancomycin. For severe cases, however, superiority was shown for treatment with vancomycin [80]. In two large randomized, controlled trials, fidaxomicin, a new macrocyclic antibiotic, fulfilled non-inferiority criteria when compared with vancomycin for the treatment of CDI[78, 79]. While metronidazole, vancomycin and fidaxomicin might be used as first-line treatment of non-severe CDI [80] (**AI**), only fidaxomicin or oral vancomycin is recommended for the treatment of severe CDI [78–80] (**AI**).

There is no evidence to support combination therapy in patients with CDI (**CIII**). Intravenously administered metronidazole at a dosage of 1500 mg qd iv for 10 days is likely to result in effective concentrations in feces and colon [90, 91] and may be an option if oral antimicrobials cannot be administered ($\mathbf{AII_u}$). In severe cases of CDI, additional administration of vancomycin by a nasogastric tube and/or by a rectal catheter or retention enema at 500 mg may be discussed [90–92] (**CIII**). In case of complicated CDI, a surgical evaluation should be obtained at an early stage of disease, however, surgical intervention in the neutropenic and/or thrombocytopenic patient should be reserved to selected complicated cases (**BIII**). To reduce costs, the intravenous formulation of vancomycin may be used for oral administration without safety or efficacy hazards [63] (**BIII**). Recommendations on the prophylaxis and treatment of CDI, including recurrences are summarized in Table 4.

other bacterial infections causing diarrhea (nontyphoidal salmonella*,* shigella*,* yersinia *or* campylobacter *spp.).* In cancer patients, infection-related diarrhea due to nontyphoidal *Salmonella*, *Shigella*, *Yersinia* or *Campylobacter* spp. (SSYC) is a rare event (0%–2.8%) [27, 93–97]. Clinical signs and symptoms include watery, mucoid or bloody diarrhea, abdominal tenderness, fever and nausea. Abdominal pain tends to be particularly severe in *Campylobacter* enteritis and may mimic appendicitis in *Yersinia* spp. and *Campylobacter* spp. infection. Gastrointestinal infections with SSYC may be followed by reactive arthritis. *Campylobacter* spp. infection has been associated with subsequent occurrence of Guillain–Barré syndrome, while hemolytic–uremic syndrome has been observed in association with *Shigella* spp. In rare cases, acute disease may be further complicated by rectal prolapse, bacteremia, ileus, toxic megacolon and perforation. Since SSYC are typically community-acquired, testing for these pathogens should be restricted to fecal samples taken within 72 h of hospital admission from symptomatic patients. In case of clinical deterioration, an abdominal ultrasound or X-ray may be carried out to detect an ileus or toxic megacolon. A thickened bowel wall may be detected by an abdominal ultrasound or a computer tomography (CT) scan. In this case, the differential diagnosis of NEC should be considered. Perforation rarely occurs in this setting and may be identified by plain abdominal X-ray.

Based on the low incidence of these entities, prophylactic treatment is not recommended [27, 93–97] (**CII**). While nonsevere cases of diarrhea caused by bacteria other than *C. difficile* may not always require antibiotic treatment, severely ill and/or immunocompromised individuals should receive systemic treatment (**BIII**). Given the lack of data in these populations, treatment recommendations for cancer patients were derived from studies carried out in immunocompetent individuals. For infections caused by *Yersinia* spp., treatment with a fluoroquinolone or trimethoprim–sulfamethoxazole (TMP–SMZ) or doxycycline is suggested [98, 99] ($\mathbf{BII_t}$). For patients with severe disease, the preferred regimen is a third generation cephalosporin combined with gentamicin [99] ($\mathbf{BII_t}$). For infections with *Campylobacter* spp., azithromycin has become the drug of choice due to an increase in fluoroquinolone resistance (19%) [100] ($\mathbf{BII_t}$). Two randomized, controlled trials on the treatment of shigellosis established ciprofloxacin or another fluoroquinolone as the treatment of choice with azithromycin being an effective alternative [167, 168] ($\mathbf{BII_t}$). Immunocompromised patients suffering from salmonellosis may benefit from therapy with ciprofloxacin. Alternatively, TMP–SMZ or amoxicillin may be administered depending on *in vitro* susceptibility test results [101] ($\mathbf{BII_t}$). In patients with *Salmonella* spp. bacteremia, treatment with a combination of ceftriaxone plus ciprofloxacin is recommended to avoid initial treatment failure before resistance test results are available and allow de-escalation to a monotherapy [101, 102] ($\mathbf{BII_t}$). Table 5 summarizes treatment recommendations for SSYC.

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Table 4. Prevention and treatment of *Clostridium difficile* infection

Clinical situation/problem	Intervention	SoR	QoE	Reference	Comments
Diarrhea with CDI suspected Light or moderate clinical disease	Empirical therapy	C	III		
Diarrhea with CDI suspected Severe[a] or complicated clinical disease	Empirical therapy	B	III		
Increased risk of CDI during antibiotic treatment	Prophylactic metronidazole or vancomycin	C	III	[63,162]	
Increased risk of CDI during antibiotic treatment	Prophylactic probiotics	C	III	[86,87]	No safety data in immunocompromised patients available
Non-severe CDI	Metronidazole 400 mg tid po for 10 days *or* Vancomycin 125 mg qid po for 10 days *or* Fidaxomicin 200 mg bid po for 10 days	A	I	[78–80]	If metronidazole 400 mg tablets not available, use 500 mg bid po
Non-severe CDI, oral administration not possible	Metronidazole 500 mg tid iv for 10 days	A	II_u	[90,91]	
Severe[a] CDI	Vancomycin 125 mg qid po for 10 days *or* Fidaxomicin 200 mg bid po for 10 days	A	I	[78–80]	
Severe[a] CDI, oral administration not possible	Metronidazole 500 mg tid iv for 10 days *plus* vancomycin 500 mg intracolonic every 4–12 h *and/or* vancomycin 500 mg qid by nasogastric tube	A C	II_u III	[90,91] [92]	
Perforation	Surgical intervention	B	III	[163]	
First recurrence	Follow treatment recommendation of first CDI episode	A	IIu	[164]	If recurrence is marked by higher severity, a switch from metronidazole to vancomycin or fidaxomicin is warranted
Second recurrence	Vancomycin 125 mg qid po for at least 10 days	B	IIu	[165]	
	Consider a pulse and taper strategy[b]	B	IIu	[165,166]	

[a]$T \geq 37.8$°C and abdominal pain and/or lack of bowel movement for ≥72 h.
[b]Vancomycin 125 mg qid po for 7–14 days, 125 mg bid po for 7 days, 125 mg qd po for 7 days, 125 mg qd po every other day, 125 mg qd po every 3 days for 14 days.
SoR, strength of recommendation; QoE, quality of evidence.

viral infections. The most common causes of viral gastroenteritis in cancer patients include norovirus (earlier known as Norwalk-like virus), rotavirus, adenovirus and cytomegalovirus (CMV). Self-limiting infections with norovirus and rotavirus may affect cancer patients of all risk groups. On the other hand, patients with impaired cellular immunity, e.g. due to a chronic lymphatic malignancy, immunosuppression after allo-SCT, treatment with alemtuzumab or other substances interfering with T-cell activity, are at an increased risk of developing clinically significant courses of viral gastroenteritis due to CMV or adenovirus, warranting treatment. These infections are unlikely to occur in patients undergoing conventional chemotherapy and those suffering from solid tumors. Impaired cellular immunity also predisposes to prolonged courses of diarrhea and viral shedding [103–107].

Norovirus is a frequent cause of acute gastroenteritis during the cold season. Transmission occurs by contact with excretions, even in the form of aerosols, and requires only 10–100 viral particles. The incubation period of 12–48 h is typically followed by vomiting, diarrhea, abdominal pain, myalgia and low fever. In the immunocompetent host, the course is self-limiting with symptoms lasting for 12–72 h and viral shedding continuing for up to 3 weeks [104]. Real-time PCR (sensitivity 94%, specificity 92%) is currently considered the mainstay of diagnosis with alternatives including norovirus antigen detection and electron microscopy [109, 110]. A considerable mortality rate of up to 25% has been attributed to norovirus gastroenteritis in allo-SCT patients [111]. No specific treatment options are currently available.

Rotavirus gastroenteritis may occur after ingestion of about 100 viral particles and an incubation period of 1–3 days. Symptoms include diarrhea, vomiting and fever for 4–7 days. Viral excretion continues for 8–14 days. Antigen tests show good sensitivity. Incidence rates of 2.5 and 1.3%, respectively,

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Table 5. Treatment of nontyphoidal *Salmonella, Shigella, Yersinia* and *Campylobacter* spp. (SSYC)

Clinical situation	Intervention	SoR	QoE	Reference	Comments
Neutropenia or immunosuppression	*Salmonella, Shigella, Yersinia* or *Campylobacter* spp. prophylaxis	C	II_u	[93,96,97]	
Diarrhea caused by nontyphoidal *Salmonella* spp.	Ciprofloxacin 400 mg bid iv *or* 500 mg bid po Alternatives: Levofloxacine 500 mg qd po *or* Amoxicillin 500 mg tid po *or* TMP–SMZ 160/180 mg bid po/iv	B	II_t	[101]	Alternative choice depending on *in vitro* susceptibility
Bacteremia caused by nontyphoidal *Salmonella* spp.	Ceftriaxone 2 g qd iv *plus* ciprofloxacin 500 mg bid iv	B	II_t	[101,102]	Start with combination therapy and de-escalate once resistance data becomes available
Diarrhea caused by *Shigella* spp.	Fluoroquinolone (e.g. ciprofloxacin 400 mg bid iv *or* 500 mg bid po, levofloxacin 500 mg qd po) *or* Azithromycin 500 mg qd iv/po	B	I_t	[167,168]	
Diarrhea caused by *Campylobacter* spp.	Azithromycin 500 mg qd iv/po Alternative: Fluoroquinolone (e.g. ciprofloxacin 400 mg bid iv *or* 500 mg bid po, levofloxacin 500 mg qd po)	B	II_t	[100]	High fluoroquinolone resistance rate of 19%
Diarrhea caused by *Yersinia* spp.	Fluoroquinolone (e.g. ciprofloxacin 400 mg bid iv *or* 500 mg bid po, levofloxacin 500 mg qd po) Alternative: TMP–SMZ 160/180 mg bid po/iv *or* doxycycline 100 mb bid iv/po	B	II_t	[98,99]	
Bacteremia caused by *Yersinia* spp.	Ceftriaxone 2 g qd iv *plus* gentamicin 5 mg/kg qd iv	B	II_t	[99]	

SoR, strength of recommendation; QoE, quality of evidence; TMP–SMZ, trimethoprim–sulfamethoxazole.

have been reported from cohorts of neutropenic high-risk and allo-SCT patients presenting with diarrhea, respectively [26, 96]. Little is known on the associated morbidity and mortality in the immunocompromised patient [103, 112].

The only available vaccine is an attenuated live vaccine; however, fatal infections have been reported in children with severe combined immunodeficiency [113] (**EII**).

A 3-day course of nitazoxanide significantly reduced the duration of rotavirus disease in immunocompetent hospitalized pediatric patients [114]. As this therapy has not been assessed in immunocompromised patients, further studies are required before a recommendation can be made (**CI**). In two patients, oral immunoglobulin has been successfully used to treat rotavirus gastroenteritis [115] (**CIII**).

Adenovirus is typically associated with gastroenteritis in newborn and children as well as with keratoconjunctivitis epidemica and acute respiratory distress syndrome. In patients with impaired cellular immunity, life-threatening courses of disease have been reported [116, 117].Regarding treatment recommendations, only limited data from case reports are available. Low-dose cidofovir (1 mg/kg thrice a week) was effective in one adult patient [116] and in a report from a pediatric hematology unit with an adenovirus outbreak, seven patients were successfully treated with cidofovir 5 mg/kg iv once weekly for 2 weeks, then once every week [118]. Treatment with cidofovir may therefore be discussed in severely ill patients with adenovirus-associated diarrhea (**BII**); however, its considerable nephrotoxicity should be taken into account.

CMV is found in blood and excretions of individuals with profound and long-lasting cellular immunosuppression and is a rare cause of gastrointestinal infections in other patient groups [119–122].

Patients may present with nausea, vomiting, bloody or non-bloody diarrhea, fever, abdominal pain and prolonged anorexia [123]. CMV infection is diagnosed by detection of antigen (pp65; antigenemia assay), DNA or mRNA. Quantification of viral load by PCR is also widely available [124]. However, for diagnosis of CMV enteritis, detection of CMV in peripheral blood is not appropriate and may be negative. Similarly, CMV detection in fecal samples does not suffice to establish a diagnosis. To this end, CMV detection in an endoscopically obtained biopsy specimen from suspicious areas in the esophagus, stomach, small bowel and large intestine is needed [125, 126]. The diagnosis is made by the association of CMV

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disease with specific mucosa pathology and appropriate symptoms [127].

Recommendations on CMV prophylaxis and pre-emptive treatment are given in the updated ECIL recommendations on the management of CMV, HHV-6, HHV-7 and Kaposi-sarcoma herpes virus (HHV-8) infections in patients with hematological malignancies and after SCT [128, 129].

We recommend treating gastrointestinal CMV disease with ganciclovir for 2 to 3 weeks with induction dosing of 5 mg/kg bid iv, followed by several weeks of maintenance therapy at a dose of 5 mg/kg qd iv on 5 to 6 days per week. The prolonged treatment interval is intended to cover the period of mucosal re-epithelialization [123] (**BII**). The addition of immunoglobulins to antiviral therapy may be considered; however, there are currently no data supporting this strategy [130–132] (**CII$_u$**). Regarding antiviral treatment alternatives, the administration of foscarnet [133] (**BI$_t$**), cidofovir [134–136] (**BII**), or the combination of foscarnet and ganciclovir may be considered [137, 138] (**BII**). Both substances, foscarnet and cidofovir, are associated with significant renal toxicity. Recommendations on the treatment of viral gastroenteritis have been summarized in Table 6.

parasitic infections. Given extensive travels, and growing populations of migrants, rising incidence rates of gastrointestinal infections with parasites are to be expected. Previous studies identified *Cryptosporidium parvum* in stools of 9.6%–14.4% of patients with hematological malignancies presenting with diarrhea. The majority of these patients had undergone allo-SCT [95, 139]. In cancer patients with chronic diarrhea, examination of stools for cysts may be warranted, if no other cause of diarrhea could be identified. In this case, other protozoans, e.g. *Isospora belli*, *Sarcocystis hominis*, *S. suihominis* and *Cyclospora cayetanensis*, should also be considered as potential causative pathogens. In rare cases, *Entamoeba histolytica*, *Giardia lamblia* and *Strongyloides stercoralis* may cause symptomatic disease in patients coming from endemic areas [140, 141].

There are currently no treatment options apart from supportive therapy for *S. hominis* and *S. suihominis*. However, symptomatic infections with *I. belli* and *C. cayetanensis* may be treated with TMP–SMZ 160 mg/800 mg bid po or ciprofloxacin 500 mg bid po for 7 days [142, 143] (**AII$_t$**). In a small case series of allo-SCT patients infected with *C. parvum*, therapy with nitazoxanide plus azithromycin yielded promising results. However, based on these data only, a reliable recommendation for antimicrobial treatment of *C. parvum* cannot be made (**CII$_u$**).

chemotherapy-associated bowel syndrome and neutropenic enterocolitis

Neutropenic enterocolitis (NEC) is a common chemotherapy-associated complication, particularly in patients with acute leukemia [16, 58, 144–146]. A pooled incidence rate of 5.3% was calculated for patients with hematological malignancies or those receiving high-dose chemotherapy for solid tumors or aplastic anemia. NEC has been associated with mortality rates between 30% and 82% [145, 147]. Administration of cytosine arabinosid and anthracyclines has been identified as major risk factors. However, many other cytostatic agents as well as radiotherapy have been identified as triggers of NEC [27, 148–157]. Mucosal barrier damage facilitates infiltration and penetration of the bowel wall by bacteria, viruses and fungi.

Table 6. Treatment of viral gastroenteritis

Clinical situation	Intervention	SoR	QoE	Reference	Comments
Rotavirus enteritis	Nitazoxanide 7.5 mg/kg bid po	C	I	[114]	Only assessed in immunocompetent pediatric patients
	Oral immunoglobulin	C	III	[115]	No sufficient evidence to recommend dosage
Adenovirus enteritis	Cidofovir 5 mg/kg iv once weekly for 2 weeks, then once every week	B	II$_u$	[116,118]	To reduce cidofovir toxicity, add at least 2 l of iv prehydration and probenecid 2 g po 3 h prior and 1 g 2 and 8 h following cidofovir
CMV enteritis	Ganciclovir 5 mg/kg bid iv for 2–3 weeks followed by several weeks of 5 mg/kg qd iv on 5 days per week	B	II	[123]	
	Alternatives:				
	Foscarnet 90 mg/kg bid iv over 2 h followed by 60 mg/kg tid iv over 1 h *or*	B	I$_t$	[133]	Used in a pre-emptive setting
	Cidofovir 5 mg/kg iv once weekly for 2 weeks, then once every week *or*	B	II$_u$	[134–136]	To reduce cidofovir toxicity, add at least 2 l of iv prehydration and probenecid 2 g po 3h prior and 1 g 2 and 8 h following cidofovir
	Foscarnet 90 mg/kg bid iv over 2 h followed by 60 mg/kg tid iv over 1 h *plus* ganciclovir 5 mg/kg bid iv for 2 to 3 weeks followed by several weeks of 5 mg/kg qd iv on 5 days per week	B	II	[137,138]	
	Addition of iv immunoglobulin	C	II$_u$	[130–132]	No sufficient evidence to recommend dosage

SoR, strength of recommendation; QoE, quality of evidence.

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From blood cultures drawn during episodes of NEC, gram-negative Enterobacteriaceae were the most frequently documented organisms [16, 26, 58]. A systematic review on fungal infections related to NEC found a pooled frequency of 6.2% [147].

Clinical signs and symptoms include abdominal pain, diarrhea, nausea and vomiting. In more severe cases rebound tenderness, decreased bowel sounds or guarding may develop. The proposed diagnostic criteria according to Gorschlüter et al. include the presence of fever, abdominal pain and a bowel wall thickening of >4 mm (transversal scan) or >30 mm (longitudinal scan) in any segment by ultrasonography (US) or CT [146].

Since this definition of NEC describes patients at a late pathophysiological stage of intestinal impairment, a clinical definition identifying neutropenic patients at risk of further clinical deterioration due to abdominal complications was recently developed. It could be shown that neutropenic patients with chemotherapy-associated bowel syndrome ($T \geq 37.8$°C and abdominal pain and/or lack of bowel movement for ≥72 h) were more likely to suffer complications and death [26].

Noninvasive imaging is generally recommended to confirm the diagnosis of NEC and to exclude bowel wall perforation. Blood cultures, stool cultures and a *C. difficile* toxin test for exclusion of NEC-associated bacteremia and colitis due to *C. difficile,* respectively, are recommended. Endoscopy to obtain biopsies is discouraged, due to the increased risk of bowel wall perforation.

Conservative therapy is preferred in most cases, consisting of a bland diet, hydration and an effective pain treatment (**BIII**). In accordance with IDSA guidelines for patients with complicated abdominal infections in non-neutropenic patients [158] and the guideline for antimicrobial therapy of unexplained fever in neutropenic patients of the AGIHO [159], we recommend administration of piperacillin/tazobactam or a carbapenem with anti-pseudomonal activity (imipenem/cilastatin, meropenem or doripenem) (**BIII**). There are no studies assessing the effect of additional metronidazole or vancomycin on patient outcome (**CIII**). Empirical antifungal therapy may be discussed if it has not yet been administered for the indication of persistent febrile neutropenia [147, 160, 161] (**BIII**). The use of hematopoietic growth factors should be considered, even though corresponding evidence is not available (**BIII**). Therapy should be administered until resolution of clinical signs and neutropenia. While a surgical consultation should be obtained at an early stage of disease evolution, surgical interventions in the neutropenic and/or thrombocytopenic patient is reserved to severe cases, e.g. patients with bowel wall perforation (**BIII**).

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Publikation X

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ORIGINAL ARTICLE

Clostridium difficile-associated diarrhoea, a frequent complication in patients with acute myeloid leukaemia

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Abstract Diarrhoea occurs frequently in neutropenic patients with acute leukaemia receiving chemotherapy and may be caused by either infection- or drug-induced cytotoxicity. Since *Clostridium difficile* is the most common cause of nosocomial infectious diarrhoea in non-haematologic patients, we were interested in its incidence in patients with acute myeloid leukaemia (AML). In this retrospective study, we analysed 134 patients with AML receiving a total of 301 chemotherapy courses. Diarrhoea occurred during 33% of all courses in 58 patients. *C. difficile*-associated diarrhoea (CDAD) occurred in 18% of all patients and 9% of all treatment courses. Almost one third of diarrhoea episodes were caused by *C. difficile*. CDAD was associated with older age (58 vs. 50 years), number of antibiotics administered (2 vs. 1), duration of antibiotic therapy (7 vs. 4 days), ceftazidime as the antibiotic of choice (75% vs. 54%) and duration of neutropenia (12 vs. 7 days) prior to onset of diarrhoea. An increased risk for CDAD was seen for prolonged neutropenia. CDAD responded well to oral metronidazole and/or vancomycin and no patient died of this complication. In conclusion, CDAD is common in patients with AML receiving chemotherapy. *C. difficile* enterotoxin testing of stool specimens should be included in all symptomatic patients.

Keywords *Clostridium difficile* · Diarrhoea · Enterocolitis · Acute myeloid leukaemia · Neutropenia

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Introduction

Patients with acute myeloid leukaemia (AML) have severe neutropenia, either due to the leukaemic burden or the cytotoxic effects of chemotherapy, which usually consists in a combination of cytarabine (Ara-C) and an anthracycline such as idarubicine or daunorubicine [1, 2] rendering patients susceptible to life-threatening infections and/or mucositis. Since infections are a major cause for morbidity and mortality in patients with acute leukaemia, institution of empirical antibiotic therapy is mandatory if fever occurs in neutropenic patients [3]. The use of antibiotic prophylaxis is still common in many centres. However, antibiotic use is an important risk factor for *Clostridium difficile*-associated diarrhoea (CDAD), since antibacterial drugs suppress resident bowel flora and thus permit overgrowth of *C. difficile* [4–7]. Enteric infections with other pathogens are also common in patients with acute leukaemia [8]. Neutropenic enterocolitis is a severe complication of aggressive chemotherapy in these patients and occurs in about 6% [8, 9] with *C. difficile* often being the underlying pathogen [10]. However, diarrhoea may be caused by abdominal infection, intestinal mucositis or other toxic effects of chemotherapy [8]. On the other hand, cytotoxic chemotherapy, such as Ara-C, may also induce *C. difficile* colitis [11, 12].

Thus, CDAD is a common complication in patients with haematological malignancies after myelosuppressive chemotherapy [13]. Since we observed an increase in the incidence of diarrhoea in patients with AML, we decided to initiate this retrospective study. The aim of this study was to evaluate clinical data and risk factors for patients with AML developing CDAD after aggressive chemotherapy.

Materials and methods

All medical records of patients diagnosed with AML at our hospital between January 2003 and March 2008 were reviewed retrospectively. Only patients receiving Ara-C/anthracycline-based chemotherapy (e.g. Ara-C/idarubicine "3+7") were included in this analysis. Patients receiving low-dose Ara-C s.c. or oral chemotherapy were excluded from this study.

In all patients with diarrhoea, stool samples for *C. difficile* enterotoxin and cytotoxin detection (toxin A and B; RIDASCREEN®, R-Biopharm, Darmstadt, Germany) had been obtained. This enzyme-linked immunosorbent assay has a sensitivity and a specificity of 91.7% and 100.0%, respectively (manufacturer's information). Furthermore, stool samples were cultured for *Salmonella*, *Shigella*, *Yersinia enterocolitica* and *Campylobacter coli/jejuni* using standard culture techniques.

Neutropenia was defined as absolute neutrophil count $<1.0\times10^9$/L. CDAD was defined as diarrhoea (≥3 unformed stools per 24 h) in the presence of a positive *C. difficile* toxin test. Diarrhoea due to other causes than *C. difficile* was termed non-CDAD. Severe enterocolitis due to *C. difficile* was diagnosed if bloody diarrhoea, fever (axillary temperature ≥38.3°C) and abdominal pain occurred.

Clinical response was defined as resolution of diarrhoea within 12 days of appropriate therapy without deterioration of other abdominal symptoms. Treatment failure was defined as deterioration of abdominal symptoms, persistence of diarrhoea after 12 days of appropriate therapy or progression to severe enterocolitis. Recurrence was defined as a new episode of diarrhoea with detection of *C. difficile* toxin during the subsequent chemotherapy course.

Antibiotic prophylaxis during neutropenia had not been used according to our institution's policy. Patients with febrile neutropenia received ceftazidime (2,000 mg t.i.d. i.v.) as first-line treatment according to our institutional guidelines. Student's *t* test, Fisher's exact test, odds ratio (OR) with the 95% confidence interval (95%CI) and Pearson's correlation coefficient (*R* value) were used for statistical analyses. Two-sided *P* values <0.05 were considered as statistically significant.

Results

General findings

In this study, 134 consecutive patients with AML receiving Ara-C-based chemotherapy were included. Mean age was 53 years (range 18–75 years), whereas 43% of the patients were ≥60 years old. The male/female ratio was equally balanced. Approximately two thirds of the patients (87 out of 134) had de novo AML. A total of 301 chemotherapy courses was administered (mean 2, range 1–5). The majority of all patients received Ara-C doses ≥6,000 mg/m^2 per chemotherapy course (67.1%, 202 out of 301). In six courses (2.0%) no Ara-C was administered, i.e. idarubicine alone or busulfan/cyclophosphamide was given. Diarrhoea occurred in 40.6% of patients. Twenty-eight episodes of CDAD occurred in 24 patients with an overall incidence of CDAD of 17.9% per patient with AML.

Diarrhoea of any cause occurred in 100 chemotherapy courses (33.2%) in 58 patients with a mean duration of 6 days (range 1–31 days). In 28 diarrhoea episodes (28.0%), *C. difficile* was found. Thus, CDAD occurred in 28 of 301 (9.3%) chemotherapy courses (Table 1). CDAD occurred during the first chemotherapy course in 44.0% of patients, followed by the second (24.0%), the third (12.0%), the fourth (12.0%) and the fifth (8.0%). Three patients had two episodes of CDAD in consecutive chemotherapy courses. Only one patient developed CDAD without prior antibiotic treatment. *Salmonella*, *Shigella*, *Y. enterocolitica*, and *C. coli/jejuni* were not found in any stool samples of AML patients with diarrhoea.

Table 1 Clinical characteristics of patients

Clinical characteristic	Value
Patients	
n	134
Age, years (range)	53 (18–75)
Sex, male/female	1:1
AML, *n* (%)	
De novo	87 (64.9)
Secondary	30 (22.4)
Relapsed	17 (12.7)
Chemotherapy courses	
Administered, *n* (mean, range)	301 (2, 1–5)
Ara-C dose ≥6,000 mg/m^2 per course, *n* (%)	202 (67.1)
Episodes of diarrhoea	
n	100
Duration, days (range)	6 (1–31)
Caused by *C. difficile*, *n* (%)	28 (28.0)

Ara-C cytarabine

Clinical features of patients with CDAD

In the comparison of the clinical features of AML patients with CDAD (n=28) and non-CDAD (n=72), we found age (58 vs. 50 years, P=0.02), number of antibiotics administered (2 vs. 1, P=0.03), use of ceftazidime (75.0% vs. 54.2%, P=0.046), duration of antibiotic use (7 vs. 4 days, P=0.01) and duration of neutropenia (12 vs. 7 days, P=0.01) prior to onset of diarrhoea to be associated with a higher risk for CDAD. However, duration of diarrhoea (8 vs. 6 days, P=0.25) and administered Ara-C dose (5,336 vs. 5,774 mg/m^2 per course, P=0.66) were not associated with a higher risk for CDAD (Table 2).

In patients with CDAD, more than one half (57.1%, 16 out of 28) had neutropenia ≥10 days, but only one third (24 out of 72) of patients with non-CDAD had prolonged neutropenia prior to onset of diarrhoea.

In univariate analysis, duration of neutropenia ≥10 days prior to onset of diarrhoea only was associated with an increased risk for CDAD (OR=2.7 [95%CI=1.09–6.52]). However, there was no significantly higher risk for older patients (age ≥60 years) (OR=1.7 [95%CI=0.67–4.14]), antibiotic therapy per se (OR=2.6 [95%CI=0.82–8.52]), duration of antibiotic therapy ≥10 days (OR=1.7 [95% CI=0.58–4.79]) prior to onset of diarrhoea and Ara-C dose ≥6,000 mg/m^2 per course (OR=0.5 [95%CI=0.21–1.24]). A trend was seen for ceftazidime therapy (OR=2.5 [95%CI=0.96–6.72]) prior to onset of diarrhoea. In contrast, correlation of risk factors with the development of CDAD is very low (Table 3).

Treatment and outcome of CDAD

In 92.9% (26 out of 28) of all CDAD episodes, patients were treated with either metronidazole 400 mg t.i.d. p.o. or vancomycin 250 mg q.i.d. p.o. In two episodes, patients received no antibiotic therapy because diarrhoea had already stopped spontaneously when the test results arrived. All four episodes of recurrent CDAD occurred in two consecutive chemotherapy courses. In three cases, metronidazole, and in one case, vancomycin was administered as primary therapy. One patient received metronidazole due to soft tissue infection prior to CDAD wherefore primary vancomycin therapy of CDAD was started. Treatment failure of primary metronidazole therapy was seen in three cases, but not of primary vancomycin therapy (Table 4). Severe enterocolitis developed in 17.9% (five out of 28) of all CDAD episodes. Of these, 80.0% (four out of five) were treated initially with metronidazole and one with vancomycin. No patient died of CDAD.

Discussion

In our retrospective single-centre study, we found that diarrhoea is a common complication among AML patients receiving chemotherapy. Diarrhoe occurred in about 40% of patients and in one third of all chemotherapy courses. *C. difficile* was the causative agent in approximately one third of all diarrhoea episodes and thus it is a major contributor to this complication. Interestingly, stool cultures revealed no other bacterial infectious agents such as *Salmonella*, *Shigella*, *Yersinia* or *Campylobacter* in any diarrhoea episode, which is an important finding, showing that diarrhoea in leukaemia patients, although a common complication, is caused rather by factors associated with the underlying disease itself or therapy complications rather than the lack of hygiene in the hospital setting.

Diarrhoea is a common adverse event in patients with acute leukaemia [8]. In AML patients treated with Ara-C, diarrhoea was seen in up to 100% in a previous study [14] and partly depended on total dose and duration of treatment [15]. Fatal infectious complications have been dreaded in patients with acute leukaemia [16]. Neutropenic enterocolitis-related death rate is with about 30% very high in these patients. Risk factors for diarrhoea and enterocolitis, respectively, are neutropenia, infections, and drug-induced alterations of the bowel mucosal surface [9].

The incidence of CDAD in patients with AML is 18% per patient and 9% per chemotherapy course. In a heterogeneous patient group with AML, acute lymphoblastic leukaemia, chronic myeloid leukaemia in blast crises, and aggressive non-Hodgkin lymphoma, the incidence of CDAD was 5–7% per chemotherapy course [8, 13].

Table 2 Comparison of clinical features of patients with diarrhoea

Clinical feature	CDAD (n=28)	Non-CDAD (n=72)	P value
Age, years (range)	58 (22–75)	50 (18–70)	0.02
Duration of diarrhoea, days (range)	8 (2–31)	6 (1–31)	0.25
Number of antibiotics[a], n (range)	2 (0–5)	1 (0–3)	0.03
Ceftazidime therapy[a], n (%)	21 (75.0)	39 (54.2)	0.046
Duration of antibiotic therapy[a], days (range)	7 (0–21)	4 (0–17)	0.01
Duration of neutropenia[a], days (range)	12 (0–33)	7 (0–22)	0.01
Ara-C dose, mg/m^2 per course (range)	5,336 (0–18,000)	5,774 (0–10,000)	0.66

CDAD C. difficile-associated diarrhoea, *non-CDAD* diarrhoea due to other causes than CDAD, *Ara-C* cytarabine

[a] Prior to onset of diarrhoea

Table 3 Risk factors for developing CDAD

Clinical feature	OR [95%CI]	*R* value	*P* value
Age ≥60 years	1.7 [0.67–4.14]	0.14	0.35
Antibiotic therapy per se[a]	2.6 [0.82–8.52]	0.15	0.13
Antibiotic therapy ≥10 days[a]	1.7 [0.58–4.79]	0.08	0.40
Ceftazidime therapy[a]	2.5 [0.96–6.72]	0.19	0.07
Neutropenia ≥10 days[a]	2.7 [1.09–6.52]	0.22	0.04
Ara-C dose ≥6,000 mg/m^2 per course	0.5 [0.21–1.24]	−0.15	0.16

Ara-C cytarabine

[a] Prior to onset of diarrhoea

Interestingly, CDAD occurred in about two thirds of the cases in the first two therapy courses. Perhaps, it is due to the leukaemic tumour burden of the bowel. In most cases, thickening of the bowel wall is not caused by mucosits but by infections. In very rare cases, thickenings are caused by leukaemic infiltration of the bowel [8]. Recently, leukaemia was identified to be a significant independent risk factor for CDAD [17].

In an in vitro study, it could be shown that Ara-C has no cytotoxic activity against *C. difficile*. In patients with leukaemia, Ara-C use represents a risk factor altering the intestinal flora and so lowering the colonisation resistance, which leads to *C. difficile* overgrowth if antibiotics are used [18]. Interestingly, a higher Ara-C dose seems to be protective for CDAD as OR=0.5. Similar results were found by Gorschlüter et al. [8]: The incidence of diarrhoea in patients who had received high-dose Ara-C was significantly lower compared with patients who were treated with standard-dose Ara-C. This observation is in contrast with reports in which the mucosal-damaging effects of high-dose Ara-C have been implicated in the pathogenesis of invasive bacterial and fungal infections [8].

Antibiotic therapy per se (OR=21.3), especially cephalosporin therapy (OR=2.6), is associated with significantly increased risk for CDAD [19]. In a recent study of antibiotic use and subsequent CDAD in hospitalised patients, ceftazidime was shown to be associated with a significantly increased risk (OR=1.8) of acquiring CDAD [20]. This is in accordance with our findings in patients with AML (OR=2.5).

Table 4 Response to therapy among patients with CDAD (*n*=28)

Treatment	*n* (%)
Metronidazole	19 (73.1)
Response	16 (84.2)
Treatment failure	3 (15.8)
Recurrence	3 (15.8)
Vancomycin	7 (26.9)
Response	7 (100.0)
Treatment failure	0
Recurrence	1 (14.3)

AML is a disease of older adults with a median age at diagnosis of 67 years [21]. In this study, CDAD was more frequent in older patients. Age as an accepted risk for developing CDAD [6, 19] may be due to the higher comorbidity rate in the elderly.

The risk of superinfection with *C. difficile* in patients with haematological malignancies and antimicrobial treatment appears to increase with the grade and duration of neutropenia [22]. In our study, we could show that neutropenia is a risk factor for developing CDAD (OR=2.7). About 85% of patients with acute leukaemia undergoing aggressive chemotherapy develop infections and/or fever during the neutropenic phase [3]. So, perhaps, the higher CDAD rate for neutropenic patients is due to the more frequent use of antibiotic agents, since it has been shown that antibiotic use is associated with CDAD. The incidence of CDAD is 7% per patient after autologous peripheral blood stem cell transplantation (SCT), slightly lower than in acute leukaemia [23]. In a cohort of patients receiving an allogenic or autologous haematopoietic SCT, the incidence of CDAD was 14% per patient [24]. The lower incidence of CDAD in patients with autologous peripheral SCT may reflect the duration of neutropenia in this setting (7 days) [23] in comparison to both allogenic or autologous SCT (14 days) [25] or conventional AML therapy (21 days) [26]. More than one half (58%) of *C. difficile* infections occurred in patients with neutropenia in comparison to the non-neutropenic phase after haematopoietic SCT [25].

Classic bacterial enteric pathogens in patients with acute leukaemia- and chemotherapy-related neutropenia have a low incidence of about 1% [8, 27]. Also, we found no enteric infection by other enteropathogenic bacteria and gram-negative sepsis, respectively. In 18% of CDAD episodes, patients developed severe enterocolitis. This was more frequently seen, as reported by Gorschlüter et al. to be 8% [13]. Fortunately, no patient died due to CDAD.

CDAD is a major concern for health care systems and clinicians [28]. Morbidity and mortality from CDAD increased in recent years [29–31], which might also have an impact on leukaemia patients. Unfortunately, clear data of increasing incidence of CDAD for patients with

haematological malignancies are not available so far. Recent outbreaks of CDAD with increased severity, high relapse rate and significant mortality have been related to the emergence of a new, hypervirulent *C. difficile* strain worldwide. The emerging strain is referred to as NAP1 and PCR ribotype 027 [31, 32]. In our series, we have not tested for hypervirulent *C. difficile* strains.

Current diagnosis of CDAD is based on methods that specifically detect toxin A and/or toxin B in stool samples or detect both toxigenic and non-toxigenic strains of *C. difficile* (e.g. by culture on selective media or detection of a *C. difficile* surrogate marker antigen in stool specimens) [5, 33]. Sensitivity and specificity of enzyme immunoassays for detection of *C. difficile* toxins A and B are 91% (range 88–93%) and 100%, respectively. These tests are valuable methods for the diagnosis of CDAD [33]. Since the sensitivity of our used toxin test is 92%, only 8% of patients with diarrhoea escape the diagnosis of CDAD. The rate of *false*-negative tests could be reduced by repetitive toxin tests within 7 days (with the highest detection rate on days 3–4) [34].

Metronidazole has been recommended as initial therapy since the late 1990s and continues to be the first choice for all but seriously ill patients and those with complicated or fulminant infections or multiple recurrences of CDAD for whom vancomycin is recommended [35]. Metronidazole should be particularly preferred due to the emergence of vancomycin-resistant enterococci (VRE) [36, 37]. *C. difficile* infection is a risk factor for bacteriaemia due to VRE in VRE-colonised patients with acute leukaemia [38]. After the emergence of hypervirulent *C. difficile* strains in 2003, vancomycin was no longer superior to metronidazole in avoiding complications of CDAD [39]. The mean response rate to metronidazole is 86% (range 74–95%). The low rate of 74% is associated with an epidemic *C. difficile* strain [35, 39]. For sick patients, such as AML patients, empirical therapy should be started as soon as CDAD is suspected [31]. In our study, the response rate to metronidazole p.o. was 84%, slightly lower than the 91% reported by Gorschlüter et al. [13]. Vancomycin p.o. is effective in metronidazole failure as the response rate was 100%.

In conclusion, diarrhoea is common in patients with AML undergoing Ara-C-based chemotherapy and CDAD accounts for one third of all episodes. Therefore, stool specimens should be tested for *C. difficile* thus prompt therapy can be initiated.

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Publikation XI

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LETTER TO THE EDITOR

The incidence of norovirus infections in cancer patients shows less seasonal variability compared to patients with other diseases

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Dear Editor,

Diarrhoea is a frequent complication in cancer patients. Causes are paraneoplastic, therapy-associated, and infection-related [1, 2]. World-wide, norovirus infection (NVI) is a major cause of acute gastroenteritis during winter, and also one of the most common cause of viral gastroenteritis in cancer patients [2] with a high mortality rate up to 25 %, especially after allogeneic transplantation [3]. Epidemiology of NVI differs among immunocompromised and immunocompetent patients [4], but data regarding NVI in cancer patients are scarce.

In order to analyse the epidemiology of NVI among cancer patients, we conducted a retrospective, monocentric study. Patients of two departments at the Medical Centre of the Otto-von-Guericke University Magdeburg, Germany, were included: Department of Haematology and Oncology (HO) and Department of Gastroenterology, Hepatology and Infectious Diseases (GHI). Cases in the cold season (October–March) were compared with cases in the warm season (April–September), and HO cancers (acute leukaemias, lymphomas) were compared with GHI cancers as well as the entire spectrum of HO patients (e.g., patients with anaemia or other benign diseases) with the entire spectrum of GHI patients (e.g., patients with gastric bleeding). Stool samples of all consecutive in-patients with suspected gastroenteritis between January 2009 and December 2012 were tested on the presence of norovirus by using an enzyme-linked immunosorbent assay (RIDASCREEN Norovirus 3rd Generation, R-Biopharm, Darmstadt, Germany).

All together, 1,766 stool samples of 673 patients (mean age 58.6 years, 54.5 % men) were tested and 66 de novo NVI cases in 60 patients were diagnosed. Thirty-one NVI cases occurred in cancer patients, of which $n=23$ (74 %) suffered from haematological cancers.

Prevalence and incidence of NVI were not significantly different among HO and GHI patients (Table 1, item 1–2). Taken together, there was no significantly increased NVI risk in the entire HO population compared to the entire GHI population, but, however, the NVI risk especially for HO cancer patients was significantly higher than for GHI cancer patients (Table 1, item 3). In the entire HO population as well as in the entire GHI population the risk for NVI occurrence in the cold season was significantly higher than in the warm season. However, there was no significantly increased NVI risk in the cold season when analysing the entire cancer population or the subgroup of HO cancer patients only (Table 1, item 4).

In general, NVI predominate in winter [4]. In contrast, few reports showed that in cancer patients, the seasonal variability of the NVI incidence is less pronounced. This concept, however, was based on few observations—on $n=9$ children [5], $n=12$ adults [6], or $n=11$ cases in outbreaks [3], respectively. Our larger series of cancer patients ($n=31$) with NVI corroborates these previous observations [3, 5, 6]. Immunosuppressive therapy is a risk factor for NVI. In immunocompromised patients NVI often persists for weeks to years [4], which may explain the *non*-seasonal occurrence of NVI in cancer patients.

In conclusion, our data clearly show less seasonal variability of NVI incidence in cancer patients compared to patients

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Table 1 Epidemiology data and risk factors for norovirus infections

	Value	*p* Value
1. NVI prevalence, % [95 % CI]		
All HO patients	0.7 [0.2–1.2]	0.36
All GHI patients	0.5 [0.2–0.7]	
2. NVI incidence, per 1,000 patient-years [95 % CI]		
All HO patients	7.1 [0–16.2]	0.44
All GHI patients	4.6 [0–9.5]	
3. NVI risk, OR [95 % CI]		
All HO vs. all GHI patients	1.3 [0.8–2.2]	0.40
HO cancer vs. GHI cancer patients	83.1 [9.8–702.5]	<0.001
4. NVI risk for occurrence in cold vs. warm season, OR [95 % CI]		
All HO patients	3.5 [1.1–10.5]	0.03
All GHI patients	2.9 [1.4–5.9]	0.003
All cancer patients	2.1 [0.6–6.9]	0.36
Only HO cancer patients	1.8 [0.2–13.2]	0.92

NVI norovirus infection, *HO* haematology and oncology, *GHI* gastroenterology, hepatology and infectious diseases, *OR* odds ratio, *95% CI* 95 % confidence interval. Student's *t* test and Fisher's exact test were used for statistical analyses; two-sided *p* values <0.05 were considered statistically significant

with other diseases. Thus, in cancer patients, NVI also have to be considered in cases of diarrhoea in summer.

Conflict of interest None.

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Publikation XII

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Central venous catheter-related infections in hematology and oncology: 2012 updated guidelines on diagnosis, management and prevention by the Infectious Diseases Working Party of the German Society of Hematology and Medical Oncology

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Background: Cancer patients are at increased risk for central venous catheter-related infections (CRIs). Thus, a comprehensive, practical and evidence-based guideline on CRI in patients with malignancies is warranted.

Patients and methods: A panel of experts by the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Medical Oncology (DGHO) has developed a guideline on CRI in cancer patients. Literature searches of the PubMed, Medline and Cochrane databases were carried out and consensus discussions were held.

Results: Recommendations on diagnosis, management and prevention of CRI in cancer patients are made, and the strength of the recommendation and the level of evidence are presented.

Conclusion: This guideline is an evidence-based approach to the diagnosis, management and prevention of CRI in cancer patients.

Key words: guidelines, central venous catheter, catheter infection, neutropenia

introduction

Central venous catheters (CVCs) are widely used in patients with malignancies. However, cancer patients are at increased risk of catheter-related infections (CRIs) that are associated with increased morbidity and hospital costs [1–6]. These updated guidelines have been developed for healthcare personnel who insert CVC and/or are responsible for surveillance and care of CVC in patients with cancer.

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methods

First, subtopics of this guideline were assigned to a panel of 14 experts in the field of infectious diseases in hematology–oncology and hospital epidemiology and infection control, respectively. Second, literature searches of the PubMed, Medline and Cochrane databases were carried out with combinations of the following search terms: central venous catheter infection, central venous catheter-related bloodstream infection, central venous catheter-associated bloodstream infection, cancer, neutropenia, definition, pathogenesis, pathogens, epidemiology, incidence, risk factors, diagnosis, treatment, management, surveillance, education and prevention. Third, the consensus process was carried out as an e-mail- and meeting-based discussion group. Criteria used to quote levels and grades of evidence are shown in Table 1 [7]. The guideline replaces our previous guideline [8],

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Table 1. Categories of evidence levels used in this guideline [7]

Category, grade	Definition
Strength of recommendation	
A	Good evidence to support a recommendation for use
B	Moderate evidence to support a recommendation for use
C	Poor evidence to support a recommendation
D	Moderate evidence to support a recommendation against use
E	Good evidence to support a recommendation against use
Quality of evidence	
I	Evidence from ≥1 properly randomized, controlled trial
II	Evidence from ≥1 well-designed clinical trial, without randomization; from cohort or case–controlled analytic studies (preferably from >1 center); from multiple time-series; or from dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees

and was finally approved by the assembly of the members of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Medical Oncology (DGHO) on 21 October 2012.

guideline

definitions

Diagnosis of infections due to CVC is based on clinical symptoms and laboratory findings not always withstanding clear definitions. However, as suggested by the Centers for Disease Control and Prevention (CDC) CRI can be subdivided in catheter colonization, different types of local CRI, infusate-related bloodstream infections (BSIs) and catheter-related BSI (CRBSI) [3, 6, 9]. Types of CRI are defined as follows:

catheter colonization. Colonization is defined by significant growth of a microorganism [>15 colony-forming units (CFU) in semiquantitative culture or >100 CFU in quantitative culture] from the catheter surface in the absence of accompanying clinical symptoms or bacteremia.

local CRI.

- Exit site infection: Clinical signs of inflammation (e.g. redness, swelling, pain, purulent exsudate) located ≤2 cm from the catheter insertion site, in the absence of concomitant BSI.
- Tunnel infection: Clinical signs of infection >2 cm from exit site along the subcutaneous part of the CVC, in the absence of concomitant BSI.
- Pocket infection: Pocket infection is diagnosed when the subcutaneous pocket of an implanted port system shows clinical signs of infection and inflammation, in the absence of concomitant BSI.

infusate-related BSI. Concordant growth of the same organism from the infusate and blood cultures (preferably percutaneously drawn) with no other identifiable source of infection [9].

catheter-related bloodstream infections. While the CDC distinguishes CRBSI from catheter-associated BSI (CABSI)—the latter being considered if a patient had a CVC ≤48 h before the development of the BSI that is not related to an infection at another site [6]—we propose for routine clinical use a distinction between 'definite', 'probable' and 'possible' CRBSI as outlined in Table 2.

pathogenesis

Potential portals of entry for infecting microorganisms are the skin, catheter hubs, and infusion solutions. In catheters used for <14 days (short-term catheters), infections are mainly due to extraluminal spread of bacteria along the outer surface of the catheter. In catheters used for ≥14 days (long-term indwelling catheters), the intraluminal pathway predominates [12, 13].

Colonization of the insertion site by normal skin flora or pathogenic organisms is a major risk factor for CRBSI [14–16]. Endogenous lining of the interior surface of the catheter with a biofilm takes place ≤24 h after insertion [17]. This biofilm is composed of polysaccharides, fibrin, fibronectin or laminin, and appears to be the most important pathogenetic mechanism for the development of CRI. Microorganisms embedded into this biofilm are shielded from host defense mechanisms and from antibiotics. Crystal deposits originating from flushed fluids may further facilitate anchoring of bacteria to the luminal catheter surface [18]. Microtrauma emerging during catheter placement results in the formation of small thrombi on the intravascular catheter tip, thus creating another breeding ground for bacteria.

epidemiology

Prospective surveillance studies in adult cancer patients reported a CRBSI/CABSI incidence of 1.1–7.5 per 1000 CVC days [19–21]. Similar incidence rates of 3.6–7.9 per 1000 CVC days CRBSI/CABSI were found in a randomized, controlled trial that investigated two alcohol-based antiseptic solutions for preparation and care of CVC insertion sites [14, 22]. The incidence of CRBSI/CABSI in hematology patients was found to be 20.3 and 22.0 per 1000 neutropenic days, respectively [23–25]. The German National Reference Center for Nosocomial Infections (ONKO-KISS) reported a CABSI incidence of 12.6 and 10.3 per 1000 neutropenic days in autologous and allogeneic stem cell transplant (SCT) recipients, respectively [26].

risk factors

Neutropenia is an independent risk factor for infection related to long-dwelling tunneled CVC in patients with cancer [27]. Further, a large prospectively collected database on patients with nosocomial BSI—83.1% of those having a CVC—showed a higher mortality rate in neutropenic (36%) compared with non-neutropenic (31%) patients [28].

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Table 2. Diagnostic criteria for CVC-related bloodstream infections (CRBSI)

Diagnosis	Criteria (I)	Criteria (II)
'Definite' CRBSI	Growth of same pathogen from blood culture of peripheral vein and from culture of CVC tip	±*in vitro* susceptibility testing results in the same resistance pattern (AI) [10]
	Growth of same pathogen from blood culture of CVC and from blood culture of peripheral vein	**and** DTTP ≥2 h (AII) **or**, for quantitative blood cultures, a ≥3-fold greater colony count of microbes grown from blood culture of CVC than the colony count from a peripheral vein (AII) [5, 10, 11]
'Probable' CRBSI	Growth of the same pathogen from blood culture of CVC and from blood culture of peripheral vein	**and** no criteria for definitive CRBSI **and** detection of coagulase-negative *Staphylococcus* spp., *S. aureus* or *Candida* spp. **and** exclusion of other infection sites (BIII)
Exit site infection	Clinical signs of infection ≤2 cm from the catheter exit	**and** BSI without criteria for definitive CRBSI (BIII)
Tunnel infection (Hickman and Broviac catheter)	Clinical signs of infection >2 cm from catheter exit site along the subcutaneous part of catheter	**and** BSI without criteria for definitive CRBSI (BIII)
Pocket infection (implanted port system)	Clinical signs of infection of subcutaneous pocket	**and** BSI without criteria for definitive CRBSI (BIII)
'Possible' CRBSI		
Catheter colonization	Growth of pathogen from CVC tip (>15 CFU in semiquantitative/>100 CFU in quantitative culture)	**and** clinical or laboratory signs of infection (e.g. leukocytosis or elevated C-reactive protein) **and** no BSI (BIII)
	Pathogen detected in blood culture that is typically causing CRI (*S. epidermidis, S. aureus, Candida* spp.)	**and** no other focus identified (BIII)
	Remission of fever in <48 h after CVC removal	**and** no other focus identified (BIII)

CRBSI, catheter-related bloodstream infection; BSI, bloodstream infection; CFU, colony-forming unit; CVC, central venous catheter; DTTP, differential time to positivity of CVC blood culture and peripheral blood culture; CRI, catheter-related infection.

The ONKO-KISS multicenter surveillance project found an increased risk for CABSI in males and in patients with acute myeloid leukemia [29]. Subclinical thrombosis of the catheterized vein, as detected by ultrasound, may be another important risk factor for subsequent CRI [15, 30], and colonization of CVC by microorganisms appears to be a major risk factor for subsequent catheter-related thrombosis [31]. Patients with hematologic malignancies are at higher risk for CRI than patients with solid tumors [32].

High level of skin colonization at the insertion site and the catheter hub/connector was shown to be a predictor for CABSI with age and male gender being independent risk factors for skin colonization before CVC placement [13, 14, 17].

pathogens

In patients with hematologic malignancies or solid tumors Gram-positive organisms account for 60%–70% of CRBSI with coagulase-negative staphylococci (CNS) being by far the most commonly isolated agents [33, 34]. Other Gram-positive organisms frequently detected are *Staphylococcus aureus*, enterococci and streptococci [14, 33, 34]. Gram-negative bacteria (*Escherichia coli, Pseudomonas aeruginosa*, *Klebsiella* spp. etc.) and *Candida* spp. are found in 20%–25% and 5%–13% of patients with CRBSI, respectively [28, 33–35].

While no data are available on antimicrobial resistance rates in cancer patients with CRBSI, an increase in antibiotic resistance in Gram-negative and Gram-positive bacteria has been reported in cancer patients with BSI [36, 37]. With respect to the general population, antimicrobial resistance rates [e.g. methicillin-resistant *S. aureus* (MRSA), methicillin-resistant CNS, vancomycin-resistant *Enterococcus faecium*, ampicillin-resistant *E. coli* and ceftazidime-resistant *P. aeruginosa*] increased in patients with BSI in the US between 1995 and 2002 [38]. However, more recent data from the USA show a decrease in the incidence of MRSA CABSI in intensive care unit (ICU) patients [39].

diagnosis

Diagnostic procedures for detecting CRI are initiated when clinical signs of infection are present (Table 3). The clinical picture may be characterized by signs of local infection, fever and/or sepsis, or a combination of these. Diagnostic procedures should not differ between short-term and long-term catheters.

Patients with febrile neutropenia suspected of having a CRI should be examined in the same way as subjects with fever of unknown origin [40]. Basic requirements are a thorough physical examination, a chest X-ray and microbiology tests (blood cultures). Other diagnostic measures depend on clinical symptoms.

diagnostic procedures for local CRI. Local CRI is primarily diagnosed on the basis of clinical signs and symptoms [5]. In case of purulent secretion at the exit site of CVC, skin swabs do

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Table 3. Standard procedures in the diagnosis of CVC-related infections (CRI)

Before removal of the CVC
Rule out other possible sources of infection by clinical examination and imaging procedures, if necessary.
Inspect the catheter insertion site or pocket or tunnel for signs of local infection. Palpate the pocket or tunnel.
Take one pair of blood cultures (aerobic and anaerobic) from the catheter and one from a peripheral vein for microbiological evaluation (AII) and determine the DTTP between the peripheral and catheter blood culture sample (AII).
In case of multilumen CVC, separate blood cultures may be drawn from each lumen (AII).
After removal of the CVC
Perform a microbiological examination of the catheter tip (AII).

DTTP, differential time to positivity; CVC, central venous catheter.

not allow for a reliable differentiation between colonizing and pathogenic organisms. If tunnel infection is suspected, ultrasound imaging along the catheter with high resolution (≥7.5 MHz) may be helpful (BII). Compared with a clinically based strategy an ultrasound-driven strategy for early detection of septic thrombophlebitis and prompt CVC removal decreases infection-related mortality in neutropenic cancer patients [41].

microbiological diagnostics without removing the CVC

blood cultures: In patients with suspected CRI, two pairs of blood cultures with adequate volumes (≥20 ml) should be taken, one from a peripheral vein and one from the CVC (AII) [42, 43].

In multilumen catheters, it is advisable to take blood cultures from all lumina, as colonization can occur in one single lumen only (AII). A prospective cohort study showed that random sampling of only one lumen in triple-lumen CVC causing CRBSI has a 60% chance of detecting significant colonization [44]. However, despite superior sterile precautions, cultures taken at CVC insertion may have a higher contamination rate than peripheral blood cultures [45].

The differential time to positivity (DTTP) of results of catheter culture and peripheral blood culture is an important diagnostic indicator [46]. This applies not only to ICU patients [47] but also to hematopoietic SCT recipients [48] and neutropenic cancer patients [33].

As the information is supplied during automatic blood culture incubation, additional resources should not be required. It is important to ensure that blood cultures are sent for processing to the microbiological laboratory ≤12 h.

Differential quantitative blood cultures from samples taken simultaneously from the catheter and a peripheral vein have been proposed to avoid unjustified removal of the catheter and the potential risks associated with the placement of a new catheter at a new site. A central-to-peripheral blood culture colony count ratio of 3:1 to 10:1 is considered indicative of CRI [5, 49]. A meta-analysis found this method to be the most accurate test for diagnosing intravascular device-related BSI [10]. However, as the procedure is elaborate and expensive, it has not become standard clinical practice.

endoluminal brushing: Endoluminal brushing, a method of sampling the internal CVC surface *in situ*, may be useful in cases where no blood can be drawn through the CVC [50, 51]. However, this method may underestimate CRI in short-term catheters where external surface colonization plays an important role. Further, this technique may carry the risk of pathogen dissemination and subsequent sepsis as well as thrombotic complications. It is thus not recommended for routine diagnostics (CIII).

microbiological diagnosis after catheter removal. If catheter removal is clinically indicated, the catheter tip should be cut to a length of ∼5 cm and placed in a sterile dry container for transport (AII). Standard methods for microbiological diagnosis of CRI after catheter removal have previously been reviewed [10, 52].

management

A suspected CRI calls for therapeutic decisions concerning the need for catheter removal as well as choice and duration of antimicrobial therapy. Specific data from the literature on neutropenic patients with CRI are sparse. Thus, more general principles must serve as a guideline.

Removal of CVC has to be balanced with the risk of prolonging the infectious episode by keeping the CVC and the risk of reinserting another CVC (BIII). However, in case of suspected CRI, removal of CVC is strongly encouraged whenever possible.

indications for catheter removal. When CRI is clinically suspected, removal of the CVC is recommended if one or more of the following is present:

- the patient's clinical state deteriorates (BIII).
- sepsis and/or septic shock (BIII) [5].
- severe complications such as endocarditis, septic thrombosis, abscess formations or osteomyelitis (BIII).
- *S. aureus* is isolated from blood cultures (AII). Prospective studies of patients with short-term and long-term catheter-associated *S. aureus* bacteremia showed that failure to remove the catheter proved to be a significant risk for hematogenous spread [53] and was the most important risk factor for subsequent relapse or death due to *S. aureus* [54]. Three retrospective studies in patients with Hickman catheters and CRI due to *S. aureus* reported a rate of successful catheter preservation ranging from 18% to 60% [55–57]. However, selection biases may have overestimated the likelihood of catheter salvage success. Notably, the failure rate was higher in tunnel or exit site infection and in methicillin resistance [57].

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- Gram-negative bacilli are isolated from blood cultures. Most Gram-negative bacilli causing CRI are non-enteric organisms acquired from the hospital environment, such as *Stenotrophomonas maltophilia*, *Pseudomonas* spp. and *Acinetobacter* spp. In this situation, early removal (<72 h) of the CVC is recommended in order to prevent relapses (BII) [58–60].
- *Candida* spp. are isolated from blood cultures. In a retrospective study on neutropenic cancer patients with mucositis, the CVC was identified as a source of candidemia in only 27% [61], whereas the gastrointestinal tract had previously been reported to be an important source of candidemia [62]. Two prospective observational studies showed catheter retention to be associated with increased risk of death on univariate and multivariate analysis [63, 64]. Notably, in one of the studies, catheter removal was associated with a lower mortality rate only in patients with neutropenia [64, 65]. Other prospective observational studies that included 427 and 118 consecutive candidemic patients with several underlying diseases also found CVC retention to be a risk factor for death on multivariate analysis [66, 67]. In contrast, in a retrospective analysis of two phase III trials, designed primarily to determine the efficacy of antifungal drugs in the treatment of candidemia, CVC removal was not associated with any clinical benefit [68]. However, only 10% of the patients included in this analysis were neutropenic, and there was a lack of statistical power for evidence against CVC removal [69]. A recent retrospective study in cancer patients with candidemia reported a poorer survival if the CVC was not removed or removed >72 h [70]. Further, a prospective cohort study found the removal of a CVC at or within 5 days associated with decreased mortality [71]. In conclusion, CVC removal is recommended in cancer patients with candidemia (AII).

catheter preservation.

- In cases of uncomplicated CRI—defined as response to antimicrobial therapy (defervescense, negative blood culture) within 72 h after start of antimicrobial treatment [5]—catheter removal may not necessarily be indicated. However, the above-mentioned issues must be considered.
- Preservation of CVC may be attempted in hemodynamic stable non-neutropenic ICU patients without proven bacteremia, no local infection and no intravascular foreign body (e.g. pacemaker, prosthetic heart valve), given the CVC is carefully watched (AI) [72].
- In cases of a BSI with CNS long-term catheters (port system, Hickman catheter) may be left in place with a combination of systemic antibacterial therapy applied (BII). No randomized trials have evaluated the treatment of CNS CRBSI. However, in two retrospective cohort studies, CVC retention did not have an impact on mortality [73] or on the resolution of CNS bacteremia [74] but was a significant risk factor of recurrence, in particular in patients with a port system [74].
- If *Corynebacterium jeikeium* has been detected as a cause for CRI in neutropenic cancer patients. However, there are no prospective data on whether or not to remove the CVC [75]. A retain of CVC along with vancomycin treatment may be acceptable in hemodynamic stable patients with tunneled CVC (BII) [76].

Of note, CVC removal is not always practical in patients with hematological malignancies. An exchange over a guidewire with uncoated CVC may contribute to the development of CRBSI and can thus not be routinely recommended [77]. However, a matched retrospective cohort study in cancer patients with CRI found a catheter exchange over a guidewire for a minocyclin/rifampin-coated catheter safe [78]. A CVC exchange over a guidewire may only be used in those patients where the risk of reinsertion outweighs the persistence of CRI complication (BIII).

local infections. Exit site infections usually respond to management by local measures and antibiotics. However, in patients with tunnel or pocket infection, catheter explantation is usually required (BIII) [5, 79].

initial antimicrobial treatment. The choice of the first-line empirical drugs should take into account the underlying malignancy, clinical presentation and severity of acute illness.

Current evidence shows that the addition of anti-Gram-positive treatment, namely glycopeptides, before documentation of a Gram-positive infection, does not improve outcomes in febrile neutropenia (EI) [80, 81]. The widespread emergence of multiresistant bacterial strains should discourage strategies, such as adding vancomycin without proof of antibiotic-resistant Gram-positive bacteria as causative pathogen and/or in patients with signs of severe sepsis and shock (DIII).

After receipt of culture results, antimicrobial treatment in CRI should be modified according to *in vitro* susceptibility testing results (AII). However, in case of CVC removal and defervescence, the initial antimicrobial regimen may be continued (BIII). Depending on the causative pathogen antibiotic treatment should be continued for at least 7 days after the first sterile blood culture has been taken (AII) [82, 83]. However, specific data from neutropenic patients for the management and duration of antimicrobial treatment are sparse.

Table 4 comprises recommendations for targeted antimicrobial treatment of the most commonly involved pathogens in patients with CRI.

antibiotic-lock technique. The use of the antibiotic-lock technique (ALT) for the treatment of CRI was investigated in small randomized trials, prospective case series or retrospective cohort studies [84–87]. The ALT mostly consisted of vancomycin, teicoplanin, daptomycin, amikacin or gentamicin usually in combination with heparin. The solution is instilled into the CVC and allowed to dwell for several hours or days. The procedure can be repeated several times. ALT resulted in overall cure rates of up to 100% [86, 87]. The optimal duration of ALT is unknown. ALT was reported to be less effective in port-associated CRI compared with infection of short-term CVC [88]. ALT for 10–14 days might be a treatment option for 'highly needed" infected catheters (BIII).

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Table 4. Antimicrobial therapy of CVC-related bloodstream infections (CRBSI) depending on causative pathogen

Pathogen	Therapy	Duration[a]
Staphylococcus aureus (methicillin-sensitive)[b]	Isoxazolylpenicillin (penicillinase-resistant penicillin)	≥2 weeks[c]
S. aureus (methicillin-resistant)[b]	Glycopeptide, linezolid, quinupristin/dalfopristin	≥2 weeks[c]
Coagulase-negative stapylococci	According to susceptibility pattern; glycopeptides only in case of methicillin-resistance	5–7 days after defervescence (in patients with persistent neutropenia)
Enterococci	Aminopenicillin; glycopeptide and aminoglycoside in case of ampicillin resistance; Linezolid or quinupristin/dalfopristin in case of vancomycin resistance	5–7 days after defervescence (in patients with persistent neutropenia)
Stenotrophomonas maltophilia	Co-trimoxazole	≥2 weeks
Candida albicans[b]	Fluconazole or echinocandine or amphotericin B lipid-based formulations	≥2 weeks
Non-albicans *Candida* spp.[b]	Amphotericin B lipid-based formulations or echinocandins or voriconazole	≥2 weeks
All other pathogens	According to susceptibility pattern	Not defined

[a]Follow-up blood cultures necessary after cessation of antibiotic/antifungal therapy in order to rule out persistence of infection (AII).
[b]Catheter removal required (AII).
[c]Higher incidence of organ infection if treatment is continued for <2 weeks (AII) [82].
CVC, central venous catheter.

prevention

surveillance—education. Prospective surveillance programs along with intensive training strategies to improve the handling of CVC are able to reduce CRI rates by up to 68% not only in ICU patients [89–94] but also in neutropenic patients with hematologic malignancies [23]. Simulation-based training in CVC insertion reduced CRBSI in a prospective cohort study in ICU patients [95]. Education and process control has been shown to decrease both CRI (in particular CABSI) [96–99] and mortality (AII) [100]. Thus, treating institutions should be encouraged to establish surveillance and education programs for nurses and physicians [4, 94, 101].

There is no role for taking prophylactic blood cultures from implanted CVC in the absence of any signs of infections (CIII).

hand hygiene—skin preparation. Hand hygiene procedures (alcohol-based hand rub), aseptic technique and maximal sterile barrier precautions are important factors in preventing CRI (AII) [4, 6, 90, 97, 100, 102]. Maximum sterile barrier precautions include wearing a sterile gown, gloves and cap and using a large sterile drape. Ultrasound-guided placement may be helpful to reduce the number of mechanical complications and cannulation attempts (BI) [103, 104].

For cutaneous antisepsis, an alcohol containing >0.5% chlorhexidine-based solution (CBA) should be used as it proved to be more efficacious in decreasing CRBSI compared with 10% polyvidone-iodine or 70% alcohol-only solutions for catheter insertion (AI) [94, 105–107]. Although a meta-analysis of >4000 catheters—of which 1493 were CVC—suggested that CBA reduced the risk of CRI relative to polyvidone iodine [108], alcoholic polyvidone-iodine solutions (A-PVP) or 70% propanolol are safe alternatives if there is a contraindication to chlorhexidine (AI) [6, 94, 105, 106, 109, 110]. This recommendation is supported by a recent cohort study that revealed no major clinical advantage of CBA use over A-PVP for preventing CRI [111].

One randomized, controlled study showed that the serial combination of alcoholic chlorhexidine solution with aqueous polyvidone-iodine was superior to either of the regimens alone [112]. In another randomized, controlled trial skin disinfection with 0.1% octenidine plus 30% 1-propanol and 45% 2-propanol proved superior to 74% ethanol with 10% 2-propanol in terms of skin colonization at the CVC insertion site, positive culture at the catheter tip and CABSI [22]. This study supported results of two prior observational studies demonstrating octenidine in alcoholic solution to be a better option than alcohol alone for the prevention of CRI [113, 114].

Thus, both serial combination of alcoholic chlorhexidine solution with aqueous polyvidone-iodine or octenidine/propanolol solutions are also useful for cutaneous antisepsis (AI).

selection of catheters and sites. As randomized studies showed similar infection rates between single-, double- and triple-lumen CVC [115, 116], a preferred use of single-lumen catheters is not supported [117]. The use of femoral lines is associated with a greater risk of infectious and thrombotic complications than the use of subclavian lines [118–121]. Thus, femoral catheterization should be avoided (DIII). While no randomized studies have directly compared infection rates as primary outcome measure between internal jugular vein and subclavian vein catheterization, the site of catheter insertion (internal jugular vein versus subclavian vein) was not noted to be a risk factor for CRI in a recent prospective randomized study on the use of antimicrobial impregnated CVC [122]. A Cochrane analysis found subclavian and internal jugular central venous access routes to have similar risks for catheter-related complications [121]. Another prospective observational study also found no differences in CRI rates between different insertion sites

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[123]. However, the risk for uncontrolled hemorrhage or pneumothorax may be higher by using subclavian lines. In a recent prospective observational study, the subclavian vein access resulted in more overall complications than the internal jugular vein access [124]. As demonstrated by one randomized study, sutureless securement devices are able to reduce the risk for infection for CVC (BI) [125].

systemic antimicrobial prophylaxis. Systemic antimicrobial prophylaxis before insertion of the catheter does not result in a significant reduction of CRI (EI) [126].

antimicrobial catheters. CVC impregnated with antiseptics (chlorhexidine and sulfadiazine silver) on the external or on both the external and internal surfaces have been evaluated in numerous randomized, controlled trials [6, 107, 110, 127–131]. While most of the studies showed a significant reduction in catheter colonization, a significant reduction in CRBSI was not consistently demonstrated. Thus, routine use of antiseptic catheters cannot generally be recommended in cancer patients (CI).

Antimicrobial-impregnated catheters (minocycline/rifampicin or miconazole/rifampicin) reduced the incidence of CRI in four of five randomized studies (AI) [132–137]. Of note, the duration of catheterization was unusually long (63 and 66 days, respectively) in the study carried out in cancer patients [134] and there is concern that resistance may develop. However, minocycline or rifampicin resistance has not been observed in a retrospective clinical cohort study over a period of 7 years [138]. Although not generally recommended, the use of antimicrobial-impregnated catheters may be useful in patients with long-term CVC if the CRI rate remains high despite implementation of educational programs and appropriate process control (BII).

antibiotic-lock technique. ALT proved to be effective for prevention of catheter hub colonization with Gram-positive bacteria and subsequent bacteremia during chemotherapy-induced neutropenia [139]. Two meta-analyses showed a reduction of CRI or BSI by using ALT solutions [126, 140]. However, the test for heterogeneity—seeking to determine whether there are genuine differences underlying the results of the studies—was statistically significant in one of the meta-analysis [140]. In a prospective, randomized, double-blind trial in patients with hematological malignancies daily administrations of ethanol locks effectively reduced the incidence of CABSI [141]. In contrast, another randomized study on the efficacy and safety of daily ethanol lock for the prevention of CRBSI showed a 3.6-fold, nonsignificant, reduction for patients receiving ethanol [142].

Depending on the baseline CRI rate, it is justified to flush a long-term CVC with a combination of an antibiotic and heparin, if the CRI rate at the institution is high [126]. However, the beneficial effects of ALT must be balanced by the potential for allergic reactions, toxicity and emergence of antimicrobial resistance (BI).

topical antimicrobials. No data are available demonstrating beneficial effects of topical application of antibiotic/antiseptic ointments at the catheter insertion site in patients with cancer. Given the risk of selecting resistant bacteria and fungi, topical antimicrobial ointments cannot be recommended (EII) [143].

catheter site dressing. Sterile gauze or transparent film should be used to cover the CVC insertion site [6]. A Cochrane review on the use of gauze, tape and transparent polyurethane dressings for CVC found that CRBSI were higher in the transparent polyurethane group when compared with gauze and tape (odds ratio = 4.19). However, this finding was based on small trials, and the confidence intervals were wide indicating high uncertainty around this estimate [144]. Two systematic reviews on the risk for CRBSI using transparent dressings versus gauze dressings found no difference between different dressing types in CRBSI, catheter

Table 5. Management of CVC-related infections (CRI)

Compliance with hygiene principles during insertion and standardized aseptic placement help to avoid infections (AII).
Education programs for nurses and physicians help to reduce the incidence of CRI (AII).
Alcoholic chlorhexidine solution with alcoholic polyvidone-iodine solutions or octenidine/propanolol solutions should be used for disinfection of the catheter insertion site (AI).
Ultrasound-guided placement may be helpful to reduce the number of mechanical complications and cannulation attempts (BI).
Routine catheter replacement to provide shorter residence times does not reduce infection rates (DI).
Systemic prophylactic antibiotic treatment before catheter insertion is not recommended (EI).
Topical application of antibiotic ointments for reducing staphylococcal colonization at the catheter insertion site is not recommended (EII).
More frequent replacement does not reduce the incidence of infection (DI).
Primary catheter removal is necessary in patients with CRBSI due to *Staphylococcus aureus* (AII).
Primary catheter removal is necessary in patients with CRBSI due to *Candida* spp. (AII).
Primary catheter removal is necessary in patients with tunnel and pocket infection (BIII).
Preservation of CVC may be initially attempted in clinically stable patients in the presence of coagulase-negative staphylococci or *Corynebacterium jeikeium* (BII).
Prompt empirical vancomycin therapy is not required (EI).
At least 2 weeks of systemic antimicrobial treatment is recommended in immunocompromised patients (BIII).
An antimicrobial-lock technique may be an option for 'highly needed' infected catheters (BIII).

CRI, catheter-related infection; CRBSI, catheter-related bloodstream infection; CVC, central venous catheter.

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Table 6. Unresolved issues

Diagnosis
Is it useful to document bloodstream clearance after completion of antimicrobial treatment in all patients with CRBSI, irrespective of catheter removal?
Can a single blood culture positive for CNS be disregarded in all cases?
Management
If catheter-drawn blood cultures are positive, but those from peripheral veins are negative, what is the optimal therapeutic approach?
How to proceed with unconfirmed CRI, pending blood culture results?
Is there a documented benefit from routine transesophageal echocardiography in patients with *Staphylococcus aureus* CRBSI? And if so, is there a difference between patients in whom the CVC is retained and those who underwent prompt CVC removal?
Is systemic antimicrobial therapy indicated in all patients with catheter-related bacteremia caused by CNS after catheter removal?
How should *Stenotrophomonas maltophilia* bacteremia be treated when co-trimoxazole fails?
If in an individual patient with catheter-related candidemia the CVC cannot be removed, should antifungal treatment with an agent that penetrates a biofilm preferred?
If a CVC of a patient with candidemia is removed, should there be a time interval before a new catheter is inserted, in order to avoid prompt colonization of the new CVC?
If ALTs are used in addition to systemic antimicrobial therapy, what is the optimal duration of this treatment?
How long should antimicrobial treatment be continued in a patient in whom the CVC could not be removed?
If in a febrile patient, one lumen of a multilumen CVC is clotted should the CVC be removed?

CRBSI, catheter-related blood stream infection; CNS, coagulase-negative staphylococci; CVC, central venous catheter; ALTs, antibiotic lock techniques.

tip colonization or skin colonization [145, 146]. Thus, gauze, tape or transparent polyurethane dressings can all be recommended for catheter site insertion dressing (AI). Chlorhexidine-impregnated sponge dressings showed a reduction in CRI rates compared with standard dressings in two randomized trials [147, 148]. However, giving the disadvantages of the sponge such as concealing the insertion site, soiling or detachment, transparent chlorhexidine-impregnated gel dressing should be preferred as it proved superior to standard dressings in a randomized, controlled trial (AI) [149].

Daily bathing with chlorhexidine reduces both CRBSI in the medical ICU [150], and CABSI in SCT recipients [151]. However, a reduction in CRI has not yet been shown in hematology patients (CIII).

Gauze dressings should be replaced every 2 days, transparent dressings every 7 days, unless local contamination, signs of inflammation or detachment are present (BI) [4, 6, 152].

replacement of CVC and administration sets. Routine catheter replacement to prevent CRI has not been shown to lower infection rates (DI) [4, 153, 154]. Infusion and tubing systems should be replaced as previously recommended [4, 6, 155].

Recommendations on management and prevention of CRI are summarized in Table 5.

unresolved clinical issues requiring further studies

As outlined in Table 6, there are a number of unresolved issues underlining the need for further studies in patients with cancer.

disclosure

MH served on the speakers' bureau for Gilead and MSD; SM served on the speakers' bureau for MSD and Pfizer; OP served on the speakers' bureau for Astellas, Gilead and MSD, and received research support from BioRaf, Fresenius and Pierre Fabre; GM served on the speakers' bureau for Gilead, MSD and Pfizer and received honoraria from Gilead, MSD and Pfizer. All remaining authors have declared no conflicts of interest.

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Muscle dysfunction in cancer patients

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Background: Muscle dysfunction is a prevalent phenomenon in the oncology setting where patients across a wide range of diagnoses are subject to impaired muscle function regardless of tumor stage and nutritional state. Here, we review the current evidence describing the degree, causes and clinical implications of muscle dysfunction in cancer patients. The efficacy of exercise training to prevent and/or mitigate cancer-related muscle dysfunction is also discussed.

Design: We identified 194 studies examining muscular outcomes in cancer patients by searching PubMed and EMBASE databases.

Results: Muscle dysfunction is evident across all stages of the cancer trajectory. The causes of cancer-related muscle dysfunction are complex, but may involve a wide range of tumor-, therapy- and/or lifestyle-related factors, depending on the clinical setting of the individual patient. The main importance of muscle dysfunction in cancer patients lies in the correlation to vital clinical end points such as cancer-specific and all-cause mortality, therapy complications and quality of life (QoL). Such associations strongly emphasize the need for effective therapeutic countermeasures to be developed and implemented in oncology practice. Significant progress has been made over the last decade in the field of exercise oncology, indicating that exercise training constitutes a potent modulator of skeletal muscle function in patients with cancer.

Conclusion: There are clear associations between muscle dysfunction and critical clinical end points. Yet there is a discrepancy between timing of exercise intervention trials, which can improve muscle function, and study populations in whom muscle function are proven prognostic important for clinical end points. Thus, future exercise trials should in early-stage patients, be powered to evaluate clinical outcomes associated with improvements in muscle function, or be promoted in advanced stage settings, aiming to reverse cancer-related muscle dysfunction, and thus potentially improve time-to-progression, treatment toxicity and survival.

Key words: skeletal muscle, muscle strength, muscle mass, cancer, exercise

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Publikation XIII

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ORIGINAL ARTICLE

Prediction of central venous catheter–related bloodstream infections (CRBSIs) in patients with haematologic malignancies using a modified Infection Probability Score (mIPS)

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Abstract The aim of this study was to predict the probability of central venous catheter–related bloodstream infections (CRBSIs) in patients with haematologic malignancies using a modified version of the Infection Probability Score (mIPS). In order to perform a prospective, mono-centric surveillance of complications in clinical routine due to short-term central venous catheters (CVCs) in consecutive patients receiving chemotherapy from March 2013 to September 2014, IPS was calculated at CVC insertion and removal ($mIPS_{in}$ and $mIPS_{ex}$, respectively). We used the 2012 Infectious Diseases Working Party of the German Society of Haematology and Medical Oncology (AGIHO/DGHO) criteria to define CRBSI. In total, 143 patients (mean 59.5 years, 61.4 % male) with 267 triple-lumen CVCs (4044 CVC days; mean 15.1 days, range 1–60 days) were analysed. CVCs were inserted for therapy of acute leukaemia (53.2 %), multiple myeloma (24.3 %) or lymphoma (11.2 %), and 93.6 % were inserted in the jugular vein. A total of 66 CRBSI cases (24.7 %) were documented (12 definite/13 probable/41 possible). The incidence was 16.3/1000 CVC days (2.9/3.1/10.1 per 1000 CVC days for definite/probable/possible CRBSI, respectively). In CRBSI cases, the $mIPS_{ex}$ was higher as compared to cases without CRBSI (13.1 vs. 7.1; $p<0.001$). The best $mIPS_{ex}$ cutoff for CRBSI prediction was 8 points (area under the curve (AUC)=0.77; sensitivity = 84.9 %, specificity = 60.7 %, negative predictive value = 92.4 %). For patients with an $mIPS_{ex} \geq 8$, the risk for a CRBSI was high (odds ratio [OR]=5.9; $p<0.001$) and even increased if, additionally, CVC had been in use for about 10 days (OR=9.8; $p<0.001$). In case other causes of infection are excluded, a $mIPS_{ex} \geq 8$ and duration of CVC use of about 10 days predict a very high risk of CRBSI. Patients with a $mIPS_{ex} < 8$ have a low risk of CRBSI of 8 %.

Keywords Central venous catheter · Bloodstream infection · Probability · IPS · Haematologic malignancies

Introduction

Central venous catheters (CVCs) are frequently used for patients with haematologic malignancies, such as acute leukaemia or malignant lymphoma especially when treated with myelosuppressive chemotherapy or autologous or allogeneic blood stem cell transplantation. In these patients, CVC-related bloodstream infections (CRBSIs) are important and common complications, especially during neutropenia. CRBSIs are associated with high morbidity and mortality [1–4]. Unfortunately, diagnosis of CRBSI is difficult and frequently based on clinical signs before removal of CVC [5, 6]. Recently, CRBSIs have been classified as 'definite', 'probable' and 'possible' to facilitate clinical use [6].

Diagnosis of CRBSI before microbiological results are available remains a clinical challenge. Removal and reinsertion of CVCs are associated with a significant risk, especially in critically ill patients with accompanying thrombocytopenia hindering clinical decision-making. Therefore, it would be of major interest to develop clinical scores to assess for the probability of CRBSI.

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In 2003, Peres Bota and colleagues developed the Infection Probability Score (IPS) [7]. The IPS is a simple score that can help to assess for the probability of infections in critical ill patients. This scoring system is based on commonly used variables such as body temperature, heart rate, respiratory rate, white blood cell count (WBC) and C-reactive protein [7]. As multi-organ failure is a strong indicator of sepsis, evaluation of organ dysfunction using the Sequential Organ Failure Assessment (SOFA) score [8] was incorporated into the IPS. The IPS is commonly used for bedside monitoring of critically ill patients. The calculated IPS has a range of 0 to 26 points with values <14 points (cutoff score) indicating a modest risk of infection of approximately 10 % [7]. However, the IPS has not been validated so far for CRBSIs.

In this study, we validated a modified version of the IPS (mIPS; including stringent criteria for neutropenia) for patients with haematologic malignancies to predict the probability and to define a mIPS cutoff value for CRBSI.

Patients and methods

This study is based on data from the prospective SECRECY registry (Study to Evaluate Central venous Catheter-related Infections in Haematology and Oncology; German Clinical Trials Register [DRKS] number, DRKS00006551). Within the SECRECY registry, documentation of prospective surveillance data of all consecutive short-term CVCs inserted for routine clinical use in our department is available. This registry was approved by the local Ethics Committee (approval no. 84/14). Due to anonymisation of patients' data, written informed consent was not required within the registry. However, written informed consent is available for the procedure of CVC insertion during routine clinical use.

All patients were ≥18 years of age. CVCs were mainly used for chemotherapy or best supportive care. All CVCs were inserted under sterile conditions and ultrasound guidance by trained and experienced physicians. Documentation of each procedure was performed by the responsible physician. Compilation of clinical and laboratory data was combined with data of microbiological testing and documented within the data bank. For this study we analysed all documented CVCs with ≥1 day in use from March 2013 through September 2014.

For definition of CSRBI, the 2012 Infectious Diseases Working Party of the German Society of Haematology and Medical Oncology (AGIHO/DGHO) criteria were used [6]. Definite, probable and possible CRBSIs were distinguished. The microbiological specimens were investigated and analysed according to standard methods [6, 9].

IPS at CVC insertion and removal (IPS_{in} and IPS_{ex}, respectively) was calculated [7]. For score assessment, body temperature, heart rate, respiratory rate, white blood cell count (WBC), C-reactive protein and the Sequential Organ Failure Assessment (SOFA) score [8] were documented. Deviant from the original IPS, we included the absolute neutrophil count (ANC), due to the fact that neutropenia is common in patients with haematologic malignancies when undergoing chemotherapy. Moreover, neutropenia defines one of the most important risk factors for severe infectious complications [10]. For neutropenic patients, we added 3 IPS points (according to the original IPS, 3 points were given for a documented WBC <5000/μl; however, a WBC of less than 5000/μl is not necessarily accompanied by neutropenia). In our data set, we defined neutropenia as presence of an ANC <1500/μl (Table 1). This modification of the conventional IPS is indicated as mIPS throughout the manuscript.

To define IPS cutoff values for CRBSI prediction, the area under the curve (AUC) of the receiver operating characteristic (ROC) was used. For CRBSI risk determination odds ratios (ORs) were calculated and stated with 95 % confidence intervals (95 % CIs). Continuous variables were compared using Student's *t* test. The X^2 statistic or Fisher's exact test was applied to compare categorical variables. Measuring the clinical relevance, the effect size Cohen's *d* was calculated in cases in which variables were compared. Effect sizes as group difference indices are calculated using means and standard deviations of outcomes which estimate the magnitude in the difference of given parameters between two groups. An effect size of 0.8 is considered large, 0.5 is considered medium, and 0.2 is considered small. There is general agreement that Cohen's *d* below 0.2 is clinically not relevant [11]. All two-sided *p* values <0.05 were considered statistically significant. The Microsoft Excel statistic tool, OpenEpi (http://www.openepi.com) and VassarStats (http://vassarstats.net/vsclin.html) were used to analyse the data.

Table 1 Scoring for the Infection Probability Score (IPS) [7]

	IPS points						
	0	1	2	3	6	8	12
BT (°C)	≤37.5		>37.5				
HR (beats/min)	≤80					81–140	>140
RR (breaths/min)	≤25	>25					
WBC (×1000/μl)		>12					
ANC (x/μl)	>1500			<1500			
CRP (mg/l)	≤6				>6		
SOFA score	≤5		>5				

Deviant from the original score, here, the IPS was adapted for leukocyte count (see text)

BT body temperature, *HR* heart rate, *RR* respiratory rate, *WBC* white blood cell count, *ANC* absolute neutrophil count, *CRP* C-reactive protein, *SOFA* Sequential Organ Failure Assessment [8]

Results

Between March 2013 and September 2014, 272 triple-lumen, non-tunnelled, short-term CVCs were inserted. Of these, 267 CVCs (including 11 coated CVCs) were in use ≥1 day and therefore included for analysis. In total, CVCs from 143 different patients were analysed. The mean age of the patients was 59.5 years (range, 25–81 years), and 61.4 % were male. CVCs were predominantly inserted for management of myelosuppressive chemotherapy of acute leukaemia (n=142, 53.2 %), multiple myeloma (n=65, 24.3 %) or malignant lymphoma (n=30, 11.2 %). In 93.6 % (n=250) of all cases analysed, the CVC were inserted into the internal jugular vein (thereof n=152, 60.8 % into the right internal jugular vein); only 4.5 % (n=12) and 1.9 % (n=5) were inserted in the subclavian vein or in the femoral vein, respectively. Within the time period analysed, 1.8 CVCs per patient were inserted. In total, 4044 CVC days (mean=15.1 days; rage, 1–60 days) were included for analysis.

In 66 cases (24.7 %), 12/13/41 (18.2 %/19.7 %/62.1 %) definite/probable/possible CRBSI, respectively, were detectable, with an incidence of 16.3/1000 CVC days (2.9/3.1/10.1 per 1000 CVC days for definite/probable/possible CRBSI, respectively). Out of 52 isolated bacteria which were responsible for CRBSI, the predominant pathogenic strain was *Staphylococcus epidermidis* in 36 cases (69.2 %). In one third of the cases (89/267), CVC removal was due to a (suspected) CRBSI, and, however, in the majority (n=57, 64.0 %), CRBSI was diagnosed. The CVC characteristics are summarised in Table 2.

There was no significant difference in mIPS values at the time of CVC insertion between patients who subsequently developed CRBSI and those who did not ($mIPS_{in}$, 6.7 vs. 6.0; p=0.39). Consecutively, a Cohen's d of 0.11 was calculated, indicating that this is not clinically relevant. In cases of CRBSI, the $mIPS_{ex}$ was significant higher as compared to cases without CRBSI (13.1 vs. 7.1; p<0.001). Therefore, a Cohen's d of 1.01 was calculated, indicating that this is of large clinical relevance. Furthermore, comparing the differences of mIPS at CVC removal and CVC insertion ($mIPS_{diff}$), we found significant higher values in cases of CRBSI than in cases of no CRBSI (6.4 vs. 1.1; p<0.001) (Table 3), with a Cohen's d of 0.75 (indicating that this is of medium clinical relevance).

The most predictive $mIPS_{ex}$ cutoff for CRBSI was 8 points (AUC=0.77; sensitivity=84.9 %, specificity=60.7 %, negative predictive value [NPV]=92.4 %). For the most frequent CRBSI subtype—possible CRBSI—we found $mIPS_{ex}$ cutoff values of 9 points to be predictive, with comparable statistical parameters (Table 4). The risk of CRBSI for patients with a $mIPS_{ex}$ ≥8 points was high with an odds ratio (OR) of 5.9 (95 % CI 2.8–12.6; p<0.001). The likelihood of CRBSI was even higher if CVC had been in use for 10 days or more with a $mIPS_{ex}$ ≥8 points (mean OR=9.5) (Table 5). However, duration of CVC use (when comparing ≥7 to ≥14 days) was not a predictive risk factor for CRBSI per se. This finding was confirmed by an OR of 1.4 (95 % CI 0.3–7.3; p=1.0) and OR of 1.3 (95 % CI 0.3–5.3; p=0.95), respectively.

Table 2 CVC characteristics

Central venous catheters	n=267
Different patients	143
Patients' age	59.5 years (range, 25–81 years)
Male	164 (61.4 %)
Female	103 (38.6 %)
CVC in use	4044 days (mean=15.1 days; range, 1–60 days)
Inserted vein	
Internal jugular vein	250 (96.6 %)
Right	152 (60.8 %)
Left	98 (39.2 %)
Subclavian vein	12 (4.5 %)
Femoral vein	5 (1.9 %)
Underlying disease	
Acute leukaemia	142 (53.2 %)
Myeloid	130 (91.5 %)
Lymphatic	12 (8.5 %)
Multiple myeloma	65 (24.3 %)
Malignant lymphoma	30 (11.2 %)
Others	30 (11.2 %)
CRBSI	n=66
Definite	12 (18.2 %)
Probable	13 (19.7 %)
Possible	41 (62.1 %)
CRBSI incidence	16.3/1000 CVC days
Definite	2.9/1000 CVC days
Probable	3.2/1000 CVC days
Possible	10.1/1000 CVC days
CRBSI incidence rate	24.7 %
Definite	4.5 %
Probable	4.9 %
Possible	15.4 %
Underlying pathogen for CRBSI	n=52
Staphylococcus epidermidis	36 (69.2 %)
Staphylococcus haemolyticus	5 (9.6 %)
Staphylococcus hominis	2 (3.8 %)
Others	9 (17.3 %)

CVC central venous catheter, *CRBSI* CVC-related bloodstream infection

Discussion

In this mono-centric, prospective surveillance study of patients with haematologic malignancies, we modified the

Table 3 mIPS at CVC insertion and removal

	CRBSI	no CRBSI	*p* value
$mIPS_{in}$	6.7 [5.2–8.2]	6.0 [5.1–6.8]	0.39
$mIPS_{ex}$	13.1 [11.8–14.5]	7.1 [6.2–7.9]	<0.001
$mIPS_{diff}$	6.4 [4.6–8.2]	1.1 [0.1–2.1]	<0.001

Values are stated as means with 95 % confidence intervals

mIPS modified Infection Probability Score, $mIPS_{in}$ mIPS at central venous catheter (CVC) insertion, $mIPS_{ex}$ mIPS at CVC removal, $mIPS_{diff}$ difference between $mIPS_{ex}$ and $mIPS_{in}$, *CRBSI* CVC-related bloodstream infection. Values were stated as means with 95 % confidence intervals

Table 5 Risk for CRBSI according to the duration of CVC use plus $mIPS_{ex} \geq 8$

	Odds ratio	*p* value
CVC in use ≥7 days plus $mIPS_{ex}$ ≥8 points	9.9 [2.3–43.2]	<0.001
CVC in use ≥10 days plus $mIPS_{ex}$ ≥8 points	9.8 [2.9–33.5]	<0.001
CVC in use ≥14 days plus $mIPS_{ex}$ ≥8 points	8.9 [3.0–26.6]	<0.001

In brackets are 95 % confidence intervals

CRBSI central venous catheter-related bloodstream infection, *CVC* central venous catheter, $mIPS_{ex}$ modified Infection Probability Score at CVC removal

conventional IPS to include more stringent criteria for neutropenia (mIPS). Using this modified version, we could define a predictive mIPS cutoff value of 8 points for the development of CRBSI. In the original description of the IPS by Peres Bota and colleagues, an IPS cutoff of 14 points was calculated to predict likelihood of infection. In this report, the negative predictive value (NPV) was 89.5 %, indicating a modest risk of infection about 10 % only if the IPS was <14 points. For this cutoff value, the AUC of the ROC curve was 0.82 [7]. Since an AUC of 0.70 to 0.90 is believed to be of modest predictive value [12], the IPS is a useful diagnostic tool for discrimination of infection. One significant power of the IPS is its ability to distinguish positive from negative patients already early in the course of infection (basically from the first day of calculation). Moreover, dynamic evaluation of the IPS may help do assess for response to therapy, because the IPS decreased over time after effective antibiotic therapy. This suggests that the IPS may be useful to guide antibiotic therapy, because a decrease in the IPS could indicate the resolution of infections [13]. Transferring this into our data set could mean that a decrease in the mIPS after CVC removal could be an indicator for CRBSI and shows a response to therapy, i.e., CVC removal. In contrast, if there is no mIPS decrease after CVC removal, this could mean that there is another infectious focus rather than CVC. Similar to the results published by Peres Bota and colleagues [7], we found an NPV of 92.4 % and an AUC of 0.77 for the cutoff value of 8 points to discriminate between being positive for CRBSI or not. Along this line, patients with a mIPS value below 8 points were at moderate risk of being diagnosed with CRBSI (8 % only). In our study, more than 50 % of CRBSI cases could be classified as possible CRBSI [6], and for this subgroup, we found comparable $mIPS_{ex}$ cutoff values and statistical parameters as for combined analysis of all CRBSI cases (Table 4).

Table 4 $mIPS_{ex}$ cutoff values for CRBSI prediction

	all CRBSI	possible CRBSI
$mIPS_{ex}$ cutoff	8	9
Area under the curve	0.77 [0.71–0.83]	0.72 [0.65–0.79]
Sensitivity	84.9 %	75.6 %
Specificity	60.7 %	62.8 %
Negative predictive value	92.4 %	93.4 %
Positive predictive value	41.5 %	27.0 %

In brackets are 95 % confidence intervals

$mIPS_{ex}$ modified Infection Probability Score at central venous catheter (CVC) removal, *CRBSI* CVC-related bloodstream infection

Thus, we think, the mIPS is a moderate but suitable diagnostic tool to rule out CRBSI in patients with haematologic malignancies. Furthermore, we found that in CRBSI-positive patients, the $mIPS_{ex}$ is significantly higher (>6 points) than in CRBSI-negative cases. This difference is not only of statistical power per se. Consistently, the effect size Cohen's *d* of >0.8 indicates a high efficiency [11]. Since we found no statistical difference between $mIPS_{in}$ for patients who tested positive for CRBSI in the course compared to patients staying negative, the mIPS at time of CVC insertion seems not to be a useful parameter in predicting CRBSI.

When comparing recently published studies, we found the IPS not to be exclusively validated for critically ill patients on intensive care units [7, 13]. The IPS was also validated for health-care-associated infections [14], bloodstream infections [15] and *Clostridium difficile*-associated disease in patients with haematologic malignancies [16] as well as for sepsis and systemic inflammatory response syndrome in standard care patients [17]. In other publications, the IPS was evaluated for its predictive value in regard to initiation of mechanical ventilation [18, 19]. With exception of one study published by Ratzinger and colleagues [17], our data show comparable quantitative results to the literature regarding the use of the IPS for prediction of infectious complications: The mean IPS cutoff value was 12 (range, 10–14), with a mean sensitivity of 63 % (range, 46–75 %), a mean NPV of 0.88 (range, 0.80–0.93) and a mean AUC of 0.75 (range, 0.62–0.96).

Of note, the mIPS cutoff value of 8 points for prediction of CRBSI was significantly lower in our investigation than the IPS in previously published reports. One possible explanation for this finding is the fact that patients with haematologic

malignancies display a distinct nosological profile compared to patients with other types of disease [14, 15]. Moreover, we found high incidence and high a priori probability of CRBSI when compared to other infectious complications. As described above, we used a modified version of the original IPS which is more stringent in regard to definition of neutropenia. This could potentially increase the mIPS (compared to the original IPS) by including ANC instead of WBC. In conclusion, the $mIPS_{ex}$ cutoff value predicting CRBSI is potentially decreased by applying more stringent criteria to one defined risk factor.

For CVCs used for less than 14 days (short-term CVCs), infections are mainly caused by extraluminal spread of bacteria along the outer surface of the CVC. In contrast, for CVCs used for more than 14 days (long-term indwelling CVCs), the intraluminal pathway may be predominant. Colonisation of the insertion site by normal skin flora or pathogenic organisms is a major risk factor for CRBSI. Moreover, endogenous lining of the interior surface of the CVC with a biofilm is known to occur within less than 24 h after insertion [6, 20], and the risk of CRBSI increases over time. Therefore, we decided to include and analyse all CVC used for more than 24 h.

One major limitation of the IPS (or mIPS) in predicting CRBSI is the need to exclude other potential infectious foci [6]. The IPS/mIPS cannot distinguish CRBSI from other infections per se. The probability of CRBSI with a calculated mIPS value of more than 8 points is only 42 %. However, this value drops to 27 % for the subgroup of possible CRBSI, and it is only 8 % in a patient with a calculated mIPS of less than 8 points.

However, not in every case CVC preservation is justified if the $mIPS_{ex}$ is <8 points. In 9 of the 66 CRBSI cases in our study (13.6 %), the $mIPS_{ex}$ was <8 points (6 of these were possible CRBSIs). In current guidelines, there are clear recommendations for CVC removal if CRBSI is suspected—irrespective of mIPS: Patient's clinical state deteriorates; sepsis and/or septic shock; severe complications such as endocarditis, septic thrombosis, abscess or osteomyelitis; isolation of *Staphylococcus aureus*, *Pseudomonas aeruginosa* or *Candida albicans*; and some others from blood cultures [6].

To the best of our knowledge, this report is the first one providing epidemiological data on CRBSIs in patients with haematologic malignancies according to the 2012 AGIHO/DGHO criteria [6]. Our analysis according to the above mentioned guidelines results in a CRBSI incidence of 16.3/1000 CVC days, which appears to be high when compared to reports on adult cancer patients (1.1–7.5/1000 CVC days) [21–23]. In a pooled analysis of 61 prospective studies, the mean incidence of CRBSIs was reported to be 2.3/1000 CVC days [24]. However, all these data need to be reviewed in the context of chosen criteria for diagnosis of CRBSI. Mollee and colleagues reported on a CRBSI incidence of 1.1/1000 CVC days, when investigating patients on a haematology/oncology ward [23]. However, these CRBSIs described in their study were exclusively definite CRBSI according to the above mentioned guidelines [6]. When applying this more stringent definition to our analysis, we found a definite CRBSI incidence of 2.9/1000 CVC days, which is comparable to the literature.

Routine CVC replacement to prevent CRBSI has not been shown to lower CRBSI rates [25]. Therefore, this procedure is not generally recommended [6]. This is supported by our study: Using CVC ≥14 days (as compared to ≥7 days) was not associated with an increased risk for CRBSI per se. However, the risk for CRBSI was significantly increased if indicated by clinical signs or elevated inflammation parameters in laboratory testing (Table 5). Therefore, use of CVC beyond 10 days and elevation of mIPS values beyond 8 points can be considered predictive parameters for CVC replacement to prevent CRBSI. However, these parameters need to be validated in prospective clinical trials.

According to the AGIHO/DGHO criteria for CRBSI diagnosis, for the definition of possible CRBSI, and, however, for one point of definite CRBSI, clinical and/or microbiological results are needed to diagnose CRBSI (culture of CVC tip, remission of fever in <48 h) [6]. At the time of CVC removal, CRBSI cannot to be diagnosed in every case. So, CRBSI diagnosis can be made sometimes in the further course only. Therefore, as stated above, due to the relative high NPV (Table 4), an advantage of CRBSI prediction at the time of the potential CVC removal due to suspected CRBSI could be to rule out CRBSI, especially in cases of possible CRBSI. If the $mIPS_{ex}$ is <8 points, the risk for possible CRBSI is 7 % only. On the other hand, a $mIPS_{ex}$ ≥8 points and longer CVC in use predict a high CRBSI risk. So, if a daily calculated mIPS increased over time, mIPS could be a decision guidance for prophylactic CVC removal to prevent CRBSI. Therefore, the mIPS could be a tool for decision guidance to remove or preserve CVC.

In conclusion, with other causes of infection being excluded, the modified IPS_{ex} ≥8 points in combination with an extended period of CVC use (≥10 days) predicts a very high risk of CRBSI. In contrast, patients diagnosed with haematologic malignancies who show a $mIPS_{ex}$ of less than 8 points have a low risk of CRBSI of 8 %.

This report provides first evidence that our modified IPS may serve as a useful tool to predict CRBSIs in patients with haematologic malignancies. Prospective multi-centre trials are clearly warranted to validate our findings.

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Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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Publikation XIV

Schalk E, Biehl LM, Färber J, Schlüter D, Vehreschild MJGT, Fischer T. Determination of a cut-off time-point for prophylactic exchange of central venous catheters for prevention of central venous catheters-related bloodstream infections in patients with hematological malignancies. **Infect Control Hosp Epidemiol 2017**;38(7):888-889

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Determination of a Cutoff Time Point for Prophylactic Exchange of Central Venous Catheters for Prevention of Central Venous Catheter–Related Bloodstream Infections in Patients with Hematological Malignancies

To the Editor—Prophylactic exchange of central venous catheters (CVC) for prevention of CVC-related bloodstream infections (CRBSI) in cancer patients is not generally recommended.[1,2] The related studies were conducted in relatively small populations in general and especially in small populations of cancer patients; in addition, thrombocytopenia, which often occurs in cancer patients, was an exclusion criterion in these trials.[3,4] However, prophylactic CVC exchange is sometimes still clinical practice in hematology, even though the optimal time point is unclear. Therefore, we aimed to investigate this question in a larger cohort of patients with hematological malignancies.

For this purpose, pooled data from the prospective Study to Evaluate Central venous Catheter-related Infections in Hematology and Oncology (SECRECY) registry (German Clinical Trial Register No. DRKS00006551)[5] and the prospective Antimicrobial Catheter Securement Dressings for the Prevention of CVC-related Bloodstream Infections in Cancer Patients (COAT) study (ClinicalTrials.gov No. NCT01544686)[6] from 11 centers in Germany were analyzed. SECRECY is an ongoing real-life registry of CRBSI in patients with hematological and oncological malignancies. COAT was a randomized multicenter trial comparing different CVC dressings in terms of CRBSI incidence in neutropenic patients.

In this study, we analyzed CRBSI due to short-term CVC (≥1 day in situ) inserted in the jugular or subclavian vein in patients with hematological malignancies. Only definitive CRBSI (dCRBSI) and the combination of definitive and probable CRBSI (dpCRBSI) according to the 2012 Infectious Diseases Working Party of the German Society for Hematology and Medical Oncology (AGIHO/DGHO) criteria[2] were considered from both data subsets. Using a receiver operating characteristic, CVC duration was used to determine a cutoff time point for CRBSI risk. An area under the curve (AUC) of <0.500 and 0.500–0.700 were considered of no and low predictive significance, respectively.[7]

Altogether, 1,194 CVC patients (median age, 59 years; range, 18–86; 59.2% men) with 20,330 CVC days (median CVC duration, 17 days; range, 1–60) were analyzed. In total, 610 CVC patients (51.1%) were from the COAT study and 584 (48.9%) were from the SECRECY registry. Underlying diseases were acute leukemia in 568 of these patients (47.6%), multiple myeloma in 316 patients (26.5%), and lymphoma in 226 patients (18.9%). The insertion site was the jugular vein in 819 of these patients (68.6%) and the subclavian vein in 375 patients (31.4%). In 890 of these patients (74.5%), chlorhexidine-containing CVC dressings were used from the beginning of the CVC insertion.

In total, 55 dCRBSIs and 137 dpCRBSIs occurred. Definitive CRBSI originated in the jugular vein CVC in 26 of these 55 patients (47.3%); dpCRBSI originated in the jugular vein CVC in 87 of 137 dp CRBSI patients (63.5%). The epidemiological data are summarized in Table 1. The CVC duration was the same for CVC with dCRBSI and dpCRBSI (median, 16 vs 16 days; $P = .62$). No significant difference was detected between dCRBSI onset and dpCRBSI onset (median, 14 vs 13 days; $P = .24$). Comparing dCRBSI onset with dpCRBSI onset in jugular vein CVC, we also found no significant

TABLE 1. Epidemiology and Characteristics of Central Venous Catheter (n = 1,194) and Central Venous Catheter-Related Bloodstream Infection

Parameter	dCRBSI (n = 55)	dpCRBSI (n = 137)
CRBSI rate, %	4.6	11.5
CRBSI incidence, no. per 1,000 CVC days	2.7	6.7
CVC duration, median d (range; IQR)	16 (3–41; 12–22)	16 (3–52; 13–22)
CRBSI onset, median d (range; IQR)	14 (3–40; 11–20)	13 (2–40; 10–17)
Jugular vein	14 (3–39; 12–21)	13 (2–39; 10–17)
Subclavian vein	14 (4–40; 10–19)	13 (4–40; 10–18)
AUC for CVC duration cutoff time point (95% CI)	0.460 (0.388–0.531)	0.415 (0.373–0.458)
Jugular vein	0.517 (0.417–0.617)	0.446 (0.394–0.498)
Subclavian vein	0.360 (0.255–0.464)	0.340 (0.262–0.417)

NOTE. CVC, central venous catheter; CRBSI, central venous catheter-related bloodstream infection; dCRBSI, definite CRBSI; dpCRBSI, combination of definite and probable CRBSI; IQR, interquartile range; AUC, area under the curve; 95% CI, 95% confidence interval.

difference (median, 14 vs 13 days; $P = .15$). We also found no significant difference between dCRBSI onset and dpCRBSI onset in subclavian vein CVCs (median, 14 vs 13 days; $P = .83$) (Table 1). There was also no difference in dCRBSI onset between jugular vein and subclavian vein (median, 14 [range, 3–39] vs 14 days [range, 4–40]; $P = .52$) and for dpCRBSI (median, 13 [range, 2–39] vs 13 days [range, 4–40]; $P = .66$), respectively.

For the CVC duration cutoff time point, an AUC of 0.460 for dCRBSI and an AUC of 0.415 for dpCRBSI were calculated. Considering only CVCs inserted in the jugular vein, an AUC of 0.517 for dCRBSI and an AUC of 0.446 for dpCRBSI were calculated. Furthermore, considering subclavian vein CVCs only, the AUCs for dCRBSI and dpCRBSI were 0.360 and 0.340, respectively (Table 1).

In conclusion, in this large cohort of patients with hematological malignancies and high risk for CRBSI, we could not determinate an optimal cutoff time point at which a prophylactic CVC exchange should be implemented in clinical care to prevent CRBSI, irrespective of the CVC insertion site (jugular vein or subclavian vein) or the strength of CRBSI definition (dCRBSI or dpCRBSI). The main reason for this finding is the very wide range of CRBSI onset. In all but 1 calculation, the AUC for CVC duration cutoff time point was <0.500; for dCRBSI and jugular vein CVC, the AUC was 0.517, but the lower bound of the 95% confidence interval was also <0.500. Therefore, CVC duration was of nonpredictive significance. Of course, the CRBSI risk increases with CVC duration.[5,8] Therefore, decision making for preventive CVC removal or exchange is based on experience of the clinicians so far. A risk score at CVC insertion would be helpful to identify high-risk CVCs.

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Publikation XV

Schalk E, Färber J, Fischer T, Heidel FH. Central venous catheter-related bloodstream infections in obese hematologic patients. **Infect Control Hosp Epidemiol 2015**;36(8): 995-996

Central Venous Catheter–Related Bloodstream Infections in Obese Hematologic Patients

To the Editor—Central venous catheter (CVC)–related bloodstream infections (CRBSI) are associated with high morbidity, especially in neutropenic patients.[1] In general, obesity is one of the risk factors associated with CRBSI. However, this finding is inconsistent in the literature and no data are available on patients with hematologic malignancies so far. CVC insertion is often technically challenging in obese patients owing to obscured landmarks of the neck.[2,3] Furthermore, with increased sweating,[4] bandages at the CVC insertion site are frequently problematic and lead to higher risk of CRBSI.[5] Therefore, we hypothesized that obese hematologic patients treated with chemotherapy are at higher risk of having CRBSI than non-obese hematologic patients.

In the monocentric, prospective SECRECY registry (Study to Evaluate Central Venous Catheter-Related Infections in Hematology and Oncology; German Clinical Trial Register number, DRKS00006551) we evaluated CRBSI in all consecutive patients in our department from March 20, 2013, through March 13, 2015. The registry was approved by the local ethics committee (approval no. 84/14). Owing to anonymization of patients' data, written informed consent was not required within the registry. However, written informed consent is available for the procedure of CVC insertion during routine clinical use. All patients were at least 18 years of age. CVCs were mainly used for chemotherapy or best supportive care. All CVCs were inserted under sterile conditions and ultrasound guidance by experienced physicians. To define CRBSI we used the 2012 criteria of the Infectious Diseases Working Party of the German Society of Hematology and Medical Oncology.[1] Obesity was defined as body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) of 30 or greater according to the commonly known World Health Organization criteria.

Altogether we analyzed 335 triple-lumen, short-time CVCs (including 11 coated CVCs) that were in use at least 1 day. The CVCs accounted for a total of 5,094 CVC days (mean [range], 15.2 [1–60] days). The mean (range) age of the 176 patients was 58.1 (25–81) years; 106 (60.2%) were men. Mostly, patients had acute leukemia (178 [53.1%]), multiple myeloma (83 [24.8%]), or malignant lymphoma (41 [12.2%]). Patients received a mean (range) of 1.9 (1–6) CVC insertions within the observation period. Most CVCs (314 [93.7%]) were inserted into the internal jugular vein. CRBSI were detected in 77 cases (12 [15.6%] definite, 21 [27.3%] probable, 44 [57.1%] possible), with an incidence of 15.1/1,000 CVC-days and an incidence rate of 23.0%. The most prevalent pathogen was *Staphylococcus epidermidis* (43 [71.7%]). At baseline—that is, at time of the first CVC insertion of the patients, the mean

TABLE 1. Data on 176 Patients, Use of 335 Central Venous Catheters (CVCs), and Occurrence of Catheter-Related Bloodstream Infection (CRBSI)

Variable	Value	
Patients, *n* = 176		
Age, mean (range), y	58.1 (25–81)	
Male sex, no. (%)	106 (60.2)	
Body mass index, mean (range)	28.0 (15–46)	
CVCs, *n* = 335		
CVC-days, total	5,094	
CVC-days, mean (range)	15.2 (1–60)	
Inserted vein, no. (%) of CVCs		
Internal jugular vein	314 (93.7%)	
Right	194/314 (61.8%)	
Subclavian vein	14 (4.2%)	
Femoral vein	7 (2.1%)	
Underlying disease in patient, no. (%) of CVCs		
Acute leukemia	178 (53.1%)	
Multiple myeloma	83 (24.8%)	
Malignant lymphoma	41 (12.2%)	
Others	33 (9.9%)	
CRBSI, *n* = 77		
Definite	12 (15.6%)	
Probable	21 (27.3%)	
Possible	44 (57.1%)	
CRBSI incidence per 1,000 CVC-days	15.1	
Definite	2.4	
Probable	4.1	
Possible	8.6	
CRBSI incidence rate	23.0%	
Definite	3.6%	
Probable	6.3%	
Possible	13.1%	
Underlying pathogens, no. (%)		
Staphylococcus epidermidis	43/60 (71.7%)	
Staphylococcus haemolyticus	5/60 (8.3%)	
Other	12/60 (20.0%)	
Obesity data		
BMI, mean (range)	27.3 (15–46)	
No. of CVCs in obese patients (% of all CVCs)	95 (28.4%)	
Risk for complicated CVC insertion, OR (95% CI)	0.99 (0.53–1.85)	$P > .99$[a]
Obese vs non-obese	17/93 (18.3%) vs 43/234 (18.4%)	
Risk for CRBSI, OR (95% CI)	0.93 (0.53–1.65)	$P = .93$[a]
Obese vs non-obese	21/95 (22.1%) vs 56/240 (23.3%)	
CVC in use		
Obese vs non-obese	13.5 days vs 15.9 days	$P = .03$[b]
mIPS at CVC insertion		
Obese vs non-obese	7.6 vs 5.8	$P = .02$[b]
mIPS at CVC removal		
Obese vs non-obese	9.7 vs 8.2	$P = .06$[b]
Age, y		
Obese vs non-obese	57.5 vs 59.5	$P = .16$[b]
Men and risk for CRBSI, OR (95% CI)	0.68 (0.32–1.45)	$P = .42$[a]
Obese vs non-obese	11/52 (21.2%) vs 42/149 (28.2%)	
Women and risk for CRBSI, OR (95% CI)	1.58 (0.64–3.92)	$P = .45$[a]
Obese vs non-obese	10/43 (23.3%) vs 14/91 (15.4%)	

NOTE. Body mass index (BMI) is calculated as weight in kilograms divided by height in meters squared. Obesity is defined as BMI ≥ 30. mIPS, modified Infection Probability Score; OR, odds ratio.

[a]Fisher exact test.

[b]Student *t* test.

(range) BMI was 28.0 (15–46). Taking all 335 CVCs together, the BMI of the patients was a mean of 27.3, whereas in 95 CVCs (28.4%), the BMI of the patients was at least 30 (for the subgroup of the obese patients the mean BMI was 33.8).

Complications of CVC insertion (bleeding, hematoma, >2 punctures, or malpositioning of the guidewire) were reported in 18.3% of obese patients and in 18.4% of non-obese patients. This indicates no increased risk for complications during CVC insertion among obese patients (odds ratio [OR], 0.99].

Comparing the CRBSI rate in obese and in non-obese patients we found no differences in CRBSI frequency (22.1% vs 23.3%; OR, 0.93).

Duration of CVC use appeared to be significantly shorter in obese compared with non-obese patients (13.5 vs 15.9 days). However, using the modified Infection Probability Score,[6] which is more stringent in defining neutropenia than the original IPS,[7] we found a higher modified Infection Probability Score at the time of CVC insertion in obese than in non-obese patients (7.6 vs 5.8). Interestingly, sex is not a risk factor for CRBSI in obese patients (men vs women, OR, 0.86 [95% CI, 0.32–2.35]; $P = .97$). CRBSI risk was increased neither for obese men (OR, 0.68) nor for obese women (OR, 1.58) (data are summarized in Table 1).

In our experience, CVC insertion with support of ultrasonography is a safe procedure in obese hematologic patients. Surprisingly, obesity could not be defined as a risk factor for CRBSI in our dataset. Using the modified Infection Probability Score[6] as a tool to describe the grade of illness of patients (with all critical parameters such as body temperature, heart rate, respiratory rate, absolute neutrophil count, and C-reactive protein as well as the Sequential Organ Failure Assessment score[8] being included), we found that obese patients had increased values and were therefore more challenged by the disease at the time of CVC insertion; however, the risk for CRBSI per se was not increased. One potential pitfall that could mask the CRBSI risk in obese patients is the duration of CVC use, which was significantly shorter (2–3 days shorter) in obese vs non-obese patients in the cohort investigated. CRBSI are known to be associated with the duration of CVC use.[6,9]

Another piece of data supporting our findings is the inverse association between obesity and risk of febrile neutropenia that has been reported recently.[10] Potential mechanisms include altered pharmacokinetics and/or reduced relative efficacy of chemotherapy due to obesity.[10]

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Patients with Psychiatric Disorders Can Also Have CLABSIs: A Response to "CLABSI or Munchausen's or Both"

To the Editor—We read with interest the recent article "CLABSI or Munchausen's or Both"[1] because, among other aspects, it addressed the interactions between patient

Publikation XVI

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ORIGINAL ARTICLE

Influenza virus infections in patients with malignancies — characteristics and outcome of the season 2014/15. A survey conducted by the Infectious Diseases Working Party (AGIHO) of the German Society of Haematology and Medical Oncology (DGHO)

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Abstract Influenza virus infections (IVI) may pose a vital threat to immunocompromised patients such as those suffering from malignancies, but specific data on epidemiology and outcome in these patients are scarce. In this study, we collected data on patients with active cancer or with a history of cancer, presenting with documented IVI in eight centres in Germany. Two hundred and three patients were identified, suffering from haematological malignancies or solid tumours; 109 (54 %) patients had active malignant disease. Influenza A was detected in 155 (77 %) and Influenza B in 46 (23 %) of patients (genera not determined in two patients). Clinical symptoms were consistent with upper respiratory tract infection in 55/203 (27 %), influenza-like illness in 82/203 (40 %), and pneumonia in 67/203 (33 %). Anti-viral treatment with oseltamivir was received by 116/195 (59 %). Superinfections occurred in 37/203 (18 %), and admission on an intensive care unit was required in 26/203 (13 %). Seventeen patients (9 %) died. Independent risk factors for death were delayed diagnosis of IVI and bacterial or fungal superinfection, but not underlying malignancy or ongoing immunosuppression. In conclusion, patients with IVI show high rates of pneumonia and mortality. Early and rapid diagnosis is essential. The high rate of pneumonia and superinfections should be taken into account when managing IVI in these patients.

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Introduction

Infections are the main cause of treatment-related mortality in cancer patients. Whereas bacterial and fungal infections are common and well-known, infections by community acquired respiratory viruses have often received less attention in the past. With the emergence of nucleic acid amplification techniques (NAT), diagnosis of specific viral infections has become easier and faster, making it possible to gain more precise information on epidemiology and outcome. Most studies with regard to infections with community acquired respiratory viruses, including influenza, in the immunocompromised host have been performed in patients with haematological malignancies, especially those following stem-cell transplantation (SCT) [1–7]. However, there is an evident need to obtain information on the impact of IVI in patients with all kinds of malignancies, as only a few studies have dealt with patients suffering from solid tumours [8]. In the 2014/15 season, the wave of IVI was particularly strong in Germany [9]. It started in October 2014 from and affecting especially the south-east of Germany spreading from there north-west over Germany, peaked in the second week of 2015, and lasted till mid-April 2015 [9]. A genetic drift occurred in the dominating influenza A (H3N2) viruses (62 %), which was not covered by the seasonal vaccine. Influenza A(H1N1)pdm09-viruses were identified in 15 % and influenza B viruses in 23 % of the samples tested positive for influenza [9].

The aim of our study was to understand the clinical epidemiology and outcome of IVI in cancer patients during the 2014/15 influenza season, in order to identify patients at risk of a severe course of infection and mortality.

Patients and methods

All patients (out- and inpatients) with active malignancy or history of malignant disease presenting with documented IVI to one of the eight participating centres of the AGIHO (at the German university hospitals of Bonn, Cologne, Halle/Saale, Heidelberg, Jena, Magdeburg, Mainz, and Munich) between November 2014 and June 2015 were included in this analysis.

IVI diagnosis was confirmed by tests using nucleic acid amplification techniques (NAT) from respiratory samples. Materials used for NAT analysis were mostly pharyngeal swabs (almost 70 %), but pharyngeal lavage fluids or bronchoalveolar lavage (BAL) fluids were also used. Further influenza A virus subtyping was performed if available. Most centres also tested for respiratory syncytial virus (RSV), whereas the panel for other respiratory viruses including parainfluenza and rhinoviruses varied according to the different laboratories, and was not prespecified.

Data were collected on each site from medical records using a predefined short questionnaire. The questionnaire included data on demographics (age, sex), type of influenza virus, clinical presentation of infection, treatment and outcome, type and treatment of underlying malignant disease, and immunosuppressive therapy, as well as presence of co-infections. Because data on vaccination status were not available from medical records in most cases, we tried to obtain additional information on this point by (telephone) interview or using the influenza registry of the health authorities in Jena, Heidelberg, and Mainz. Patients were followed with regard to outcome until clinical resolution of the infection, discharge from hospital, or death. Data were transferred to the coordinating centre (Jena) in an anonymised form.

Influenza-like illness (ILI) is defined according to the European Centre for Disease Prevention and Control (ECDC) by at least one of four systemic symptoms (fever, malaise, headache, or myalgia) and at least one respiratory symptom (cough, sore throat, or shortness of breath). A sudden onset of symptoms is mandatory [10].

Upper respiratory tract infection (URTI) is anatomically defined to include sinusitis and rhinitis and is characterized by new onset of symptoms including at least one of cough, coryza, sore throat, or shortness of breath.

Lower respiratory tract infection (LRTI) involving the pulmonary parenchyma, is defined by clinical or radiological evidence of pneumonia [11]. Severe LRTI was defined as requirement of treatment on intensive care unit (ICU) or death.

Detection of bacterial or fungal pathogens in BAL or blood culture (BC) was considered a relevant superinfection except for the following conditions: In the case of coagulase-negative staphylococci, the detection of the pathogen in at least two different BC was required for definition as relevant superinfection. *Enterococcus spp*. were considered relevant if detected in BC but not if derived from respiratory samples. *Escherichia coli*, *Pseudomonas aeruginosa*, and *Stenotrophomonas maltophilia* cultured from pharyngeal lavage fluids were considered contaminants. Detection of respiratory viruses in samples derived from the respiratory tract was considered a relevant co-infection, whereas detection of herpes viruses was classified as endogenous reactivation secondary to IVI. For statistical analysis, all types of relevant infection were summarized and classified as superinfection.

Statistical analysis was performed with IBM SPSS statistics software, version 21. Proportions were analysed using chi-square tests. Time to event data were analysed using the Kaplan–Meier method and the log-rank for univariable analyses. Multivariable analyses are based on Cox regression models. A two-sided p-value <0.05 was considered significant.

Results

A cohort of 210 cancer patients presenting with IVI was identified. Of those, complete clinical information was available in

203 patients who were included in the final analysis. The median follow- up interval was 127 days (range 0–236 days). The median age was 61 years (interquartile range [IQR] 49–65 years) and 61 % of the patients were male (123/203, Table 1). The majority of patients (158/203, 78 %) suffered from haematological malignancies, and most (106/203, 52 %) had received any type of SCT. There was also a considerable number of patients with solid tumours (21/203, 10 %). About half of the patients (109/203, 54 %) had active malignant disease at the time of IVI diagnosis (Table 1).

Initial clinical presentation included symptoms related to URTI in 55 patients (27 %), ILI in 82 patients (40 %), and

Table 1 Patient characteristics

	All $N = 203$	Myeloid malignancies[a] $N = 51$	Lymphoid malignancies[b] $N = 107$	Solid tumours [c] $N = 21$	Others[g] $N = 24$	P value[d]
Age (median, IQR)	61 (49–65)	57 (48–62)	61 (49–70)	63 (61–73)	62 (47–64)	0.019
Male: *n*/*N* (%)	123/203 (61 %)	26/51 (51 %)	69/107 (65 %)	14/21 (67 %)	14/24 (58 %)	0.39
Active malignant disease: *n*/*N* (%)	109/200 (55 %)	15/49 (31 %)	69/107 (65 %)	15/21 (71 %)	10/23 (44 %)	<0.001
Stem cell transplantation: *n*/*N* (%)	105/202 (52 %)					<0.001
- Autologous	28/202 (14 %)	0/51	28/106 (26 %)	0/21	0/24	
- Allogeneic	77/202 (38 %)	37/51 (73 %)	28/106 (26 %)	0/21	12/24 (50 %)	
Type of influenza: *n*/*N* (%)						0.33
- A	155/201 (77 %)	41/51 (80 %)	80/107 (75 %)	15/21 (71 %)	19/24 (79 %)	
- B	46/201 (23 %)	10/51 (20 %)	25/107 (23 %)	6/21 (29 %)	5/24 (21 %)	
- Not specified	2/201 (1 %)	0/51	2/107 (2 %)	0/21		
Sample collected: *n*/*N* (%)						0.07
- Swab	139/203 (69 %)	33/51 (65 %)	75/107 (70 %)	9/21 (43 %)	22/24 (92 %)	
- Pharyngeal lavage fluid	42/203 (21 %)	11/51 (22 %)	22/107 (21 %)	7/21 (33 %)	2/24 (8 %)	
- BAL	19/203 (9 %)	6/51 (12 %)	8/107 (8 %)	5/21 (24 %)	0/24	
- Other	3/203 (1 %)	1/52 (2 %)	2/107 (2 %)	0/21	0/24	
Initial symptoms: *n*/*N* (%)						0.005
- Asymptomatic	9/203 (4 %)	0/51	7/107 (7 %)	1/21 (5 %)	1/24 (4 %)	
- URTI	55/203 (26 %)	15/51 (29 %)	19/107 (18 %)	7/21 (33 %)	14/24 (58 %)	
- ILI	82/203 (39 %)	25/51 (49 %)	47/107 (44 %)	7/21 (33 %)	3/24 (13 %)	
- Pneumonia	57/203[f] (27 %)	11/51 (22 %)	34/107 (32 %)	6/21 (29 %)	6/24 (25 %)	
ICU: *n*/*N* (%)	26/201 (13 %)	6/50 (12 %)	17/107 (16 %)	3/21 (15 %)	0/24	0.2
Death from influenza: *n*/*N* (%)	17/200 (9 %)	5/50 (10 %)	10/105 (10 %)	1/21 (4 %)	1/24 (4 %)	0.7
Treatment with oseltamivir: *n*/*N* (%)	116/195 (60 %)	31/49 (63 %)	59/102 (58 %)	14/21 (67 %)	12/23 (52 %)	0.7
Superinfection[e]: *n*/*N* (%)	37/201 (18 %)	12/51 (24 %)	21/106 (20 %)	6/20 (30 %)	3/24 (13 %)	0.73
- Bacterial	14	5	7	2	0	
- Fungal	10	2	6	2	0	
- Viral	18	5	8	2	3	

[a] acute myeloblastic leukaemia (AML) = 43, chronic myeloid leukaemia (CML) = 3, myelodysplastic syndrome (MDS) = 5

[b] acute lymphoblastic leukaemia (ALL) =13, Hodgkin's lymphoma =11, Non Hodgkin's lymphoma (NHL) =36, multiple myeloma (MM) = 47

[c] gastrointestinal tumours = 4, lung cancer = 9, gynaecological cancer = 3, primitive neuroectodermal tumour (PNET) = 1, sarcoma = 1, urothel carcinoma = 1, melanoma = 1, larynx carcinoma = 1

[d] Chi-square test

[e] including co- infections and viral reactivation

[f] ten additional patients developed pneumonia later on.

[g] underlying malignancy not specified

pneumonia in 57 patients (28 %). Another ten patients (5 %) developed pneumonia later on, to account for an overall rate of pneumonia of 33 %. Unexpectedly, 21 patients (10 %) also complained of gastrointestinal symptoms such as diarrhoea. Nine patients (4 %) were asymptomatic at the time of diagnosis.

In accordance with the general epidemiology, the dominating influenza virus genus was influenza A (155/201, 77 %), including H3N2 (28 patients) and A(H1N1)pdm09 (six patients) or influenza B (46/201, 23 %; Table 1).

In total, 37 patients (18 %) were considered suffering from relevant superinfection. Two or more different relevant pathogens were detected in samples from seven patients. Ten patients had bacteraemia (one with viral co-infection), and three patients had bacterial pneumonia without positive BC. Another ten patients had fungal pneumonia (one of them with concomitant *E. coli* bacteraemia and one as a double infection with *Aspergillus fumigatus* and *Pneumocystis jirovecii*). The remaining 14 patients had one or more co-infecting viruses. For a list of pathogens causing super- and co-infection, see Table 2. The most frequent pathogens were respiratory viruses, enteric bacteria, and fungi. To a lesser extent, we detected non-fermenting Gram-negative bacteria and Gram-positive bacteria. In four cases we also found reactivation of herpesviridae (HSV, CMV, and HHV6) during IVI, *E. faecium* and *S. maltophilia* in respiratory samples in three cases and in one case respectively, and contamination with coagulase-negative staphylococci in three cases. These findings were considered clinically irrelevant and thus ignored [12].

One hundred and fourteen patients (56 %) received antiviral treatment. In one case with co-infection with RSV and parainfluenza, ribavirin was administered; all others were treated with oseltamivir. The dose of oseltamivir was 150 mg/d in 89/114 patients (78 %), but some also received a lower dose of 30 to 75 mg/d (14/114, 12 %). The median duration of treatment was 7 days (IQR 6.5–7.5 days).

Information on vaccination against influenza was available in 34 patients only. Twelve of 34 patients were vaccinated in 2014, whereas the other 22 received no vaccination.

Severe course of illness required treatment on intensive care unit (ICU) in 26 cases (13 %). Of 67 patients with LRTI, 23 (34 %) had to be treated on the ICU (nine with bacterial, four with fungal, and two with viral superinfection) and 12 of these patients (18 %) died. Overall, 17/200 patients (9 %) died in the course of IVI (Table 3).

In univariable analysis, prognostic factors for higher mortality were bacterial and fungal superinfection ($p = 0.0035$, Fig. 1a) and presence of pneumonia ($p < 0.001$, Fig. 1b). It should be noted that all patients who died were suffering from LRTI. Furthermore, time from onset of symptoms to diagnosis of IVI was significantly different between survivors and non-survivors (3 days [CI 95 % 2–4 days] versus 7 days [CI 95 % 5–9 days], $p = 0.002$). Patients deceased from influenza-associated causes were older (63 years [IQR 23–85 years]) than patients who survived (57 years [IQR 20–85 years], $p = 0.043$). In contrast, sex, type and activity of malignant disease (Fig. 1c), immunosuppressive therapy, graft versus host disease (GvHD) (Fig. 1d), and treatment with oseltamivir did not significantly influence the outcome in univariable analysis. Likewise, vaccination did not seem to influence mortality significantly (data not shown). Concerning the different viral subtypes, two out of six patients with known A(H1N1)pdm09 infection died, in contrast to four out of 27 with known H3N2 infection ($p = 0.08$).

Multivariable analysis revealed superinfection (hazard ratio [HR] 3.4 [95 % confidence interval (95%CI) 1.09–10.6, $p = 0.03$) and duration from onset of symptoms to diagnosis

Table 2 Pathogens detected in respiratory samples and blood cultures

Pathogens	Blood	BAL	Sputum/pharyngeal lavage fluid
Viruses			
- RSV			11
- Influenza B virus[$]			1
- Metapneumovirus			1
- Adenovirus			1
- Parainfluenza virus			1
Fungi			
- *Aspergillus spp.*		9	
- *Pneumocystis jirovecii*		1	
- *Scedosporium prolificans*		1	
Gram-positive bacteria			
- *Staphylococcus aureus*			1*
- *Streptococcus pneumoniae*	1		
- *Streptococcus mitis/oralis*	1		
- *Enterococcus faecium*	1		
Gram-negative bacteria			
- *Escherichia coli*	3	3	
- *Enterobacter cloacae*	2		
- *Klebsiella pneumoniae*		1	
- *Serratia marcescens*	1	1	
- *Pseudomonas aeruginosa*	3		
- *Stenotrophomonas maltophilia*		1	

BAL = bronchoalveolar lavage fluid

RSV = respiratory syncytial virus

Double and triple infections:

1× Parainfluenza virus and RSV in pharyngeal lavage fluid,

1× Pseudomonas and *E. coli* in BC,

1× *S. mitis* and *E. coli* in BC in addition to *E. coli* in BAL

1× Aspergillus and *E. coli* in BAL,

1× Pseudomonas in BC and adenovirus in sputum,

1× Aspergillus and pneumocystis in BAL

[$] in a patient with influenza A

* in a patient with pneumonia

Table 3 Characteristics[§] of deceased patients

Case number	Sex	Age (years)	Malignant disease	Active disease	SCT	Immuno-suppression[a]	Influenza virus genera and subtype	Time to diagnosis [b] (days)	Time to death[c] (days)	Clinical presentation	Oseltamivir	Superinfection	ICU
1	m	48	AML	unknown	allo	unknown	A[+]	6	−2	LRTI	yes	bacterial	yes
2	m	64	MM	no	auto	yes	A[+]	−1	2	LRTI	no	no	no
3	f	66	gynaecological carcinoma	yes	no	no	A H3N2	4	0	LRTI	no	fungal	yes
4	m	52	Hodgkin's Lymphoma	no	auto	no	A(H1N1)pdm09	7	3	ILI, later LRTI	yes	unknown	yes
5	m	64	AML	no	allo	no	A H3N2	12	17	LRTI	yes	bacterial	yes
6	m	68	NHL	yes	no	yes	B	17	14	LRTI	yes	fungal	yes
7	m	71	MM	yes	auto	yes	A[+]	4	28	LRTI	yes	no	yes
8	f	51	AML	yes	no	yes	A[+]	unknown	9	URTI, later LRTI	yes	viral	yes
9	m	23	ALL	no	allo	no	A[+]	21	11	LRTI	yes	bacterial	yes
10	f	61	MM	yes	auto	yes	A(H1N1)pdm09	8	12	LRTI	yes	fungal	yes
11	f	64	AML	no	allo	no	A H3N2	7	22	LRTI	yes	no	no
12	f	78	MM	yes	no	yes	A[+]	unknown	1	LRTI	unknown	no	no
13	m	68	NHL	no	allo	yes	B	-2	25	ILI, later LRTI	no	no	yes
14	f	85	"other"	yes	no	no	B	21	2	LRTI	no	no	no
15	f	65	AML	no	allo	no	A[+]	3	104*	ILI, later LRTI	yes	bacterial	yes
16	m	77	NHL	yes	no	no	A[+]	15	2	ILI, later LRTI	no	no	no
17	m	65	NHL	yes	yes	no	A H3N2	unknown	87	LRTI	yes	no	yes

[§] Status of vaccination against influenza unknown in all patients

[a] Any kind of ongoing immunosuppressive therapy

[b] Duration from start of symptoms to diagnosis influenza

[c] Duration from diagnosis to death

m = male, f = female,

auto = autologous, allo = allogeneic

ILI = influenza-like illness, LRTI = lower respiratory tract infection, URTI = upper respiratory tract infection

[+] Influenza A virus not subtyped

*Patient died because of pneumonia, Influenza A was always detected

SCT = stem cell transplantation, AML = acute myeloblastic leukaemia, MM = multiple myeloma, NHL = Non Hodgkin's lymphoma, ALL = acute lymphoblastic leukaemia

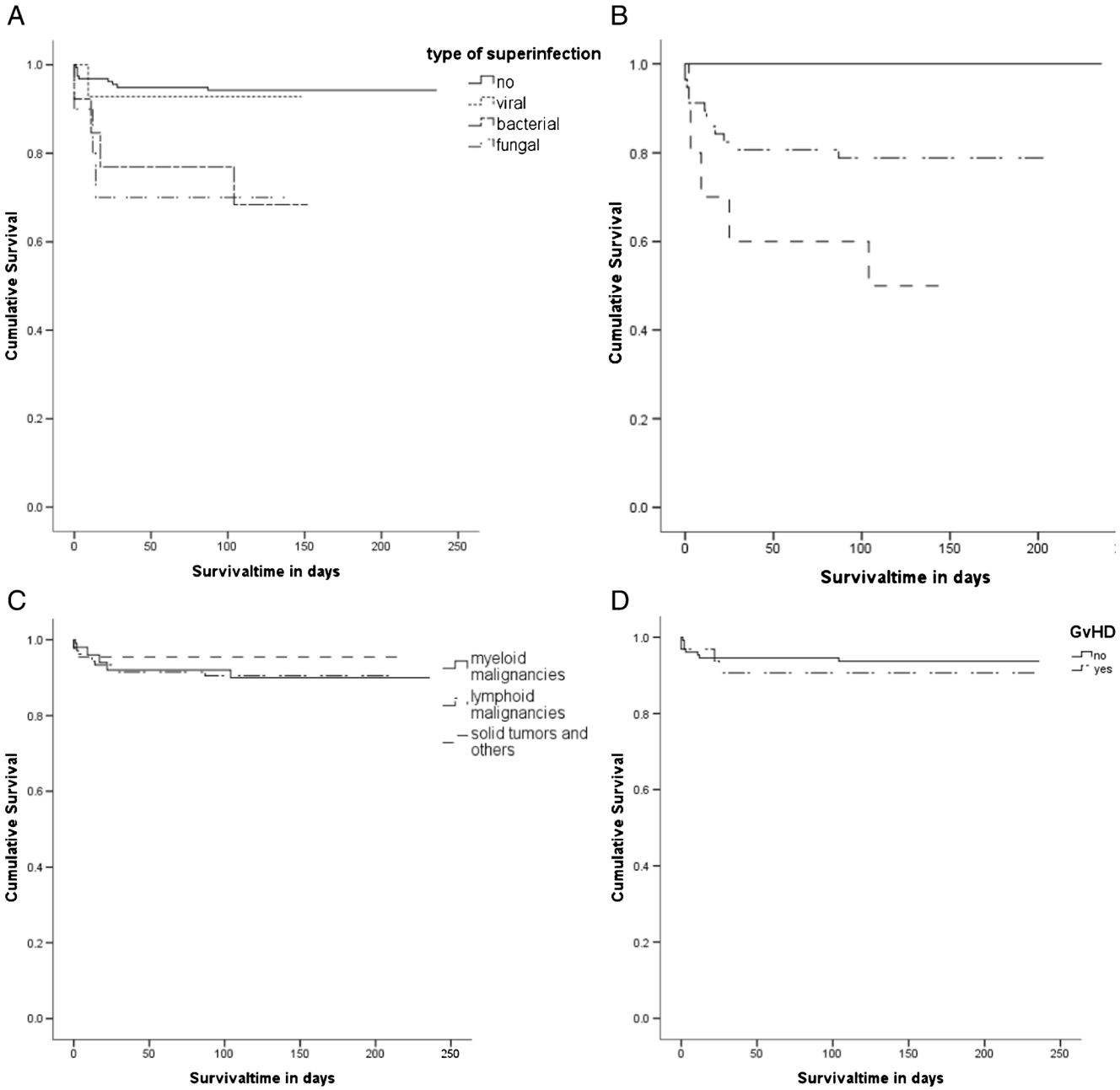

Fig. 1 **a** Survival of patients with or without superinfection, $p = 0.0035$ (log-rank). **b** Survival of patients with or without pneumonia, $p < 0.001$ (log-rank). **c** Survival with respect to underlying malignancy, $p = 0.594$ (log-rank). **d** Survival of patients with or without GvHD, $p = 0.542$ (log-rank)

(HR 1.1 [95%CI 1.01–1.2], $p = 0.02$) as independent prognostic factors.

Discussion

Due to a high rate of LRTI and a high associated mortality rate, the influenza season 2014/15 represented a relevant threat to cancer patients. At presentation, a third of patients were asymptomatic or presented with URTI only, which was relatively unexpected from a clinician's point of view. In line with other reports [13], influenza-associated URTI itself was not particularly harmful for the patients as all patients dying from influenza suffered from or developed pneumonia in the course of the illness. However, those patients who developed LRTI during the course of the disease showed a relevant impairment in survival (Fig. 1b), emphasising the need to take IVI seriously regardless of initial presentation.

In our cohort, presence of superinfection and prolonged duration from first symptoms to diagnosis were the sole

independent prognostic factors associated with higher mortality. A variety of studies investigating the causes of death in patients with IVI found that notably bacterial and fungal superinfections played an important role with regard to morbidity and mortality [14–16]. However, it seems that the mortality in these patients varies widely between the different cohorts [15], but the reasons for this wide scope are not clear. *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, *E. coli*, and *A. fumigatus* are the superinfecting pathogens most frequently described to date [17]. Studies on the pandemics in the twentieth century suggest a high mortality due to superinfections with these pathogens [14]. However, in the era of widespread vaccination against pneumococci in children and the elderly, this might not necessarily be true anymore, as suggested by Tief et al., who reported a low disease severity in children co-infected with influenza and *S. pneumoniae* [18]. In our cohort, 7/23 patients with bacterial or fungal infection died (30 %), showing superinfection to be the strongest predictor of death. Interestingly, we also found *A. fumigatus* to be a relevant pathogen, whereas bacteria typically associated with influenza were outnumbered by enteric bacteria and other Gram-negative bacteria such as *Pseudomonas aeruginosa*. The underrepresentation of Gram-positive bacteria is remarkable and differs from previous reports [15]. The species of bacteria found in our cohort may represent a microbial spectrum originating from the patient's flora or from the local health care environment. Nosocomial infections like ventilator-associated pneumonia are known to be caused by both Gram-negative organisms such as *Pseudomonas spp*., members of the *Enterobacteriacae*, *Acinetobacter spp*., or *S. maltophilia*, as well as by some Gram-positive organisms such as *S. aureus* [19–22]. Unfortunately, we did not record specifically whether patients were treated as inpatients or outpatients. However, it is not surprising to find a similar spectrum of bacteria in all patients with malignant disease, who, if not hospitalised, usually have close contact to health care institutions. Thus, our findings emphasise that antibiotic therapy for suspected bacterial superinfection in cancer patients with influenza needs to cover Gram-positive as well as Gram-negative bacteria. Moreover, superinfections with *A. fumigatus* are frequent in patients with malignant disease and IVI, highlighting the need for a thorough diagnostic workup and optional antifungal therapy. Screening for viral co-infection was not consistent between the participating centres, which may lead to underestimation of the impact of viral co- infection on the course of IVI in patients with underlying malignant disease.

Time to diagnosis was identified as a second independent prognostic factor for mortality in our study cohort. This may be due to the fact that patients with pneumonia or critically ill patients are usually considered to have other causative pathogens than influenza virus. Therefore, especially at the beginning of a wave of influenza, these patients might be diagnosed too late. Another possible explanation might be that patients with prolonged diagnosis bear the risk of delaying the initiation of treatment with oseltamivir, potentially leading to impaired efficacy of the drug [23]. In our study, time from onset of symptoms to initiation of antiviral treatment was not recorded, therefore we were not able to draw any definite conclusion regarding this point. Nevertheless, our data support the imperative of immediate NAT testing when cancer patients are suspected to suffer from IVI, even at the stage of URTI, to ensure early treatment as recommended [24, 25].

In addition to the microbial and therapy-associated risk factors mentioned above, risk factors for severe influenza in SCT recipients as described by the European Conference on Infections in Leukaemia (ECIL) are: older age, lymphopenia, first 12 months post SCT, GvHD, and immunosuppressive therapy, as well as having an unrelated or mismatched related donor [23]. In our study cohort, we were able to confirm that age has an impact on mortality, whereas GvHD or immunosuppression and prior SCT did not influence the outcome. It is noteworthy that severe disease did not only occur in patients with profound immunosuppression but also in patients with no ongoing active cancer treatment or those with solid tumours, resulting in comparable survival rates (Fig. 1c). This is unexpected, since most reports of life-threatening IVI originate from patients after allogeneic SCT, where substantial immunosuppression is usually an important risk factor [1, 4, 26].

Data on influenza in patients with solid tumours are generally scarce. A large study of 115 patients with solid tumours suffering from influenza found similar results to our cohort of 21 patients with solid tumours: 23 % of these cancer patients presented with pneumonia, and a mortality rate of 10 % was reported [8]. In line with our results, mortality was associated with prolonged duration to diagnosis of IVI. In contrast to our results, ongoing immunosuppression such as cancer treatment was associated with a severe course of viral infection, which was not seen in our patient cohort. Additionally, in this study detailed information on treatment with oseltamivir was provided, showing a benefit for patients being treated early [8]. In our study, oseltamivir did not influence the outcome significantly, possibly due to a delay of therapy.

As we conducted a retrospective study there are several limitations of our analysis due to a lack of data with regard to several issues. Exact information on start of antiviral therapy is lacking as well as the inpatient/outpatient status of the patients. Also, data on vaccination status and subtype of virus are very limited, and we are not able to draw any conclusions regarding the efficacy of vaccination or the virulence of virus subtypes. These questions will have to be addressed in future prospective studies. Nevertheless, all contacts of patients with malignant disease, e.g., partners, household members, and health care workers, should be urged to undergo seasonal influenza vaccination to better protect this vulnerable collective.

Conclusion

Albeit retrospective, some conclusions can be drawn from our analysis:

Influenza is potentially dangerous due to high rates of pneumonia and high mortality irrespective of the underlying malignant disease and therefore should be taken seriously in all groups of cancer patients. Therefore, an early diagnosis of IVI is imperative. Superinfections need to be addressed immediately and efficiently since this is the most dangerous complication.

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Compliance with ethical standards

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Ethical approval The study was approved by the ethics committee of Jena University Hospital (3785-05/13).

Informed consent No informed consent was required since this was a retrospective study.

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Review

Community acquired respiratory virus infections in cancer patients—Guideline on diagnosis and management by the Infectious Diseases Working Party of the German Society for haematology and Medical Oncology

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Superinfection;
Influenza;
Respiratory syncytial virus;
Parainfluenza

Abstract ***Background:*** Community acquired viruses (CRVs) may cause severe disease in cancer patients. Thus, efforts should be made to diagnose CRV rapidly and manage CRV infections accordingly.
Methods: A panel of 18 clinicians from the Infectious Diseases Working Party of the German Society for Haematology and Medical Oncology have convened to assess the available literature and provide recommendations on the management of CRV infections including influenza, respiratory syncytial virus, parainfluenza virus, human metapneumovirus and adenovirus.
Results: CRV infections in cancer patients may lead to pneumonia in approximately 30% of the cases, with an associated mortality of around 25%. For diagnosis of a CRV infection, combined nasal/throat swabs or washes/aspirates give the best results and nucleic acid amplification based-techniques (NAT) should be used to detect the pathogen. Hand hygiene, contact isolation and face masks have been shown to be of benefit as general infection management. Causal treatment can be given for influenza, using a neuraminidase inhibitor, and respiratory syncytial virus, using ribavirin in addition to intravenous immunoglobulins. Ribavirin has also been used to treat parainfluenza virus and human metapneumovirus, but data are inconclusive in this setting. Cidofovir is used to treat adenovirus pneumonitis.
Conclusions: CRV infections may pose a vital threat to patients with underlying malignancy. This guideline provides information on diagnosis and treatment to improve the outcome.
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1. Introduction

The importance of community acquired respiratory virus (CRV) infections is increasingly recognised. CRV are responsible for respiratory infections, which usually present as a common cold in the immunocompetent individual but may be life-threatening in the immunocompromised host. Usually, orthomyxoviridae (influenza A, B and C), paramyxoviridae (including parainfluenza 1–4 [PIV], respiratory syncytial virus A and B [RSV], and human metapneumovirus [hMPV]), coronaviridae, picornaviridae (including >100 different serotypes of rhinovirus and enterovirus), adenoviridae, polyomavirus type 1 and bocavirus are regarded as potential causes of CRV infection. This guideline is intended to give haematologists and oncologists a broad overview with regard to clinical relevance and diagnosis of CRV infection and management of cancer patients affected by CRV. Detailed information on respective viruses including emerging resistance is not the scope of this guideline. Most data on this topic originate from patients following allogeneic stem cell transplantation (allo-SCT), and we know little about CRV infections in cancer patients outside the setting of allo-SCT. However, in recent years increasing evidence has been gathered about other cancer patients, revealing clinical relevance of CRV infections in non-transplant patients. Therefore, this guideline discusses CRV infections in all cancer patients with ongoing relevant immunosuppression. It is left to the treating physician to assess the degree and relevance of immunosuppression in the individual patient.

2. Methods

This guideline has been developed by a panel from the Infectious Diseases Working Party (AGIHO) of the German Society of Haematology and Medical Oncology including 17 experts certified in internal medicine, haematology/oncology, infectious diseases, microbiology/virology or radiology and one medical student. First, predefined topics were delivered by the designated coordinator (MvLT) to all participants of the panel to form subgroups. Data were extracted and tabulated after a systematic literature search by subgroup members and revised in several steps by the

members of the panel on the basis of an email-based discussion process and a face-to-face meeting. Finally, preliminary recommendations of the panel were discussed, revised and approved by the AGIHO assembly.

In May 2014, the first literature search was performed for CRV and immunosuppression using the terms '-virus' and 'immunocompromised' (for example: 'adenovirus immunocompromised'). This search was performed for adenovirus, bocavirus, coronavirus, enterovirus, hMPV, influenza, PIV, parechovirus, RSV and rhinovirus. The references were then screened by the subgroup members and relevant articles retrieved as full papers. Wherever applicable, additional papers were identified in the reference lists and treated as described. In February 2016, an update of the literature search was performed.

For grading, the system applied by the European Society of Clinical Microbiology and Infectious Diseases as proposed by Ullmann *et al.*, in 2012 [1] was used (Table 1) with one modification: other than Ullmann *et al.*, we used the same grading of the strength of recommendation for diagnostic measures as for interventions (Table 1). The results of the literature search and the following grading process were used to develop recommendations wherever possible. Recommendations and evidence were then presented at and approved by the AGIHO assembly during the spring meeting on 6th March 2015. Following the update of the literature search in February 2016 no relevant changes were made.

Table 1
Grading of evidence as suggested by the ESCMID [1].

Strength of recommendation	
A	Strongly support a recommendation for use
B	Moderately support a recommendation for use
C	Marginally support a recommendation for use
D	Support a recommendation against use
Quality of evidence for interventions—level	
I	Evidence from at least one properly designed randomized, controlled trial
II*	Evidence from at least one well-designed clinical trial, without randomization; from cohort- or case-control analytic studies (preferably from more than one centre); from multiple time series; or from dramatic results from uncontrolled experiments.
III	Evidence from opinion of respected authorities, based on clinical experience, descriptive case studies, or report of expert committees
*Added index	
R	Meta-analysis or systematic review of randomized controlled trials
T	Transferred evidence, i.e. results from different patients' cohorts or similar immune status situation
H	Comparator group is a historical control
U	Uncontrolled trial
A	Abstract published at an international meeting
Quality of evidence for diagnostic measures—level	
I	Evidence from at least one properly designed multicentre cross-sectional or cohort study
II	Evidence from (1) At least one well-designed prospective singlecentre cross-sectional or cohort study or (2) A properly designed retrospective multicentre cross-sectional or cohort study or (3) From case-control studies
III	Evidence from opinion of respected authorities, based on clinical experience, descriptive case studies, or report of expert committees

3. Diseases caused by CRV

CRVs cause respiratory tract infections, which can be divided into upper respiratory tract infection (URTI), influenza-like illness (ILI) and lower respiratory tract infection/pneumonia (LRTI). Commonly, URTI can be assumed, if a patient has a new onset of symptoms including at least one of cough, coryza, sore throat or shortness of breath which is deemed to be due to an infection by the treating physician. LRTI requires clinical or radiological evidence of pneumonia [2]. ILI is diagnosed in patients with a sudden onset of new symptoms including at least one of fever or feverishness, malaise, headache or myalgia and at least one of the respiratory symptoms cough, sore throat or shortness of breath [3]. To be certain of the viral origin, the detection of the virus from respiratory samples like swabs, nasopharyngeal aspirates or bronchoalveolar lavage fluid is required. Of note, surveillance studies showed some patients to be asymptomatic but still shedding the virus [2,4–7]. For that reason, some authors distinguish between respiratory infection (detection of virus independent of symptoms) and respiratory infection disease (detection of virus and respective symptoms) [8]. However, for the purpose of this guideline, we omit this distinction and define URTI, LRTI and ILI as described above.

4. Epidemiology and clinical relevance

Some CRV like influenza or RSV have a seasonality with most infections occurring during the winter months [2,9,10]. Others like rhinovirus or parainfluenza are independent of seasonality [11]. Thus, an appropriate diagnostic work-up and clinical management is warranted in any patient presenting with typical symptoms regardless of the time of the year. As may be expected considering the nature of the disease, CRV frequently cause outbreaks in health care settings [7,12–15]. Importantly, outbreaks may also occur in outpatient settings [16] emphasising the need for awareness during all periods of cancer treatment.

Generally, viral URTI in cancer patients has some impact on the clinical course because the patients are symptomatic to a degree that frequently requires postponement of chemotherapy [17]. However, critical

illness and mortality due to viral URTI are rare. In contrast, most patients who died were suffering from LRTI, which thus poses the biggest threat to cancer patients. Rates of LRTI and mortality differ amongst the respective CRV [18] and exact estimation is hampered by the fact that fatal cases are probably over-reported. We have tried to deduce reliable information on LRTI and mortality from the literature for various CRV: influenza appears to have a high rate of LRTI with approximately 30% and an associated mortality rate of approximately 25% [19–22]. RSV appears to be at least as dangerous with a rate of LRTI of approximately 33% and an associated mortality rate of 27% [16]. However, it has to be kept in mind, that most data regarding RSV originate from SCT-recipients and very little is known regarding patients with other forms of malignancy. On the other hand, there are several reports of outbreaks in general haematology/oncology units, which showed a significant disease burden even in patients not undergoing stem cell transplantation [12].

With regard to hMPV and PIV, exact information on the clinical relevance is even more difficult to obtain. However, although both viruses may cause asymptomatic infection [6,23], the available evidence suggests a similar overall rate of LRTI and mortality [7,11,13,24–28] compared with influenza and RSV. In contrast, despite case reports of fatal outcomes of infections with rhinovirus and coronavirus, these viruses as well as bocavirus appear to be rarely the cause of LRTI and dangerous only when patients are coinfected with other pathogens [2,5,29]. Herpesviridae like herpes simplex virus, human herpes virus 6, cytomegalovirus, varicella zoster and Epstein–Barr virus as well as polyomaviruses or parechoviruses usually do not cause CRV infection. Pneumonia due to reactivation of herpesviridae in severely immunocompromised patients is not an infection by CRV and thus not covered by this guideline.

In CRV infection, coinfection with bacteria, fungi or even other viruses appears to occur in approximately 30% of the patients [10,11,28]. They play a vital role with regard to outcome of patients since patients with bacterial or fungal superinfection have a dramatically higher mortality rate than those with viral infection only [11,28]. Therefore, possible co- or superinfection should be considered when managing cancer patients with CRV. In addition to LRTI and bacterial or fungal superinfection, other risk factors for adverse outcome include haematological malignancy [22], severe immunosuppression such as steroid use or graft versus host disease or cytopenias [30–32] or low immunoglobulins [12].

Epidemiology of adenoviruses is somewhat different from the other CRV: often, the source of infection is a childhood infection in children under 5 years [33] and reactivation as well as new infection have been described to be the cause of disease [34,35]. Other than CRVs like RSV or influenza, adenoviruses can cause a variety of symptoms such as conjunctivitis, haemorrhagic cystitis, gastroenteritis, and URTI in immunocompetent patients and hepatitis, colitis, nephritis, meningoencephalitis and LRTI in the immunocompromised host. In adult allo-SCT recipients, DNAemia occurs in up to 20% [36–38], but symptomatic disease by adenovirus is much less common with T-cell suppression being the predominant risk factor [36]. Again, coinfection is an important risk factor for severe illness [39].

5. Diagnosis of CRV infection

5.1. Virology—material

Cancer patients presenting with symptoms consistent with CRV infection should be diagnosed using material from the respiratory tract (Table 2). Serology is not useful to detect ongoing CRV infection and thus not recommended (D III). Regarding material used for microbiological diagnosis, a variety of approaches are used in various centres. As a general rule, a close collaboration with the local microbiology laboratory is highly recommended because this may determine which material should be used preferably since commercially available test kits are licensed for specific materials. For example testing for viral antigens usually requires more thorough sampling like combined nasal/throat swabs than testing for viral nucleic acids which can often be performed reliably on gargles alone. It is therefore essential for the clinician to be aware of the tests used in the respective laboratory. The overall evidence in the literature is best for combined nasal/throat swabs and nasopharyngeal aspirates (A IIt, Table 2).

5.2. Virology—test

The best evidence for reliable detection of a CRV present in respiratory samples exists for nucleic acid amplification based-techniques (NAT) like PCR. Therefore, the use of NAT is highly recommended (A II, Table 2) and any methods involving the detection of antigen appear to be second best in immunosuppressed cancer patients (C II [40–42]). Also, culture methods are not commonly used anymore and cannot be recommended for general diagnosis, but they are essential in individual cases in which no known virus can be detected or results of PCR-analysis are inconclusive (A II, [43]). In the era of multiplex-test kits, it is difficult to make a definite recommendation with regard to which viruses should be looked for. In the absence of any reliable data regarding this question, the panel feels that it is wise to search for influenza, RSV, PIV and viruses currently prevalent in the local environment in all immunosuppressed cancer patients presenting with symptoms. Patients with more severe disease (for

Table 2
Recommendations regarding diagnostic approaches in cancer patients with symptoms of CRV infection.

Population	Intention	Intervention	SoR	QoE	Reference
Symptomatic IS	To detect viral pathogen and diagnose infection	Serology	D	III	[94]
Symptomatic IS	To detect viral pathogen	Combined nasal/throat swabs or washes/aspirates	A	II	[95–103]
Symptomatic IS	To detect viral pathogen	NAT	A	II	[42,94,104–107],
Symptomatic IS	To detect LRTI in patients with CRV infection	Chest X-ray	D	II	[108]
Symptomatic IS	To detect LRTI in patients with CRV infection	CT scan	A	II	[44,46,47,69,108–115],

SoR, strength of recommendation; QoE, quality of evidence; IS, immunosuppressed cancer patients; NAT, nucleic acid amplification techniques; LRTI, lower respiratory tract infection; CRV, community acquired respiratory virus; CT, computer tomography.

example pneumonia or critical illness) may have the panel broadened to include hMPV and adenovirus and even viruses that only rarely cause LRTI like rhinovirus and coronavirus. However, evidence for this approach is low and it is strongly advisable to define local guidelines on this topic. It should be kept in mind, that herpesviridae are not the cause of CRV infection. Therefore, there is no rationale to look for cytomegalovirus, Epstein–Barr virus, herpes simplex virus or varicella zoster in patients with typical symptoms of CRV infection only.

5.3. Radiology

In patients with symptoms of LRTI, it is essential to determine the degree of pulmonary involvement. CRV can affect the tracheobronchial system or the lung parenchyma [44]. Generally, a chest X-ray has been proven to be unhelpful to diagnose pathologic changes in this setting because of lack of sensitivity. It is therefore not recommended (D II, see Table 2). In contrast, there is good evidence to recommend a CT scan of the chest to detect LRTI in patients with CRV infection (A II, see Table 2). Bronchial wall thickening as well as interstitial infiltrates presenting as ground-glass opacities may be detected. These are defined as increased lung density, whereas underlying lung architecture is still detectable. Ground-glass opacities may be patchy or diffuse [44–47] and can be well distinguished from consolidations, which show higher density obscuring e.g. the pulmonary vessels and which are typical for other differential diagnoses including bacterial infection. Affection of the terminal bronchioles might lead to visibility of those usually invisible structures at CT as small centrilobular nodules or 'tree-in-bud' sign [45] or evidence of bronchiolitis causing air-trapping. To reliably detect air-trapping while inspiratory CT is normal, a CT scan in expiration is necessary [44]. In addition to good diagnostic accuracy with regard to the diagnosis of a viral LRTI, the CT scan may also reveal evidence for an outbreak, since specific viruses tend to present with a typical pattern in the CT scan [45]. For an example see Fig. 1.

6. Management of CRV infection

6.1. Infection control

In the light of the danger of outbreaks with fatal consequences, the most important measure in the management of cancer patients with CRV infection is infection control (Table 3). Local authorities should give exact guidance on the necessary precautions in the respective institutions. The following statements intend to give a general overview.

There is sufficient evidence to recommend stringent hand hygiene (A IIt), the use of face masks (B IIt) and contact isolation (A III, Table 3). Importantly, shedding of CRV in cancer patients often lasts 2 weeks or longer [5,10,48]. It is therefore wise to perform follow-up testing of respiratory material in index patients and stop contact isolation only when they became negative. Of note, early implementation of infection control appears to be more effective than late implementation [49] which gives reason to recommend infection control as soon as symptoms appear and not only after evidence of CRV.

6.2. Supportive measures

Almost anybody who catches a cold applies some form of home remedies convinced that they ease the symptoms and positively influence the course of the disease. In contrast to this widespread use, there is very little evidence to recommend any such measures. In particular with regard to cancer patients, evidence is too poor to give a sound recommendation in favour of the use of vitamin C [50], echinacea [51], garlic [52], zinc [53], humidified hot air [54] or Chinese herbal medicine [55]. Surprisingly, even painkillers [56] and non-steroidal anti-inflammatory drugs [57] may ease the pain but have little influence on severity and duration of the CRV infection. However, as there is some evidence towards a considerable placebo effect [58], it can be argued that patients should be allowed to continue their home remedies provided there is no reason to assume harmfulness as may be the case for some Chinese herbal

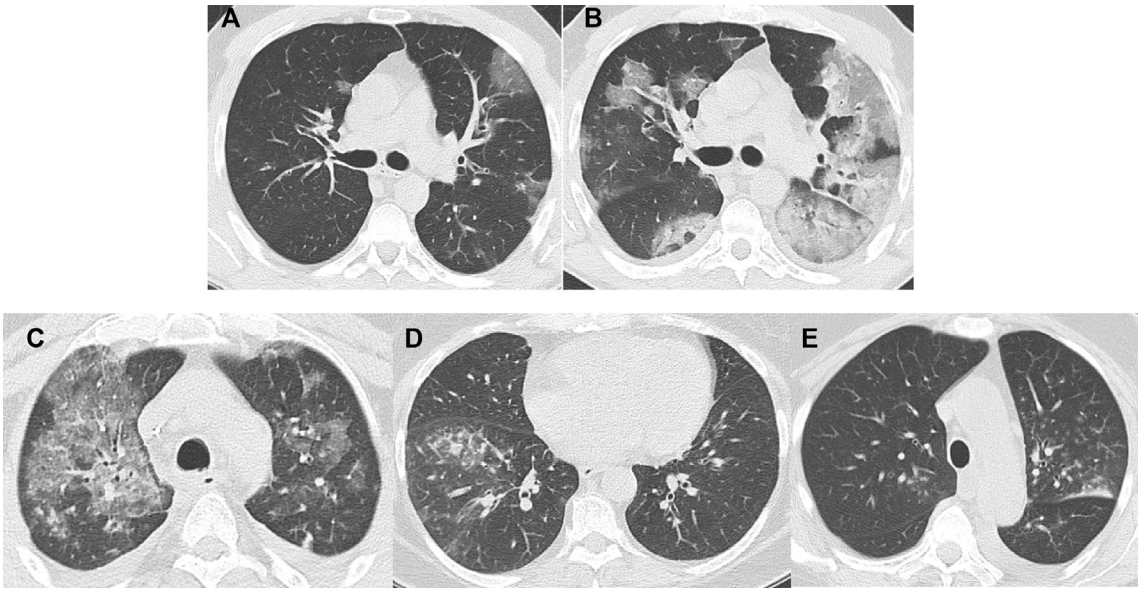

Fig. 1. A–B: pneumonia caused by influenza, first CT scan (A) and follow-up scan after 4 d (B). The bilateral diffuse ground-glass opacities progress over time to cover most parts of the lung. In addition, consolidations with positive bronchopneumogram develop, indicative of possible bacterial superinfection. C–E: CT scans from three different patients with pneumonia caused by RSV. Again, ground-glass opacities can be found but are of a more patchy character (Fig. 1C). They are often combined with centrilobular nodules (tree-in-bud, Fig. 1D). In some cases, only nodules with a ground-glass character are detected (Fig. 1E). RSV, respiratory syncytial virus.

Table 3
Recommendations regarding general management of cancer patients with CRV.

Population	Intention	Intervention	SoR	QoE	Reference
IS, infected persons, Contact persons	Infection control—prevent transmission	Hand hygiene	A	IIt	[49,116]
IS, Infected persons, Contact persons	Infection control—prevent transmission	Face mask	B	IIt	[49,116]
Infected persons	Infection control—prevent outbreak	Contact isolation	A	III	[117]
allo-SCT and evidence of CRV	Prevent disease, improve survival	Delay conditioning	A	II	[17]
All other chemotherapy and CRV	Prevent disease, improve survival	Delay chemotherapy if possible	C	III	[61]
allo-SCT and LRTI due to adenovirus	Prevent disease, shorten duration	Reduce immunosuppression	A	II	[36,62]
allo-SCT and LRTI due to CRV	Prevent disease, shorten duration	Reduce immunosuppression	A	IIt	[36,62]
allo-SCT and URTI	Prevent disease, shorten duration	Reduce immunosuppression	C	III	
IS with evidence of CRV	Reduce morbidity	Steroids >2 mg/kg	D	III	[10]
IS with evidence of RSV	Prevent LRTI, improve survival	IVIG	B	III	[30,82]
IS with evidence of influenza, PIV, hMPV	prevent LRTI, improve survival	IVIG	C	III	[69,92,118,119]

SoR, strength of recommendation; QoE, quality of evidence; IS, immunosuppressed cancer patients; URTI, upper respiratory tract infection; LRTI, lower respiratory tract infection; CRV, community acquired respiratory virus; IVIG intravenous immunoglobulins; allo-SCT, allogeneic stem cell transplantation; RSV, respiratory syncytial virus; PIV, parainfluenza virus; hMPV, human metapneumovirus.

medicines contaminated with heavy metals [59] or the possibility to contract invasive fungal infection from inhaling contaminated air.

Needless to say, there is little to be gained from treating a viral infection with antibiotics [60], which is also true for cancer patients (D IIr,t for treating viral infections with antibiotics). However, having in mind the high rate of superinfection, cancer patients with viral LRTI and suspected or proven bacterial/fungal coinfection have to be treated accordingly (A III).

In cancer patients who present with symptoms consistent with CRV infection prior to initiation of chemotherapy, delaying treatment should be considered. Since a retrospective study with 2 groups showed a benefit, if treatment was delayed in patients undergoing allo-SCT, we clearly recommend delaying conditioning in those patients who are scheduled for allo-SCT and have evidence of CRV infection (A II, see Table 3). The situation is less clear for patients with less aggressive treatment, since there have been reports of uneventful courses of even high-dose chemotherapy in patients with initial CRV infection [61]. Therefore, the recommendation to delay the chemotherapy if possible to be on the safe side is merely a weak one (Table 3).

Similarly, reducing immunosuppression in patients with LRTI due to adenovirus-infection after allo-SCT is well founded [36,62] on retrospective cohort studies with 2 groups and is thus clearly recommended (A II, Table 3). Data can be transferred to the situation of other LRTI caused by CRV, therefore, reduction of immunosuppression is also recommended in allo-SCT recipients with LRTI caused by other CRV (A IIt, Table 3). In contrast, the situation is less clear in patients with URTI and therefore only a very weak recommendation can be made (C III, Table 3).

With regard to supportive application of systemic medication other than antivirals, no recommendation can be made for the use of steroids, since they show no effect and prolong viral shedding (D III, Table 3). In contrast, intravenous immunoglobulins (IVIGs) are a therapeutic option in RSV infection (B III) and may also be beneficial in influenza, PIV and hMPV infection (C III, Table 3). Because of lack of data, no recommendation can be made regarding the use of IVIG in other CRV infections.

7. Causal treatment

7.1. Influenza

If causal treatment was deemed necessary, influenza A was traditionally treated with amantadine or rimantadine. Nowadays, resistance rates are so high that neither can be recommended (D II [63–66]). In contrast, despite ongoing discussion regarding the balance of efficacy and side effects [67,68] the treatment of choice appears to be a neuraminidase inhibitor, be it oseltamivir, zanamivir or peramivir. They are recommended as prophylaxis as well as for treatment (for example http://www.rki.de/DE/Content/InfAZ/I/Influenza/IPV/IPV_Node.html or [63,69,70]). However, data regarding the efficacy of prophylactic use of neuraminidase inhibitors in cancer patients are very weak and almost exclusively in the setting of stem cell transplantation [71,72]. Therefore, the authors believe it is not justified to give any recommendation in favour of or against their use in cancer patients in general. Thus, prevention of influenza by application of neuraminidase inhibitors remains one of the unresolved issues requiring further study. Still, we have included information on dose and duration in Table 5.

Treatment of influenza is usually recommended in symptomatic patients at high risk preferably <48h after the onset of symptoms [63]. Cancer patients might be regarded as high-risk patients per se, which is why neuraminidase inhibitors (usually oseltamivir) are often routinely given to patients with malignancies and influenza [69,70,73], since mostly retrospective data show a benefit of (early) antiviral treatment with regard to development of LRTI or further complications [10,20,74–76]. Thus, we do recommend the use of oseltamivir or zanamivir (B II, Tables 4 and 5). There is evidence to recommend early initiation of treatment, but that does not necessarily mean later treatment is futile [77] and therefore many authors recommend treatment regardless of timepoint [70]. However, we do not think either dose (150–300 mg/d) nor duration (5–10 d or longer) are well defined from the available evidence and need determination by local specialists. The reasons usually given for higher doses and longer treatment duration in high-risk patients is the prolonged viral shedding observed in cancer patients and a thus deduced susceptibility to develop resistances if not treated effectively [69,70].

Peramivir has received FDA approval during the 2009 pandemic and is recommended for patients with H1N1 infection unable to take oral medication [78]. It is not available in Germany but included in this guideline for the sake of completeness (Table 5). The authors advise its use in severe cases, when oral intake or inhalation is not possible (CIII). Another salvage option may be the combination of zanamivir or oseltamivir with ribavirin, since that has shown some efficacy in older studies [79].

7.2. RSV

RSV is usually treated with intravenous immunoglobulins (IVIG, B III, Table 3) and ribavirin. In Europe, the monoclonal antibody palivizumab is licensed for prevention of RSV in children only. In addition, the benefit over polyclonal IVIG is not entirely conclusive [80]. For these reasons, we do not make a clear recommendation for or against its use in cancer patients, since we regard

Table 4
Recommendations regarding causal treatment of influenza, RSV, parainfluenza and adenovirus.

Population	Intention	Intervention	SoR	QoE	Reference
IS and influenza	Shorten duration and prevent LRTI	Oseltamivir	B	II	[10,74,76,77]
IS and influenza	Shorten duration and prevent LRTI	Zanamivir	B	II	[75,76]
IS and RSV	Prevent LRTI and improve survival	Ribavirin	B	II	[12,30,80–82,86,87]
IS and PIV	Prevent LRTI and improve survival	Ribavirin	C	III	[11,24,79,86,88,89]
Adenovirus-associated pneumonitis	Cure	Cidofovir	B	II	[120–122]

SoR, strength of recommendation; QoE, quality of evidence; IS, immunosuppressed cancer patients; LRTI, lower respiratory tract infection; CRV, community acquired respiratory virus; RSV, respiratory syncytial virus; PIV parainfluenza virus.

Table 5
Information on specific drugs.

Name	Class	Indication	Dose	Application mode	Duration	Comment	Reference
Oseltamivir	Neuraminidase inhibitor	Prophylaxis influenza	75 mg/d	Oral	As needed in seasonal prophylaxis; 10d in post-exposure prophylaxis	Caveat: data too weak to make a recommendation, local strategies needed	[63,69,71]
Oseltamivir	Neuraminidase inhibitor	Treatment influenza	2 × 75-150 mg/d	Oral	5–10 d		[10,74,76,77]
Zanamivir	Neuraminidase inhibitor	Prophylaxis influenza	10 mg/d	Inhalation	As needed in seasonal prophylaxis; 10d in post-exposure prophylaxis	Caveat: data too weak to make a recommendation, local strategies needed	[63,69]
Zanamivir	Neuraminidase inhibitor	Treatment influenza	2 × 10 mg/d	Inhalation	Until negativity		[75]
Peramivir	Neuraminidase inhibitor	Treatment influenza	600 mg/d	Intravenous		Not available in Germany	[78]
Ribavirin	Nucleoside inhibitor	Treatment RSV, PIV, hMPV	Daily dose: 2 g for 2 h every 6 h or 6 g over 18 h	Inhalation	7–10 d	Be aware of potential teratogenic effect—special precautions needed	[82]
Ribavirin	Nucleoside inhibitor	Treatment RSV, PIV, hMPV	Different schedules[a]	Oral		Be aware of potential hepatic and renal toxicity, haemolysis	[12,30,80–82,86,87]
Ribavirin	Nucleoside inhibitor	Treatment RSV, PIV, hMPV	10–30 mg/kg/d	Intravenous		Be aware of potential hepatic and renal toxicity, haemolysis	[87]
Cidofovir	DNA polymerase inhibitor	Treatment adenovirus	Cidofovir 3–5 mg/kg iv once weekly for 2 weeks, then once every week	Intravenous		To reduce cidofovir toxicity, add at least 2 l of iv Prehydration and probenecid 2 g po 3 h prior and 1 g 2 and 8 h following cidofovir	[120–124]

RSV, respiratory syncytial virus; PIV, parainfluenza virus; hMPV, human metapneumovirus.
[a] For example: loading dose: 10 mg/kg, then 3 × 400 mg d2, 3 × 600 mg from d3 [30]; 1800 mg/d [87]; <65 kg body weight: 2 × 400 mg/d; 65–80 kg body weight: 2 × 500 mg/d; >80 kg body weight: 2 × 600 mg/d [12]; <75 kg body weight: 2 × 600 mg/d and ≥75 kg body weight: 2 × 800 mg/d [81]; 20 mg/kg/d in four divided doses increasing every 24–48 h to 60 mg/kg/d in four divided doses, if tolerated [86].

the question whether to use palivizumab instead of IVIG as an unresolved question requiring further study.

Ribavirin is the agent of choice in the treatment of RSV infection. Most available data concern allo-SCT recipients [80], but recent evidence also suggests a benefit in less severely immunosuppressed cancer patients [12,81]. It appears to lower the progression rate to LRTI [82] and is reported to have a positive influence on survival [12]. However, some authors report favourable outcome of RSV infections without any causal treatment [61,83,84]. Traditionally, it is used as an aerosol (see Table 5), but this application mode is cumbersome and may be associated with a teratogeneic effect [85]. Also, patients may not be able to inhale for such a long time or they may react with bronchospasm. Thus, oral application has been used increasingly with a similar efficacy [12,30,81,86,87] and even intravenous application is reported [87]. Despite some reports with a good outcome without treatment, we believe the available evidence justifies a recommendation for the use of ribavirin in cancer patients with RSV infection (B II, Table 4). Also, at least in high-risk patients the treatment should be given at the stage of URTI, since this has shown a benefit (B II [82]).

7.3. Parainfluenza (PIV)

Experience with antiviral therapy (generally ribavirin) in patients with parainfluenza infection is not very large and the efficacy is not entirely convincing [11,24,79,86,88,89]. This may be partly because causal treatment is started too late in the course of the disease and partly because the cause of death often is a coinfection requiring antibiotic therapy [7,28]. Nonetheless, it may be reasonable to attempt therapy with ribavirin in patients with parainfluenza infection (C III, Table 4).

7.4. Adenovirus

Causal therapy with cidofovir is justified in immunosuppressed cancer patients with LRTI caused by adenovirus (B II, Tables 4 and 5). More experimental therapies, which are employed in the setting of allo-SCT include donor-lymphocyte infusions [90] or adaptive transfer of specific T-cells [91]. However, to date evidence is too weak to justify a recommendation in favour of or against the use of these treatment modalities.

7.5. Human metapneumovirus (hMPV), rhinovirus, coronavirus and others

Causal therapy with ribavirin has been attempted in patients with infections caused by hMPV [92,93], albeit with unconvincing results. There is not enough evidence to make a definitive recommendation for or against the use of any specific antiviral drug or other causal treatment approaches like interferon for any of the CRV other than the ones discussed above.

8. Conclusion and outlook

Early diagnosis and general infection prevention may improve the outcome of cancer patients with CRV infections. Despite some data regarding some viruses (influenza, RSV) and patient populations (HSCT-recipients), there is still a lack of information on most CRV and on other patient populations (for example those with solid tumours). Also, almost no prospective randomised trials have been performed for the treatment of CRV infections in cancer patients. Thus, most recommendations have to be deduced from other populations and further study is urgently needed.

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MC has received research funding from Deutsche Forschungsgemeinschaft (DFG) and Erich und Gertrud Roggenbuck Stiftung, been a speaker for MSD and Basilea, has been a consultant for MSD and Basilea, received travel grants from Celgene, Takeda, Gilead and MSD and is a recipient of the MSD stipend oncology 2013.

MH served on advisory boards of Gilead, Roche Pharma and Takeda and served on the speakers' bureau for Celgene, Novartis, Janssen and Amgen.

CPH is a stock owner of Stada and GSK and has received consultation fees and/or honoraria from Schering-Plough, Pfizer, Basilea, Boehringer Ingelheim, Novartis, Roche, Astellas, Gilead, MSD, Lilly, Intermune, Fresenius, Olympus, Gilead, AstraZeneca, Bracco, MEDA Pharma, Chiesi, Siemens, Covidien, Pierre Fabre, Grifols and research funding from Siemens, Pfizer, MeVis and Boehringer Ingelheim.

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MJGTV is a consultant to: Berlin Chemie, MSD/Merck and Astellas Pharma; has served at the speakers' bureau of: Pfizer, Merck/MSD, Gilead Sciences, Organobalance and Astellas Pharma; received research funding from: 3M, Astellas Pharma, DaVolterra and Gilead Sciences.

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