UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL

Faculdade de Medicina

Programa de Pós-Graduação em Medicina: Ciências Médicas

Desfechos Clínicos em Neutropenia Febril

Regis Goulart Rosa

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Desfechos Clínicos em Neutropenia Febril

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RESUMO

Neutropenia febril (NF) constitui complicação frequente do tratamento quimioterápico do câncer e está associada a altas taxas de morbimortalidade. O reconhecimento dos principais fatores associados ao desenvolvimento de desfechos clínicos desfavoráveis na NF é fundamental, uma vez que estes podem ser utilizados como marcadores prognósticos ou alvos terapêuticos.

Este estudo objetiva determinar os principais fatores associados com mortalidade, tempo de hospitalização, incidência de bacteremia por patógenos multirresistentes e incidência de choque séptico no início da febre em pacientes hospitalizados com NF secundária à quimioterapia citotóxica para o câncer.

Na presente coorte prospectiva composta por 305 episódios consecutivos de NF (em 169 pacientes com câncer) realizada em um hospital terciário no período de outubro de 2009 a agosto de 2011, as seguintes questões de pesquisa foram avaliadas: impacto do tempo de início da antibioticoterapia na mortalidade em 28 dias; fatores relacionados com tempo de hospitalização; impacto dos fatores microbiológicos da bacteremia no desenvolvimento de choque séptico no início do episódio de NF; fatores de risco para bacteremia por patógenos multirresistentes; impacto da bacteremia por *Staphylococcus* coagulase-negativo na mortalidade em 28 dias.

Em 5 publicações distintas, os seguintes resultados foram notados: o atraso do início da antibioticoterapia está associado a maiores taxas de mortalidade em 28 dias; neoplasia hematológica, regimes quimioterápicos de altas doses, duração da neutropenia e bacteremia por Gram-negativos multirresistentes estão associados com períodos prolongados de internação por NF; infecção de corrente sanguínea polimicrobiana, bacteremia por *Escherichia coli* e bacteremia por *Streptococcus* viridans estão associados a choque séptico no início do episódio de NF; idade avançada, duração da neutropenia e presença de cateter venoso central estão associados com bacteremia por patógenos multirresistentes; bacteremia por *Staphylococcus* coagulase-negativo está associada a menores taxas de mortalidade em 28 dias quando comparado à bacteremia por outros patógenos.

Palavras-Chave: Neutropenia febril; Desfechos clínicos; Fatores de risco; Mortalidade; Tempo de hospitalização; Choque séptico; Resistência antimicrobiana; Tempo de início do tratamento; Bacteremia.

ABSTRACT

Febrile neutropenia (FN) is a common complication of cancer chemotherapy and is associated with high morbidity and mortality rates. Recognition of the main factors associated with the development of adverse clinical outcomes in FN is crucial, given that these factors can be used as prognostic markers or therapeutic targets.

This study aims to determine the main factors associated with mortality, length of hospital stay, incidence of bacteremia by multidrug-resistant pathogens and incidence of septic shock at the onset of fever in hospitalized patients with FN secondary to cancer cytotoxic chemotherapy.

In the present prospective cohort of 305 FN episodes (in 169 cancer patients) conducted at a tertiary hospital from October 2009 to August 2011, the following research questions were evaluated: impact of time to antibiotic administration on 28-day mortality; factors associated with length of hospital stay; impact of microbiological factors of bacteremia on the development of septic shock at the onset of FN; risk factors for bacteremia by multidrug-resistant pathogens; impact of coagulase-negative *Staphylococcus* bacteremia on 28-day mortality.

In 5 distinct publications, the following results were noted: delay of antibiotic administration is associated with higher 28-day mortality rates; hematologic malignancy, high-dose chemotherapy regimens, duration of neutropenia and bacteremia by multidrug-resistant Gram-negative bacteria are associated with prolonged length of hospital stay; polymicrobial bloodstream infection, bacteremia by *Escherichia coli*, and bacteremia by viridans sreptococci are associated with septic shock at the onset of FN; advanced age, duration of neutropenia and presence of indwelling central venous catheters are associated with bacteremia by multidrug-resistant pathogens; coagulase-negative *Staphylococcus* bacteremia is associated with lower 28-day mortality rates compared with bacteremia by other pathogens.

Keywords: Febrile neutropenia; Patient outcome assessment; Risk factors; Mortality; Length of stay; Shock, septic; Drug resistance, bacterial; Time-to-treatment; Bacteremia.

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BSI	Bloodstream Infection
CLSI	Clinical and Laboratory Standards Institute
CoNS	Coagulase-negative *Staphylococcus*
ESBL	Beta-lactamase de espectro estendido
FN	Febrile Neutropenia
HSV	Vírus Herpes Simples
LOS	Length of Hospital Stay
MASCC	Multinational Association for Supportive Care in Cancer
MDR	Multi-Drug-Resistant
NF	Neutropenia Febril
SIRS	Síndrome da Resposta Inflamatória Sistêmica
SS	Septic Shock
TTA	Time to Antibiotic Administration

ÍNDICE

1. INTRODUÇÃO

Apesar dos avanços no tratamento de suporte do câncer ocorridos nas últimas décadas, infecções em pacientes com neutropenia secundária à quimioterapia citotóxica continuam a se correlacionar com elevadas taxas morbimortalidade e com elevados custos assistenciais [1,2]. O curso clínico imprevisível das infecções em pacientes neutropênicos, devido à sutileza ou, até mesmo, à ausência de sinais e sintomas de infecção - pela atenuação da resposta inflamatória - torna o manejo da neutropenia febril (NF) um verdadeiro desafio, pois pacientes clinicamente estáveis podem, subitamente, progredir para quadros de sepse grave ou choque séptico [3]. Estas complicações em muito contribuem para as altas taxas de mortalidade por episódio, as quais podem atingir valores tão altos quanto 10% em centros especializados [4,5].

Além disso, o tratamento da NF pode ter um impacto negativo nos custos e na utilização de recursos do sistema de saúde uma vez que procedimentos diagnósticos e terapêuticos na NF são comumente acompanhados de altos gastos. Por exemplo, estima-se que o custo médio por hospitalização em decorrência da NF alcance a faixa de U$ 24.000,00, com um excesso de custo atribuível de cerca de U$ 12.000,00 [1,6].

O aumento da incidência de neoplasias associado ao uso cada vez mais frequente de esquemas quimioterápicos citotóxicos e à crescente complexidade dos pacientes oncológicos (estes progressivamente com idades mais avançadas e com mais comorbidades) contribuem para o aumento da incidência de NF na medicina atual, tornando a NF complicação comum do tratamento atual do câncer [7,8].

Esta associação preocupante entre alta incidência, alta morbimortalidade e alto custo torna a investigação de fatores de rico para o desenvolvimento de desfechos clínicos desfavoráveis na NF de suma importância para o ramo da medicina que aborda o tratamento de suporte aos pacientes com câncer. Entre os desfechos clínicos relevantes na NF, pode-se citar: mortalidade em 28 dias, tempo prolongado de hospitalização, incidência de choque séptico e incidência de infecção por patógenos multirresistentes [5,9-11]. A investigação continuada dos fatores de risco para a ocorrência destes desfechos desfavoráveis pode constituir um grande passo para a redução das complicações associadas à NF, uma vez que estes fatores de risco podem ser utilizados como marcadores prognósticos ou possíveis alvos terapêuticos.

2. REVISÃO DA LITERATURA EM NEUTROPENIA FEBRIL

2.1. Definição

NF é definida pela presença de febre (temperatura oral única ≥ 38,3°C ou temperatura oral ≥ 38,0°C por um período maior do que 1 hora) em vigência de neutropenia (contagem de neutrófilos < 500 células por microlitro ou < 1000 células por microlitro com perspectiva de queda a valores < 500 células por microlitro em 48 hs) [12].

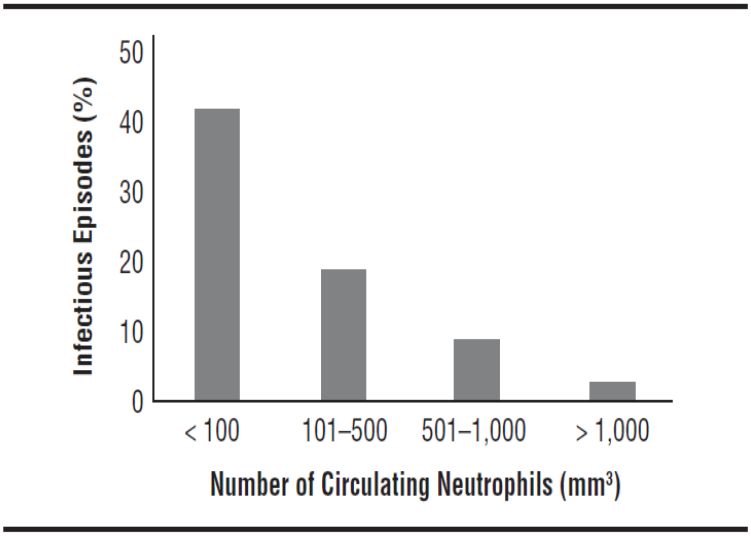
2.2. Fisiopatogenia

Neutrófilos são células brancas granulocíticas responsáveis pela resposta imune imediata do organismo a infecções bacterianas e fúngicas. Eles correspondem a aproximadamente 60% dos leucócitos circulantes e sua produção costuma ocorrer na medula óssea durante um período de 10 a 14 dias. Uma vez liberados na circulação sanguínea, costumam sobreviver por apenas 4 a 8 horas até encontrarem um alvo para fagocitar e destruir. Os neutrófilos da corrente sanguínea são direcionados ao patógeno infectante através de sinalização de antígenos liberados pelo próprio microorganismo – processo denominado de quiomiotaxia. Através da marginação, os neutrófilos aderem à superfície de células endoteliais e pelo mecanismo de diapedese passam do espaço intravascular para o sítio de infecção. Após a localização do infectante, o neutrófilo invagina-se de modo a englobar o patógeno – processo chamado de fagocitose. O complexo vaculolar contendo o microorganismo fagocitado (fagossoma) é então fusionado ao lisossoma, formando o fagolisossoma que, através da ação enzimática, destrói o patógeno fagocitado [13].

Neutropenia é complicação frequente do tratamento quimioterápico do câncer. A incidência varia de 10 a 50% para pacientes com neoplasia sólida e pode acometer até 80% dos indivíduos com neoplasia hematológica [14,15]. A quimioterapia, através de ação citotóxica direta, suprime a habilidade da medula óssea em manter uma adequada produção de neutrófilos [16] e, também, reduz a atividade fagocitária dos neutrófilos circulantes [17]. Tanto a severidade quanto o risco de infecção são inversamente proporcionais à quantidade de neutrófilos no sangue periférico (figura 1) [16]. Pacientes com contagens de neutrófilos < 500 células/mm³ possuem uma chance maior de infecção quando comparados com indivíduos com contagens ao redor de 1000 células/mm³, por exemplo. O tempo de neutropenia é igualmente determinante no risco de infecção; pacientes com neutropenia prolongada

(exemplo, > 7 dias) apresentam risco adicional de infecção. No entanto, não é apenas pela indução de neutropenia que o paciente sob tratamento oncológico tem risco aumentado para infecções; a quimioterapia também provoca quebra da barreira mucosa do trato gastrointestinal, facilitando a translocação de patógenos para o sangue. Além disso, a própria imunossupressão induzida pelo câncer e a frequente necessidade de implante de cateteres venosos para realização do tratamento, o que acaba por criar uma "porta de entrada" para germes colonizadores da pele, são fatores que potencializam o risco de infecção no paciente em quimioterapia [18].

Figura 1. Severidade da Neutropenia e Risco de Infecção



Fonte: Quantitative Relationships Between Circulating Leukocytes and Infection in Patients with acute Leukemia. Bodey, et al. Annals of Internal Medicine 1966; 64: 330.

2.3. Aspectos Microbiológicos

Infecção clinicamente documentada costuma ocorrer em 20 a 30% dos indivíduos com NF. Os sítios mais comuns de infecção são trato gastrointestinal, o aparelho respiratório e a pele. Bacteremia ocorre em 10 a 25% dos pacientes, sendo esta mais frequente em um contexto de neutropenia prolongada (> 7 dias) e profunda (contagem de neutrófilos < 100 células/mm³) [19].

No decorrer dos últimos 40 anos, flutuação na epidemiologia das bactérias isoladas de hemoculturas de neutropênicos febris tem ocorrido. Logo após o desenvolvimento da quimioterapia citotóxica, durante as décadas de 1960 e 1970, houve predomínio de bactérias Gram-negativas. Após, com o uso disseminado de dispositivos intravenosos nas décadas de 1980 e 1990, houve mudança do perfil microbiológico dos germes isolados de hemoculturas de pacientes com NF, passando a preponderar os Gram-positivos. Atualmente, em decorrência da emergência de bactérias Gram-negativas multirresistentes, há uma tendência de retorno do predomínio de infecção por Gram-negativos em determinados centros. Por outro lado, estudos recentes, nos quais houve uso de profilaxia antibacteriana por grande parte dos pacientes, têm evidenciado uma soberania de infecção por bactérias Gram-positivas (tabela 1) [20-24].

Na maioria dos hospitais onde ocorre o manejo de pacientes neutropênicos febris, o germe mais amiúde isolado em hemoculturas é o *Staphylococcus coagulase-negativo*, seguido por bactérias da família *Enterobacteriaceae* (*Escherichia coli, Klebsiella spp, Enterobacter spp*, entre outras), bactérias gram-negativas não-fermentadoras (*Pseudomonas spp, Acinetobacter spp, Stenotrophomonas spp*) e outras bactérias gram-positivas (*Streptococcus spp, Enterococcus spp e Staphylococcus aureus*) [12,20]. Entre as bactérias mutirresistentes, *Enterobacteriaceae* produturas de β-lactamases de espectro estendido (ESBL), Gram-negativos produtores de carbapenemases, *Staphylococcus aureus* resistentes à meticilina e *Enterococcus spp* resistente à vancomicina são mais comumente isolados [21-24]. Fungos são raramente responsáveis por infecção no início do curso da neutropenia febril. Eles costumam ser encontrados após a primeira semana de neutropenia e de uso de antibioticoterapia empírica. Entre os fungos, a *Candida spp* e o *Aspergillus spp* são os mais corriqueiros [12,15, 25].

Tabela 1. Microorganismos Isolados de Pacientes com Neutropenia Febril de Alto Risco e a Influência da Profilaxia Antibacteriana no Perfil dos Patógenos Isolados. Fonte: Changes in the Etiology of Bacteraemia in Febrile Neutropenic Patients and the Susceptibilities of the Currently Isolated Pathogens. Ramphal R. Clinical infectious diseases, 2004; 39: S25-31.

Fator ou patógeno	Winston et al	Feld et al	Del Favero et al.	Cordonnier et al.

Profilaxia (%)	0	40	90	100
Bactérias Gram-positivas	127 (44.4)	41 (44.1)	166 (66.1)	112 (67.1)
Staphylococcus coagulase negative	44 (15.4)	11 (11.8)	110 (43.8)	52 (31.1)
Staphylococcus aureus	14 (4.9)	2 (2.2)	14 (5.6)	14 (8.4)
Streptococcus spp	41 (14.3)	26 (28.0)	31 (12.4)	34 (20.4)
Enterococcus spp	14 (4.9)	1 (1.1)	5 (2.0)	6 (3.6)
Outros	14 (4.9)	1 (1.1)	6 (2.4)	6 (3.6)
Bactérias Gram-negativas	159 (55.6)	52 (55.9)	85 (33.9)	55 (32.9)
Escherichia coli	63 (22.0)	20 (21.5)	41 (16.3)	30 (18.0)
Klebsiella spp	39 (13.6)	13 (14.0)	4 (1.6)	...
Pseudomonas spp	5 (1.7)	6 (6.5)	24 (9.6)	13 (7.8)
Outros	52 (18.2)	13 (14.0)	16 (6.4)	12 (7.2)
Total	286	93	251	167

Nota: dados expressos em número (%).

2.4. Quadro Clínico

A Febre pode ser o único sintoma de infecção grave nos pacientes neutropênicos. A falta de células mediadoras da resposta imune imediata faz com que os sinais e sintomas inflamatórios sejam muito sutis e, às vezes, ausentes [3,5]. Por exemplo, pacientes com pneumonia bilateral podem apresentar-se apenas com discreta tosse seca e raio-X de tórax normal; indivíduos com pielonefrite podem não apresentar piúria no exame comum de urina; faringites costumam não cursar com secreção purulenta na orofaringe, infecções cutâneas podem se manifestar apenas com discreta hiperemia na pele.

Infecções que em indivíduos imunocompetentes costumam ser bem localizadas e, às vezes, autolimitadas, nos pacientes com NF podem rapidamente se disseminar e provocar quadro de sepse grave ou choque séptico. Esta combinação de dificuldade diagnóstica associada à rápida progressão de infecções devido à redução da intensidade da resposta inflamatória, torna o paciente com neutropenia febril um doente potencialmente grave que, apesar de oligossintomático, necessita de avaliação médica imediata [3,5,12,25].

2.5. Estratificação de Risco

A estratificação de risco do paciente com neutropenia febril é fundamental na decisão se o paciente receberá tratamento hospitalizado ou ambulatorialmente, por via oral ou intravenosa [12,25]. Classicamente, os fatores relacionados a baixa probabilidade de complicações clínicas durante o episódio de NF incluem neoplasia sólida, regime de quimioterapia ambulatorial, expectativa de duração da neutropenia < 7 dias, estabilidade hemodinâmica, Raio-X de Tórax normal, ausência de anormalidades laboratoriais de provas de função renal e hepática, ausência de sinais de comprometimento do sistema nervoso central, neoplasia em remissão e evidência de recuperação medular precoce [12,25].

O escore Multinational Association for Supportive Care in Cancer (MASCC) é o sistema de estratificação de risco em NF mais utilizado atualmente que visa, principalmente, a identificação de pacientes de baixo risco elegíveis para o tratamento ambulatorial [26]. O MASCC consiste em um escore de fácil aplicação que leva em consideração idade, status clínico na apresentação do episódio, procedência, presença de comorbidades e a doença de base do paciente (tabela 2). Indivíduos com escore ≥ 21 são classificados como de baixo risco. O ponto de corte de 21, proposto pelos autores, apresenta valor preditivo para baixo risco de 94% e sensibilidade de 80%. A mortalidade de acordo com o escore MASCC varia desde 3% para pacientes com escore > 21 até 36% para pacientes com pontuação < 15 (5).

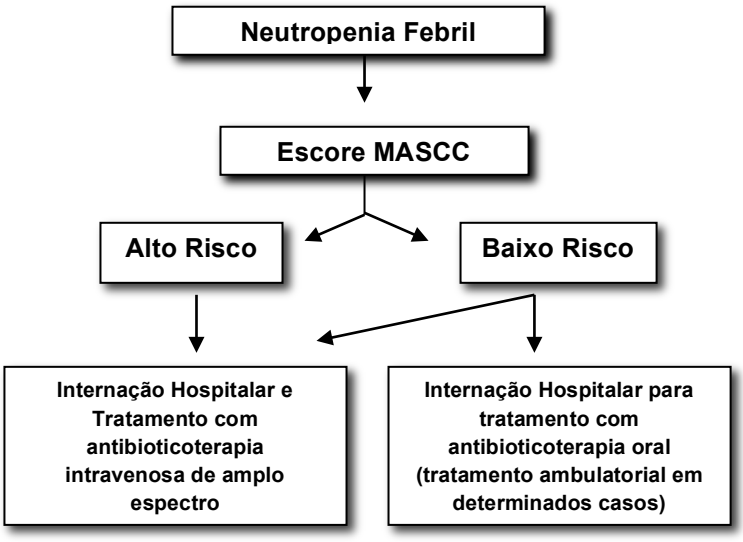
Adultos com NF classificados como baixo risco podem ser tratados com antibióticos orais, desde que manifestem como único sintoma a febre, não apresentem sinais de comprometimento sistêmico (hipotensão e calafrios, por exemplo), tenham uma previsão de recuperação das contagens dos neutrófilos em < 7 dias e não apresentem fatores que possam prejudicar a absorção do antimicrobiano (diarreia e vômitos, por exemplo) (figura 2) [12,25]. Alguns pacientes classificados como baixo risco podem ser tratados ambulatorialmente, desde que tenham fácil acesso a cuidados médicos. Outra estratégia possível inclui breve internação com uso de antimicrobianos intravenosos e exclusão de infecções graves antes da alta com plano de uso de antibiótico oral em seguida [12]. Pacientes de alto risco ou de baixo risco que não preenchem critérios para tratamento oral, devem ser hospitalizados para tratamento com antibioticoterapia intravenosa de amplo espectro [12,25].

Tabela 2. Escore MASCC. Fonte: Association for Supportive Care in Cancer Risk Index: a Multinational Scoring System for Identifying Low-Risk Febrile Neutropenic Cancer. Klastersky J. et al. Journal of Clinical Oncology 2000; 18: 3038-51.

Característica	Pontuação
Sintomas	
- Leves ou ausentes	5
- Moderados	3
Ausência de Hipotensão	5
Ausência de Doença pulmonar Obstrutiva Crônica	4
Tumor Sólido ou Ausência de Infecção Fúngica Prévia	4
Paciente ambulatorial (febre < 48hs de internação)	3
Ausência de desidratação	3
Idade < 60 anos	2

Nota: ≥ 21 pontos = baixo risco; < 21 pontos = alto risco.

Figura 2. Algoritmo de Decisão do Local de Tratamento e da Via de Administração dos Antimicrobianos em Neutropenia Febril.



Fonte: Management of Febrile Neutropenia: ESMO Clinical Practice Guideline. De Naurois, et al. Annals of Oncology 2010; 21(5): v252-6.

2.6. Tratamento

2.6.1. Antibioticoterapia Inicial

O principal objetivo da terapia antimicrobiana empírica inicial é redução de morbimortalidade por infecções bacterianas até que os resultados das culturas estejam disponíveis para guiar o tratamento [12,25]. Em pacientes de baixo risco selecionados, o uso da associação de amoxicilina/clavulanato com ciprofloxacino por via oral é segura [27-29]. Outros esquemas utilizados, mas menos estudados nesta situação, são levofloxacino em monoterapia e a combinação de ciprofloxacino com clindamicina [12].

Para pacientes de alto risco, ou de baixo risco que não preenchem critérios para tratamento por via oral, é recomendado o tratamento intravenoso com antibiótico β-lactâmico de amplo espectro com atividade antipseudomonas em monoterapia (figura 3) [12,25]. A comparação de monoterapia com terapia combinada em pacientes com NF não complicada não evidenciou diferença em mortalidade entre os dois grupos de tratamento, apenas maior taxa de reações adversas no grupo da terapia combinada [30]. Esquemas eficazes incluem ceftazidime, cefepime, piperacilina/tazobactam, imipenem ou meropenem [12,25,31]. No entanto, cautela necessita ser tomada em relação à ceftazidime, por apresentar diminuição de eficácia contra bactérias Gram-negativas (principalmente as produtoras ESBL) e Gram-positivas em determinados centros [32]. Uma metanálise questionou a segurança do uso de cefepime na neutropenia febril ao encontrar maior mortalidade no grupo tratado com a cefalosporina de 4° geração [33]; contudo, os dados não foram reprodutíveis por metanálise publicada posteriormente pelo Food and Drug Administration [34], a qual evidenciou taxas de mortalidade em 30 dias estatisticamente semelhantes entre o grupo tratado com cefepime (7,8%) e o grupo tratado com outros antimicrobianos (6,8%).

A associação de uma segunda classe de antimicrobianos ao esquema inicial é indicada em situações especiais. Estudos randomizados que avaliaram a vancomicina como parte da terapia antimicrobiana empírica inicial, não encontraram menores taxas de mortalidade nos pacientes tratados com esta terapia [35]; contudo, em determinadas situações, a adição de vancomicina faz-se necessária: presença de hipotensão, infecção de pele ou partes moles, infecções associadas a cateteres venosos, pneumonia, mucosite severa [12,25,31]. O acréscimo de metronidazol ao esquema inicial é indicado em casos de ocorrência de sintomas gastrointestinais (diarreia, dor abdominal, dor perianal) devido à possibilidade de infecção por *Clostridium difficile* [12,25,31]. A adição de tigeciclina ao esquema com

betalactâmico antipseudomonas pode ser alternativa em centros com alta prevalência de infecções por Gram-negativos multirresistentes. No ensaio clínico randomizado de Bucaneve e colaboradores, por exemplo, maiores taxas de sucesso de tratamento foram demonstradas com a combinação piperacilina-tazobactam mais tigeciclina comparado ao grupo tratado apenas com piperacilina-tazobactam, sem diferença de mortalidade entre os dois grupos [36].

A cobertura antimicrobiana empírica inicial de patógenos multirresistentes pode se fazer necessária em pacientes previamente colonizados ou infectados por patógenos multirresistentes ou em instituições com alta prevalência de infecções por bactérias multirresistentes [12,31]. Os seguintes antimicrobianos podem ser utilizados na suspeita de infecção por patógenos multirresistentes específicos: vancomicina, linezolida ou daptomicina para *Staphylococcus aureus* resistente à meticilina; linezolida, daptomicina ou quinupristin-dalfopristin para *Enterococcus spp* resistente à vancomicina; imipenem ou meropenem para bacilos Gram-negativos produtores de ESBL; polimixina B ou tigeciclina para bacilos Gram-negativos produtores de carbapenemases.

2.6.2. Tempo de Início da Antibioticoterapia

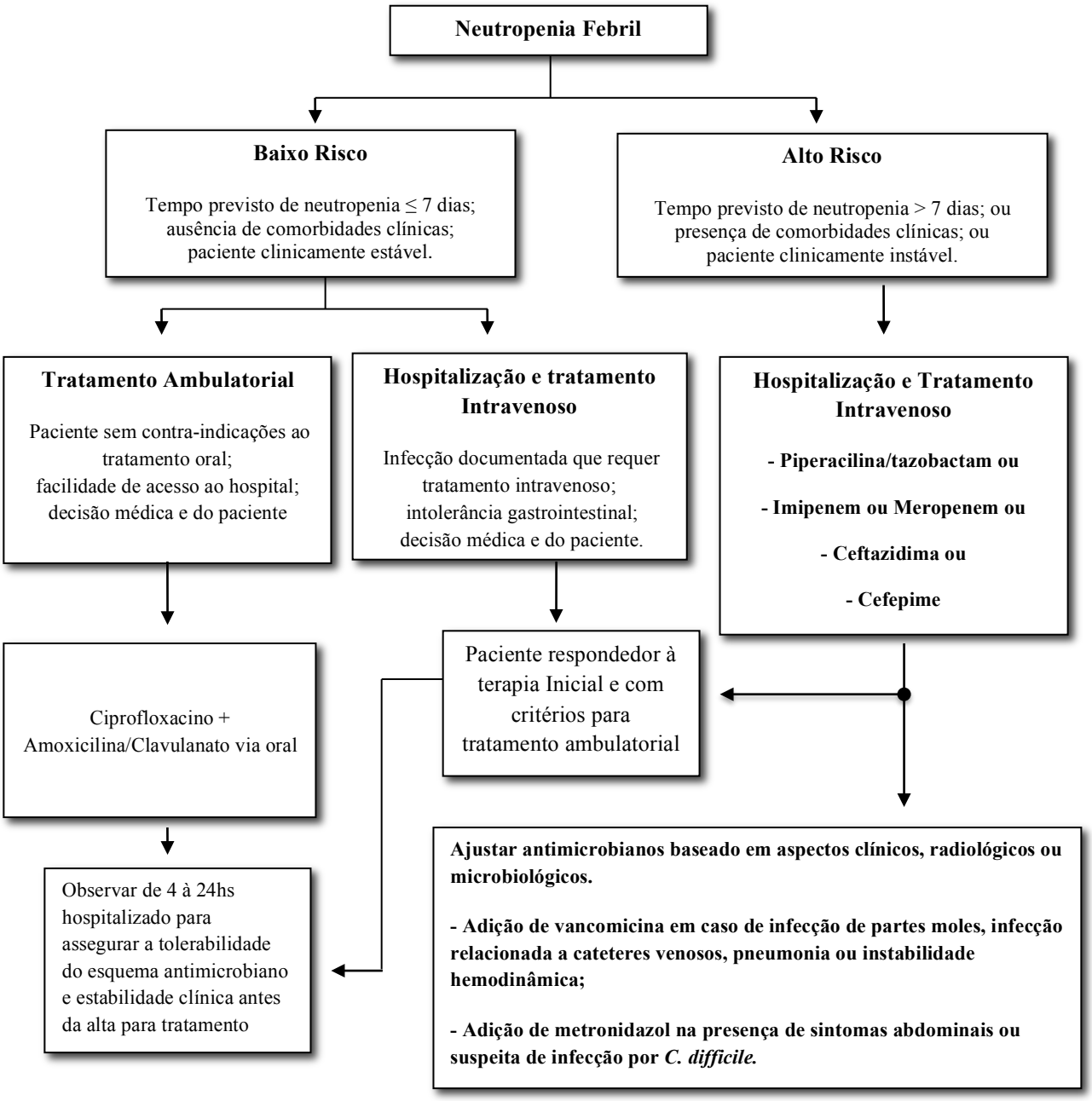
O tempo ideal de início da antibioticoterapia eficaz nos pacientes com NF não é conhecido. Em pacientes criticamente enfermos com sepse grave ou choque séptico, o tempo de início da antibioticoterapia empírica inicial é uma variável que possui impacto em mortalidade; quanto menor o tempo entre o início dos sintomas de infecção e a administração da antibioticoterapia eficaz, menor a taxa de mortalidade [37,38]. Com base nestes resultados, diretrizes atuais para o manejo de sepse grave/choque séptico e NF recomendam a administração de antibioticoterapia empírica dentro da primeira hora após identificação dos sintomas [12,39].

2.6.3. Duração do Tratamento

O tempo de duração da terapia com antimicrobianos é definido pelo organismo causador e o sítio de infecção. A maioria das infecções de corrente sanguínea, pneumonias e infecções de partes moles necessitam de 10 a 14 dias de tratamento. Recomenda-se que os antibióticos sejam mantidos pelo menos até que haja sinais de recuperação medular (neutrófilos > 500 células/mm^3) e o paciente esteja afebril por no mínimo 24hs a 48hs [12,25]. O mesmo vale para pacientes com febre sem isolamento de patógeno em cultura. Nos episódios de neutropenia prolongada, nos quais houve

resolução dos sinais e sintomas de infecção após ciclo completo de antibioticoterapia e nenhum patógeno foi isolado em cultura, alguns autores recomendam o uso de profilaxia com fluoroquinolonas até que ocorra recuperação medular; todavia, esta conduta carece de evidências de efetividade [12].

Figura 3. Manejo Inicial da Neutropenia Febril.



Fonte: Clinical Practice Guideline for The Use of Antimicrobial Agents in Neutropenic Patients with cancer: 2010 Update by the Infectious Diseases Society of America. Freifeld AG, et al. Clinical infectious Diseases 2011; 52(4): e56-e93.

2.6.4. Mudanças no Tratamento Inicial

Modificações no esquema antibacteriano inicial devem ser orientadas pelos achados clínicos e microbiológicos. O paciente com febre persistente a despeito da terapia inicial sem outros comemorativos clínicos e que encontra-se estável, raramente necessita de troca do esquema antibacteriano inicialmente instituído [4,25,31,36]. A conduta mais adequada para este caso é aguardar o resultado das culturas, investigar possíveis sítios de infecção e ajustar a terapia antimicrobiana de acordo com os achados microbiológicos. Pacientes de baixo risco que vinham em regime de tratamento ambulatorial, na presença de febre persistente, devem ser imediatamente hospitalizados e tratados como pacientes de alto risco com antibioticoterapia intravenosa [12,25,31]. Indivíduos que evoluem com instabilidade hemodinâmica ou insuficiência respiratória durante os primeiros dias da terapia inicial, devem ter o espectro do esquema antimicrobiano ampliado de modo a cobrir bactérias resistentes Gram-negativas, Gram-positivas, anaeróbios e fungos [12,25,31]. Este objetivo pode ser atingido, por exemplo, trocando-se uma cefalosporina prescrita inicialmente por carbapenêmico e associando-se vancomicina e equinocandina.

Terapia empírica com antifúngico de classe diferente daquele usado como profilaxia deve ser considerada no paciente de alto risco que permanece febril após 4 a 7 dias de antibioticoterapia empírica, especialmente se o tempo de neutropenia previsto é prolongado [12,25,31]. Não existem evidências de diferença de eficácia entre a maioria dos antifúngicos sistêmicos disponíveis (anfotericina B deoxicolato, preparações lipídicas de anfotericina B, voriconazol ou echinocandinas) no contexto de NF. O que parece diferenciar as opções é a maior nefrotoxicidade, evidenciada em alguns estudos, da anfotericina B convencional em relação às outras alternativas que são financeiramente mais onerosas [40]. Costuma-se utilizar anfotericina B ou voriconazol para pacientes com neutropenia profunda e prolongada com infiltrados ou nódulos pulmonares, pela maior chance de infecção por *Aspergillus spp* neste contexo [12]. O uso de equinocandina (micafungina, anidulafungina ou caspofungina) costuma ser preferido em casos nos quais os pacientes não vinham em uso de profilaxia antifúngica, pois neste cenário, costumam predominar as infecções invasivas por *Candida spp* [12,25]. Outra abordagem aceitável e cada vez mais empregada, nos casos clinicamente estáveis, é o tratamento antifúngico preemptivo, no qual associa-se antifúngico apenas naqueles pacientes com evidência adicional de infecção fúngica invasiva (achados radiológicos compatíveis, níveis séricos do antígeno

galactomannana elevados, evidência microbiológica) [12,41]. Esta estratégia tem se associado a redução da utilização desnecessária antifúngicos [12].

2.7. Profilaxias

2.7.1. Profilaxia Antifúngica

Profilaxia antifúngica é indicada para aqueles pacientes de alto risco que apresentam chance aumentada de candidíase invasiva, especialmente pacientes em transplante alogênico de medula óssea ou submetidos à quimioterapia intensiva de indução ou resgate para leucemia aguda [42]. O agente mais comumente utilizado é o fluconazol; contudo, itraconazol, voriconazol, posaconazol, micafungina e caspofungina são alternativas aceitáveis. A profilaxia antifúngica de rotina não é indicada para os pacientes de baixo risco [12].

2.7.2. Profilaxia Antiviral

Profilaxia para infecção por vírus herpes simples (HSV) deve ser realizada em indivíduos soropositivos para HSV que serão submetidos à transplante alogênico de medula óssea ou que serão submetidos à terapia de indução para leucemia aguda [43]. A vacinação anual para influenza é indicada para todos os pacientes com câncer [12]. O melhor momento é motivo de discussão, mas a vacinação entre os ciclos de tratamento – idealmente > 7 dias após término da quimioterapia e > 2 semanas antes do início do próximo ciclo é plausível.

2.7.3. Profilaxia Antibacteriana

Estudos demonstraram menores taxas de bacteremia e menores taxas de mortalidade para pacientes neutropênicos afebris de alto risco, nos quais se esperava tempo prolongado de neutropenia, submetidos à profilaxia com fluoroquinolona [44,45,46]. No entanto, a longo prazo, tal estratégia pode ter um impacto negativo na flora microbiológica institucional, uma vez em que a aplicação rotineira desta estratégia pode estar associada ao aumento das taxas de resistência antimicrobiana [47-48].

2.7.4 Profilaxia com Fatores de Crescimento Hematopoiéticos

O uso profilático de fatores estimuladores de colônia granulocítica (exemplo, filgrastina) é indicado apenas naqueles pacientes em quimioterapia em que se espera uma incidência de NF ≥ 20%. O uso de fatores de crescimento hematopoiéticos durante episódio de NF não obteve impacto em redução de mortalidade em estudos randomizados [49].

2.8. Desfechos Clínicos em Neutropenia Febril

Desfechos clínicos em NF são eventos considerados importantes no transcorrer da síndrome que interferem no tempo ou qualidade de vida do paciente (morte, tempo de hospitalização e incapacidade funcional, por exemplo) [50]. Estes costumam ser utilizados como medidas objetivas, em estudos observacionais e de intervenção, na avaliação de marcadores prognósticos e da eficácia de intervenções em cuidados de saúde [51]. Quanto mais objetivo for o desfecho clínico (*hard endpoint*), menor será a sua susceptibilidade a viés de aferição. Por exemplo, mortalidade em 28 dias configura um desfecho menos susceptível a viés de aferição quando comparado à resolução do processo infeccioso, pois a definição do segundo pode incluir aspectos subjetivos com grande variabilidade interobservadores [52]. Desfecho intermediário (*surrogate endpoint*) configura medida biológica que guarda relação causal com o desfecho clínico [50,51]. Por exemplo, a queda dos níveis séricos de procalcitonina no decorrer do curso da NF pode ser utilizada como desfecho intermediário da resolução do processo infeccioso (este um desfecho clínico). A avaliação de desfechos intermediários é menos onerosa em relação à avaliação de desfechos clínicos; contudo a força do estabelecimento de uma relação causa-efeito é maior nos estudos que utilizam desfechos clínicos [50-52].

Entre os desfechos clínicos mais relevantes em NF pode-se citar morte, incidência de choque séptico, resposta ao tratamento antimicrobiano, tempo de hospitalização e incidência de infecção por patógenos multirresistentes.

2.8.1 Mortalidade

A taxa de mortalidade do episódio de NF habitualmente gira em torno de 10% para pacientes hospitalizados [4,15]. Esta taxa de mortalidade pode variar de acordo com a presença de outros determinantes de sobrevida. Por exemplo, em pacientes neutropênicos admitidos em unidade de terapia intensiva com choque séptico, a taxa de mortalidade por episódio pode atingir valores tão altos quanto 88% [5]. Classicamente a mortalidade costuma ser maior nos indivíduos com idade avançada (≥ 65

anos), neoplasia hematológica, comorbidades clínicas, alto risco de complicação pelo escore MASCC, diagnóstico de pneumonia, bacteremia documentada, infecção por patógenos multirresistentes e choque séptico [5,27]. Pelo fato de a NF se tratar de um evento agudo, cuja resolução encontra-se intimamente relacionada à duração da neutropenia (nadir mediano 12 dias após primeiro dia da quimioterapia), estudos que avaliam mortalidade na NF costumam utilizar os pontos de corte de 28 ou 30 dias.

2.8.2. Taxa de Resposta ao Tratamento

A taxa de resposta clínica ao tratamento em NF configura um critério subjetivo com variações entre os estudos que utilizam este desfecho. Classicamente os critérios resposta ao tratamento antimicrobiano implementado incluem: defervescência e resolução dos sinais clínicos e laboratoriais de infecção em 3 ou 7 dias de tratamento [53-55]. A taxa de resposta microbiológica constitui erradicação do patógeno causador da infecção em culturas de seguimento. As taxas de resposta clínica e microbiológica costumam ser maiores do que 85 a 90% para esquemas antimicrobianos eficazes [53-55]. Alguns especialistas criticam a adoção de taxa de resposta clínica como desfecho primário em estudos de eficácia, uma vez em que este desfecho reflete muito mais a modificação do esquema antibiótico inicial do que a eficácia real do antimicrobiano [56].

2.8.3. Sepse Grave e Choque Séptico

O principal mecanismo fisiopatológico que pode levar o paciente com NF ao óbito é a progressão da infecção para quadros de sepse grave ou choque séptico [5]. Sepse é definida pela suspeita de infecção associada a pelo menos 2 dos seguintes achados de síndrome da resposta inflamatória sistêmica (SIRS): temperatura corporal > 38°C ou menor do que 36°C; frequência cardíaca > 90 batimentos por minuto; frequência respiratória > 20 movimentos por minuto (ou $PaCO_2$ < 32 mmHg); contagem total de leucócitos > 12000 ou menor 4000 células/ mm^3 (ou presença de mais de 10% de formas jovens na contagem diferencial do leucograma) [39]. A presença sinais ou sintomas que indicam lesão em órgão alvo (hiperlactatemia, encefalopatia, insuficiência renal, Insuficiência respiratória, por exemplo), associados aos critérios de sepse, caracterizam o quadro de sepse grave [39]. Hipotensão (pressão arterial sistólica < 90 mmHg) sustentada a despeito de reposição volêmica (geralmente 20 mL/Kg de solução cristalóide) na presença de critérios de sepse, define o diagnóstico de choque séptico [39]. Quanto maior o número de critérios de SIRS no início do quadro de NF, maior o

risco de progressão para choque séptico, variando de 0% para 3% para 30% para pacientes com 2, 3 ou 4 critérios, respectivamente [5].

A gravidade do episódio de NF é resultado da interação patógeno e hospedeiro. A virulência do patógeno responsável pelo quadro infeccioso pode representar risco para o desenvolvimento de sepse grave ou choque séptico, como já determinado em populações de pacientes não-neutropênicos [57]. Por exemplo, infecções por *Pseudomonas aeruginosa* e *Staphylococcus aureus* têm sido associadas a cursos infecciosos mais graves, em contrapartida, infecções por *Staphylococcus* coagulase-negativo têm sido associadas a uma menor probabilidade de evolução para sepse grave ou choque séptico.

2.8.4. Tempo de Hospitalização

Tempo de hospitalização constitui um importante marcador de severidade clínica e consumo de recursos de saúde. Tempo prolongado de hospitalização está associado a episódios mais graves de NF, bem como a maiores gastos financeiros [1,2,4-6]. Além disso, o próprio tempo prolongado de internação pode se constituir em um fator prognóstico negativo devido ao fato de aumentar o risco de atraso do tratamento da doença de base e de aumentar o risco de infecção por patógenos multirresistentes [14,22]. Dados da literatura indicam que o tempo médio de internação por episódio de NF varia de 8.1 dias para pacientes com tumores sólidos a 19.7 dias para pacientes com tumores hematológicos [4].

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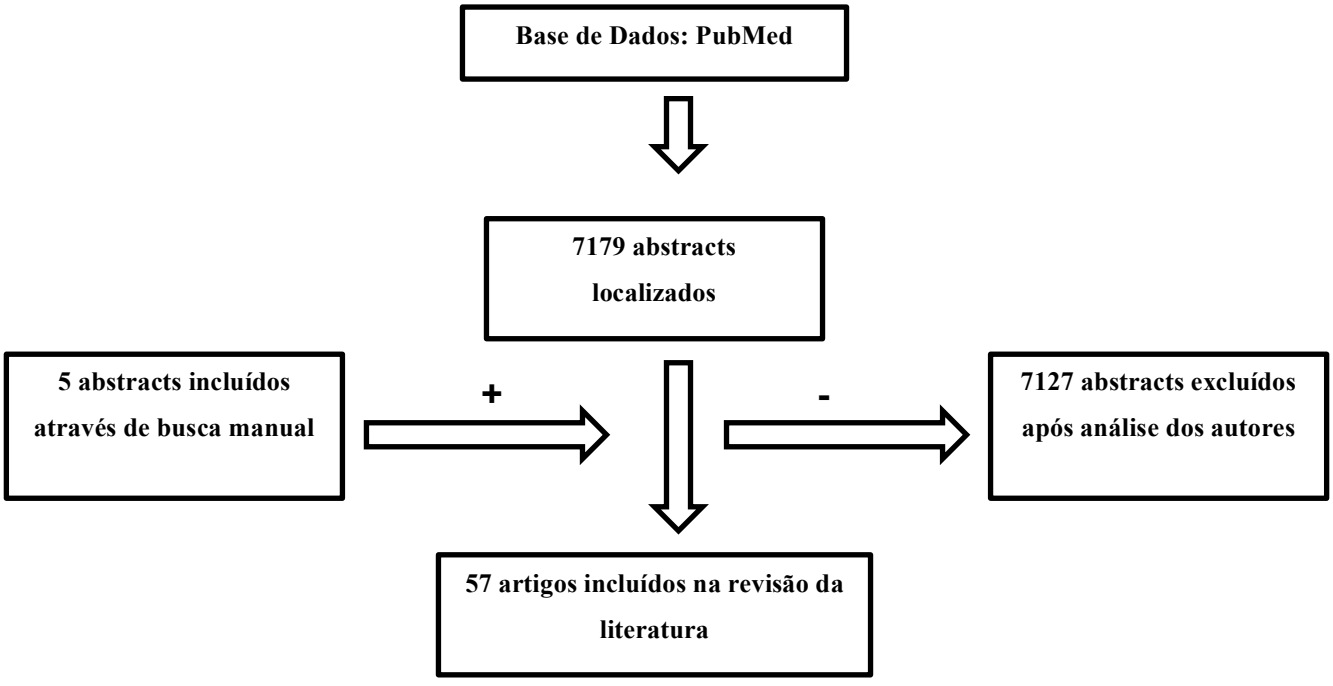
3. ESTRATÉGIAS PARA LOCALIZAR INFORMAÇÕES

Esta revisão está focada nos aspectos relacionados aos principais desfechos clínicos em pacientes adultos com neutropenia febril secundária a quimioterapia citotóxica. A estratégia de busca envolveu a base de dados do PubMed. A busca de artigos foi realizada utilizando-se os seguintes termos: “Chemotherapy-Induced Febrile Neutropenia”[Mesh] OR "Febrile Neutropenia"[Mesh] OR "Neutropenia"[Mesh]. Os seguintes filtros foram aplicados: Species: Humans; Languages: English; Ages: Adult (19+ years). Buscas manuais nas referências dos artigos encontrados também foram realizadas. O resultado da busca de referências está sumarizado na figura 4. Os autores (aluno e orientador) selecionaram as referências incluídas na revisão teórica através da avaliação dos títulos e abstracts resultantes da busca acima mencionada.

Figura 4. Fluxograma da Estratégia de Busca de Referências Bibliográficas.



4. JUSTIFICATIVA

A investigação de fatores associados à ocorrência de desfechos clínicos desfavoráveis em NF é de suma importância, uma vez em que a identificação destes fatores pode contribuir para o aperfeiçoamento assistencial de uma síndrome associada com altas taxas de morbimortalidade.

5. OBJETIVOS

Este estudo objetiva determinar os principais fatores associados com mortalidade, tempo de hospitalização, incidência de bacteremia por patógenos multirresistentes e incidência de choque séptico no início da febre em pacientes hospitalizados com neutropenia febril secundária à quimioterapia citotóxica para o câncer.

Cohort Study of the impact of time to antibiotic administration on mortality in patients with febrile neutropenia

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Running title: Time to antibiotic in febrile neutropenia.

ABSTRACT

Background: Time to antibiotic administration (TTA) has been proposed as a quality-of-care measure in febrile neutropenia (FN); however, few data regarding the impact of TTA on mortality of adult cancer patients with FN are available.

Objective: To determine whether TTA is a predictor of mortality in adult cancer patients with FN.

Methods: A prospective cohort study of all consecutive cases of FN, evaluated from October 2009 to August 2011, at a single tertiary referral hospital in Southern Brazil was performed. TTA was assessed as a predictive factor for 28-day mortality using the Cox proportional hazards model. Kaplan-Meier curves were used for assessment of mortality rates according to different TTAs; the log-rank test was used for between-group comparisons.

Results: In total, 307 cases of FN (169 subjects) were evaluated. During the study period, there were 29 deaths. In a Cox regression analysis, TTA was independently associated with 28-day mortality (HR 1.18 [95% CI 1.10 to 1.26]); each increase of 1 h in the TTA raised the risk of 28-day mortality by 18%. FN episodes with TTA ≤30 min had lower 28-day mortality rates compared with those with TTA between 31 min and 60 min (3.0% versus 16.6%; log-rank *P*=0.0002).

Conclusions: Early antibiotic administration was associated with higher survival rates in the context of FN. Efforts should be made to ensure that FN patients receive effective antibiotic therapy as soon as possible. A target of 30 min to TTA should be adopted for cancer patients with FN.

Keywords: Anti-bacterial agents/administration and dosage; Febrile neutropenia; Mortality; Time to treatment.

INTRODUCTION

Febrile neutropenia (FN) may represent the only sign of severe infection in cancer patients, because symptoms and signs of inflammation are typically attenuated due to reduced absolute neutrophil count (ANC) [1,2]. The frequent need for indwelling central venous catheters in association with damage to the gastrointestinal mucosa caused by anti-cancer agents, provides a portal of entry for pathogenic bacteria, which in turn predisposes patients to bacteremia [3]. This fact, in association with an impaired host response to infection due to neutropenia and decreased cellular immunity secondary to intensive chemotherapy, leads to increased risk for severe infections in cancer patients. Despite recent improvements in managing FN, infections in the context of neutropenia continue to be associated with substantial mortality, which may reach values of approximately 10% in specialized centers [4].

Time to antibiotic administration (TTA) is a well-recognized determinant of mortality in patients with severe sepsis or septic shock [5]. Current guidelines for treatment of sepsis and FN [6,7], based mainly on studies involving immunocompetent subjects, recommend administration of broad-spectrum β-lactam antibiotic monotherapy with antipseudomonal activity within 1 h after the onset of fever in neutropenic patients; furthermore, many oncology centers use a benchmark of <60 min to antibiotic administration [8,9]. However, few studies investigating the impact of TTA on mortality of patients with FN are available. Moreover, the ideal TTA in this setting is not well established, which raises questions about the potential benefit of TTAs shorter than those recommended by current guidelines. Accordingly, we performed the present study to determine whether TTA is a predictor of mortality in adult cancer patients with FN and to define the optimal TTA for patients with FN secondary to cytotoxic chemotherapy.

METHODS

Study design, patients and setting

A prospective cohort study was conducted at a single tertiary center. The present study followed all cancer patients >18 years of age who were consecutively admitted to the Hematology ward of the *Hospital de Clínicas de Porto Alegre* (Porto Alegre, Brazil) with neutropenia (i.e., an ANC

<500 cells/mm³ or <1000 cells/mm^3 with expectation of a decrease to <500 cells/mm³ during the ensuing 48 h) and fever (i.e., a single axillary temperature measurement ≥38.5°C or sustained temperature ≥38.0°C over a 1 h period). Subjects who were receiving palliative treatment only, had an indication for outpatient treatment or had neutropenia due to a specific etiology other than an adverse reaction to chemotherapy were excluded. Subjects were allowed to re-enter the study after an initial episode of FN if they remained free from signs or symptoms of infection for at least seven days after completing the treatment for the first episode and if all causative organisms, if any, were eradicated.

Treatment protocol

In our institution, the immediate antibiotic administration in patients with FN is recommended. To ensure the shortest possible TTA, a protocol for the management of FN was created with the involvement of nursing, medicine and pharmacy teams. According to this protocol, all neutropenic patients were routinely screened for fever by the nurse staff (every 4 h or every 20 min if temperature ≥37.5°C) with a standardized axillary thermometer calibrated for the range of 32.0 – 42.0°C, in steps of 0.1°C. All neutropenic patients were evaluated straightaway after the onset of fever by a medical fast response team, which defined the initial antimicrobial therapy; a pharmacy unit within the hematology ward immediately dispensed the antibiotic regimen prescribed. FN patients were treated according to the 2002 guidelines of the Infectious Diseases Society of America [10]. The initial antimicrobial treatment regimen was performed using β-lactam monotherapy with antipseudomonal activity (cefepime, piperacillin-tazobactam or a carbapenem); vancomycin was recommended as part of the initial empirical regimen only in cases with hemodynamic instability, suspected catheter-related infection, or infection of the skin and soft tissue. In patients with clinically or microbiologically documented infections, the duration of antimicrobial therapy was dictated by the particular organism and site of infection; appropriated antibiotics were continued until ANC ≥500 cells/mm^3. Empirical antifungal therapy with amphotericin B deoxycholate was administered to patients with persistent fever after four days of treatment with broad-spectrum antibiotics. Antibacterial prophylaxis was not administered to any patient. Antifungal prophylaxis with fluconazole was routinely performed for patients in whom the anticipated duration of neutropenia was >7 days. Acyclovir antiviral prophylaxis was administered for herpes simplex virus seropositive patients undergoing allogenic hematopoietic stem-cell transplantation or leukemia induction chemotherapy.

Definitions

The primary independent variable in the study was TTA, which was defined as the time between the onset of fever in neutropenic patients and antibiotic administration. The Multinational Association for Supportive Care in Cancer (MASCC) risk index score [11] was applied at the onset of fever to determine the risk for serious complications during FN; episodes were classified as high risk if the score was <21 points and as low risk if the score was ≥21 points. Clinical comorbidity was defined as the presence of heart failure, diabetes mellitus, chronic pulmonary disease, chronic liver disease or chronic renal failure. The patients were divided into two groups based on their chemotherapy regimen: the high-dose chemotherapy group included patients who underwent hematopoietic stem cell transplantation or induction chemotherapy; and the standard-dose chemotherapy group included patients who underwent consolidation or maintenance chemotherapy. Microbiological studies were performed at the onset of fever according to the standards of practice and included two separate blood samples drawn from two different sites for aerobic culture. In our institution, anaerobic blood culture is not routinely performed due to low incidence of anaerobic bacteremia even in the context of FN (data not shown). In the absence of an indwelling central venous catheter, the two blood samples were obtained from two distinct peripheral veins. When an indwelling central venous catheter was present, one sample for blood culture was obtained through the indwelling central venous catheter and the other was collected from a peripheral vein. Bacteremia caused by coagulase-negative *Staphylococcus* spp was defined as two positive results from two independent cultures. Bacteremia in one positive culture was considered to be diagnostic for other microorganisms. Antibiotic susceptibilities of the isolated pathogens were evaluated according to the recommendations of the Clinical and Laboratory Standards Institute [12].

Outcome and follow-up

The primary outcome of the study was all-cause mortality 28 days after the onset of FN. The patients were followed-up through interviews and medical record reviews using a standardized case report form by researchers who were not associated with the assistant physician's team. The follow-up was maintained for 28 days after the onset of fever in the neutropenic patients. For subjects who were discharged before 28 days, follow-up telephone calls were made on the 28th day after the onset of FN to

determine whether they remained alive. If a patient was deceased at the time of the telephone call, the survival time was calculated based on the date of death reported by the family.

Statistical analysis

A multivariate Cox proportional hazards model was performed to determine whether TTA was a predictor of 28-day mortality. All variables with $P<0.15$ in the univariate analysis were included. In the multivariate model, independent variables were eliminated from the highest to the lowest P value but remained in the model if $P<0.05$. The hazard ratios (HRs) were estimated along with the 95% confidence intervals (CIs). Kaplan-Meier curves were used to evaluate the time-dependent occurrence of death according to TTA; the log-rank test was applied for between-group comparisons. The Bonferroni correction was applied as protection against multiple comparisons (i.e., type I error). Given that two comparisons of mortality rate according to TTA were planned (TTA 31 min to 60 min versus TTA ≤30 min in all cases of FN and TTA 31 min to 60 min versus TTA ≤30 min only in cases with the first episode of documented bacteremia), the adjusted α level for the log-rank test was set at 0.025. STATA version 12 (Stata Corp LP, USA) was used for statistical analysis.

Ethics issues

The Institutional Review Board of the *Hospital de Clínicas de Porto Alegre* approved the study and written informed consent was obtained from all study participants.

RESULTS

During the study period, 307 cases of FN (169 patients) were analyzed. Seventy-one subjects (42% of the study population) had two or more episodes of FN. The characteristics of all episodes of FN are shown in Table 1. Hematological malignancies accounted for most cases of cancer (78.8%). The predominant neoplastic diseases were acute myeloid leukemia (48.5%), lymphoma (16.6%), acute lymphoblastic leukemia (14.6%) and multiple myeloma (9.7%). High-dose chemotherapy regimens were performed in 53.4% of the study population. FN occurred after 48 h of hospitalization in 81.4% of cases. Bloodstream infections were responsible for 37.4% of all episodes of FN: in descending order, the most common blood isolates were: *Escherichia coli*, coagulase-negative staphylococci, *Klebsiella*

pneumoniae, *Pseudomonas aeruginosa*, viridans streptococci and *Enterococcus* spp. All episodes of FN were treated for the entire course as inpatients. No case with an incorrect antibiotic dose, according to the institutional FN treatment protocol, was documented in the present cohort.

During the study period, there were 29 deaths (9.4 % of all cases of FN or 17.1% of all study patients), although no deaths occurred during the coincident follow-up period of ≥2 FN episodes in the same patient. The assessment of whether mortality was attributable to infection was concordant in all 29 patients who died. In the univariate analysis of the risk factors for 28-day mortality (Table 2), relapsing underlying disease status (P=0.001), standard-dose chemotherapy regimens (P=0.02), bloodstream infection (P=0.001) and presentation with a high-risk MASCC score (P<0.001) were more frequent in non-survivors. TTA was also directly associated with the hazards for death (P<0.001). After a multivariate analysis was conducted, the variables that constituted independent risk factors for mortality included relapsing underlying disease status (HR 6.66 [95% CI 2.36 to 18.79]), bloodstream infection (HR 3.64 [95% CI 1.49 to 8.88]), presentation with a high-risk MASCC score (HR 4.21 [95% CI 1.82 to 9.72]) and TTA (HR 1.18 [95% CI 1.10 to 1.26]). Each hour of delay in TTA raised the 28-day mortality risk by 18%. The distribution of TTAs for each episode of FN is shown in Figure 1; the median TTA was 0.33 h (interquartile range [IQR] 1.0 h) and 1.66 (IQR 5.17 h) for survivors and non-survivors, respectively.

Figure 2 shows the subgroup analysis of mortality rate according to TTA. Episodes of FN with TTA ≤30 min had lower mortality rates compared with those with TTA of between 31 min and 60 min (3.0% versus 16.6%; log-rank P=0.0002). A second analysis comparing TTA between 31 min and 60 min versus TTA ≤30 min was performed only in cases with the first episode of documented bacteremia (figure 3). This procedure was conducted in order to confirm the benefit of early TTA in patients with documented bloodstream infections and to avoid possible confounding by evaluating multiple episodes of FN; also in this analysis, TTA <30 min was associated with decreased likelihood of death when compared with TTA between 31 and 60 min (6.4% versus 27.2%; log-rank P=0.020). The rate of *in vitro* sensitivity of blood isolates to initial antibiotic treatment for cases with TTA ≤30 min and those with TTA between 31 min and 60 min were 87% and 90%, respectively (Fisher's exact P=0.77).

DISCUSSION

In the present study, TTA was independently associated with all-cause 28-day mortality in the context of FN after cytotoxic chemotherapy: each hour of delay in TTA raised the risk for death by 18%. Moreover, our study findings demonstrated that patients with TTA ≤30 min had lower mortality rates than those with TTA between 31 min and 60 min.

Previous research involving distinct populations have confirmed the impact of early antibiotic administration on clinical outcomes. For example, the study by Gaieski et al [13] showed a relative risk reduction of mortality by 70% for non-neutropenic intensive care patients with severe sepsis and septic shock treated with an appropriate antibiotic within 1 h of triage compared with those with TTA >1 h (P=0.02). The retrospective cohort in the study by Fletcher et al [14] found that TTA ≤60 min, when compared with a TTA of 61 min to 120 min, was associated with a lower incidence of a composite end point that included in-hospital mortality, intensive care unit admission and fluid resuscitation >40 mL/kg within 24 h of presentation in pediatric FN patients. In a study by Hamandi et al [15], there was a significant association between increasing TTA (24 h increments) and increased hospital mortality rates in solid-organ transplant patients. Similarly, our study showed a reduction in the mortality risk from early TTA in a specific population of high-risk neutropenic patients in whom the correct implementation of antimicrobial strategy is of paramount importance. Beyond that, we went further and evaluated the benefit of earlier TTA compared with TTA ≤1 h recommended by current practice.

The considerable reduction in risk of mortality associated with a target TTA ≤30 min (compared with the typical target of ≤1 h recommended by current guidelines) observed in the present study has scientific plausibility because a population with a high risk for morbidity and mortality due to severe and prolonged immunosuppression is expected to benefit from prompt administration of effective antimicrobial agents. This finding underscores the importance of validated institutional strategies focused on reducing any delay in starting antimicrobial treatment for neutropenic cancer patients [16-18].

The strengths of the present study include its prospective design, the implementation of follow-up by a research team that was not responsible for providing care for the patients, the proper measurement of variables and outcomes with previously defined objective criteria, and the appropriate use of subgroup analysis through a conservative approach to avoid type I error. The main limitations of the present study were related to its single-center design and possible systematic errors related to

observational studies, given that we cannot be certain that we identified all potential confounding factors. Additionally, important pharmacokinetic aspects of the initial antimicrobial treatment administered (e.g., antibiotic serum levels) were not controlled.

Identifying the optimal TTA for patients with FN is of paramount importance to clinical practice because immediate antibiotic therapy is one of the few available treatments that effectively reduce mortality in the context of immunosuppression and infection. In addition, improvement to strategies focused on early, effective empirical antimicrobial administration usually requires nothing more than institutional organization and commitment. Taking into account the magnitude of these results, further research investigating strategies to ensure prompt, effective antibiotic administration within 30 min after the onset of FN in cancer patients undergoing cytotoxic chemotherapy is warranted.

ACKNOWLEDGMENTS

The authors thank the data collection team who created the database, as well as the *Hospital de Clínicas de Porto Alegre* (HCPA), particularly the Infection Control Committee, for their support in conducting the study. This study received financial support from FIPE/HCPA. The authors have no conflicts of interest to report.

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Table 1. Study population characteristics and microorganisms isolated in 307 cases of febrile neutropenia.

Age, mean years ± SD	40.7 ± 14.2
Female sex	148 (48.2)
Type of cancer	
Acute myeloid leukaemia	149 (48.5)
Acute lymphoblastic leukaemia	45 (14.6)
Chronic myeloid leukaemia	18 (5.8)
Multiple myeloma	30 (9.7)
Lymphoma	51 (16.6)
Other solid tumours	14 (4.5)
Relapsing underlying disease	155 (50.4)
Clinical comorbidity	76 (24.7)
Phase of chemotherapy	
Induction	76 (24.7)
Consolidation	86 (28.0)
Maintenance	57 (18.6)
HSCT	88 (28.7)
ANC at the time of diagnosis of FN, median cells/mm^3 (IQR)	130 (260)
Duration of neutropenia, median days (IQR)	9 (12)
Nosocomial-acquired episodes of FN	250 (81.4)
Bloodstream infection[†]	115 (37.4)
Escherichia coli	48 (41.7)
Coagulase-negative staphylococci	36 (31.3)
Klebsiella pneumonia	13 (11.3)
Pseudomonas aeruginosa	11 (9.5)
Viridans strepcococci	8 (6.9)
Enterococcus spp	4 (3.4)
Serratia spp	2 (1.7)
Enterobacter spp	2 (1.7)

Candida spp	2 (1.7)
Salmonella spp	1 (0.8)
Staphylococcus aureus	1 (0.8)
Kocuria varians	1 (0.8)

Data presented as n (%) unless otherwise indicated. SD Standard deviation; ANC Absolute neutrophil count; HSCT Hematopoietic stem cell transplantation; †There were 12 cases of polymicrobial bloodstream infections.

Figure 1. Distribution of time to antibiotic therapy in 307 cases of febrile neutropenia.

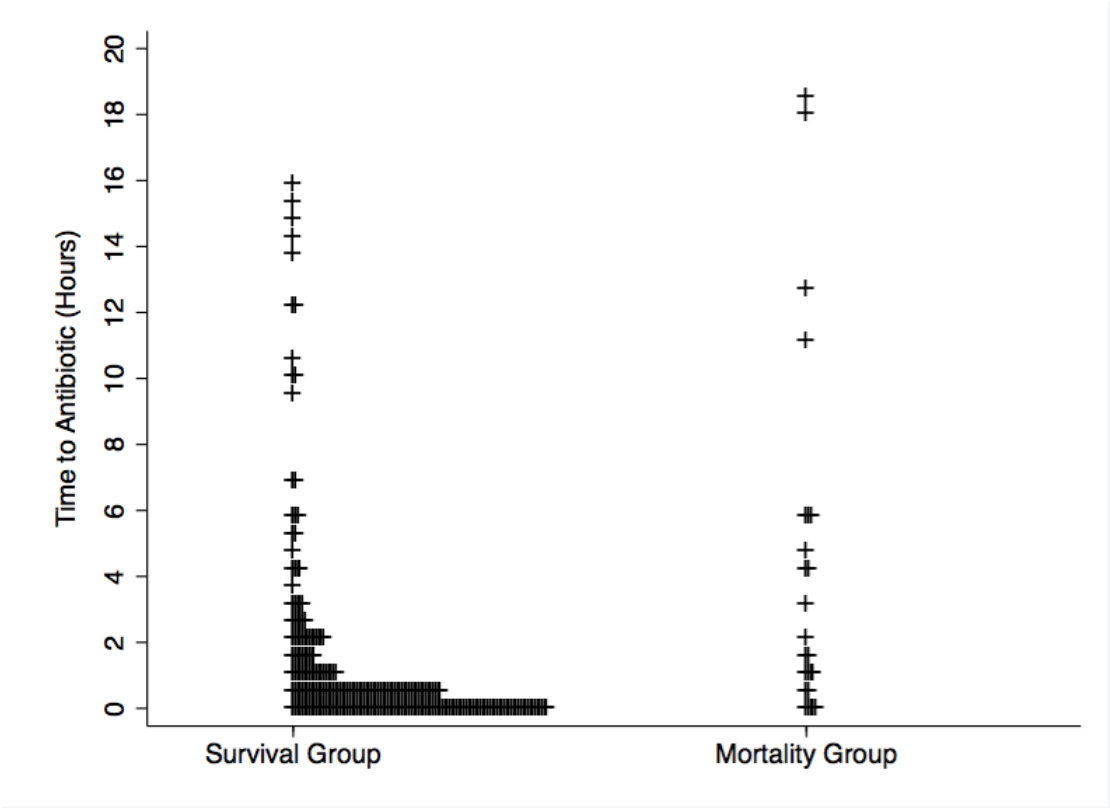
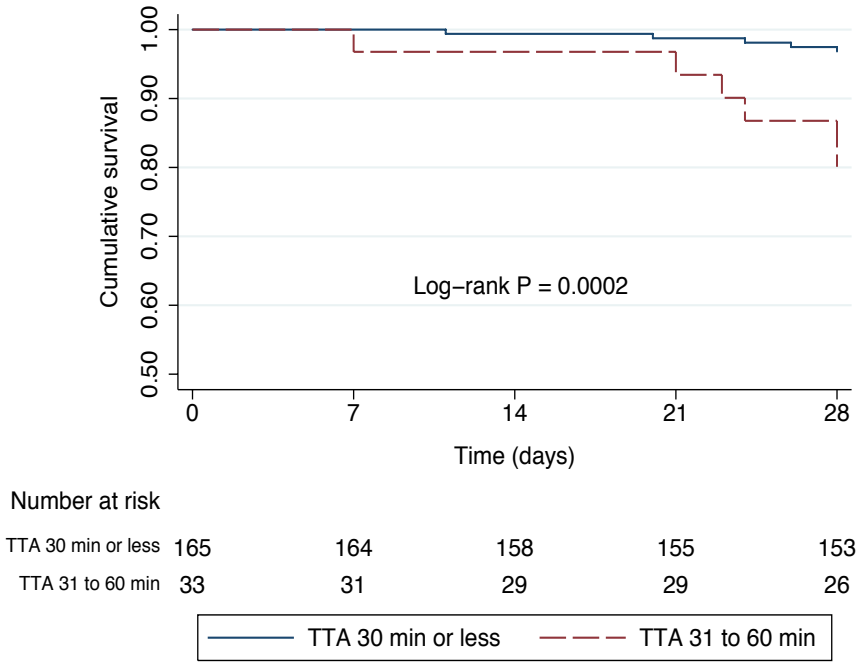


Table 2. Predictors of 28-day mortality in febrile neutropenia (FN) patients according to Cox regression analysis.

Variables	Mortality group (n=29)	Survival group (n=278)	Univariate analysis		Multivariate analysis	
			HR (95% CI)	*P*	HR (95% CI)	*P*
Age, mean years (SD)	41.6 (15.0)	40.6 (14.1)	1.00 (0.98-1.03)	0.62	…	…
Female gender	13 (44.8)	135 (48.5)	0.85 (0.41-1.78)	0.68	…	…
Clinical comorbidity	6 (20.6)	70 (25.1)	0.82 (0.33-2.01)	0.66	…	…
Type of neoplastic disease						
Hematologic	24 (82.8)	218 (78.4)	1.20 (0.45-3.15)	0.70	…	…
Solid tumour	5 (17.2)	60 (21.6)	…	…	…	…
Relapsing underlying disease status	23 (79.3)	132 (47.4)	4.30 (1.75-10.58)	0.001	6.66 (2.36-18.79)	< 0.001
High-dose chemotherapy regimens	9 (31.0)	155 (55.7)	0.39 (0.17-0.86)	0.02	…	…
ANC at the time of the diagnosis of FN, median cells/mm³ (IQR)	130 (260)	130 (260)	1.00 (0.99-1.00)	0.37	…	…
ANC <100 cells/mm³ at the time of the diagnosis of FN	16 (55.1)	114 (41.0)	1.68 (0.80-3.49)	0.16	…	…
Duration of neutropaenia, median days (IQR)	8 (16)	9.5 (11)	0.97 (0.93-1.01)	0.23	…	…
Bloodstream infection	20 (68.9)	95 (34.1)	3.91 (1.78-8.60)	0.001	3.64 (1.49-8.88)	0.004
High-risk MASCC score	18 (62.0)	65 (23.2)	5.03 (2.37-10.65)	<0.001	4.21 (1.82-9.72)	0.001
In vitro sensitivity of blood isolates to initial antibiotic treatment	22 (75.8)	246 (88.4)	0.47 (0.20-1.10)	0.08	…	…
Time to antibiotic, median hours (IQR)	1.66 (5.17)	0.33 (1.0)	1.14 (1.07-1.22)	<0.001	1.18 (1.10-1.26)	< 0.001

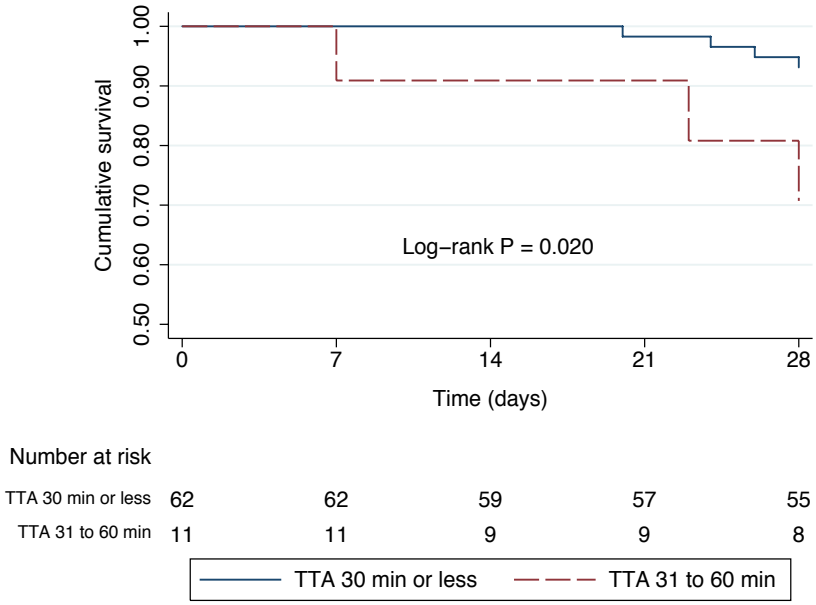
Data presented as n (%) unless otherwise indicated. HR Hazard ratio; 95% CI 95% confidence interval; SD Standard deviation; ANC Absolute neutrophil count; IQR Interquartile range (P75 – P25); MASCC Multinational Association for Supportive Care in Cancer

Figure 2. Comparison of survival curves of FN cases with time to antibiotic administration (TTA) between 31 min and 60 min versus those with TTA ≤30 min. All episodes of FN.



The Bonferroni corrected α level is 0.025.

Figure 3. Comparison of survival curves of FN cases with time to antibiotic administration (TTA) between 31 min and 60 min versus those with TTA ≤30 min. FN Cases with the first episode of documented bacteremia.



The Bonferroni corrected α level is 0.025.

Factors Associated with Hospital Length of Stay among Cancer Patients with Febrile Neutropenia

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Running title: Length of hospital stay in febrile neutropenia.

ABSTRACT

Purpose: This study sought to evaluate factors associated with hospital length of stay in cancer patients with febrile neutropenia.

Methods: A prospective cohort study was performed at a single tertiary referral hospital in southern Brazil from October 2009 to August 2011. All adult cancer patients with febrile neutropenia admitted to the hematology ward were evaluated. Stepwise random-effects negative binomial regression was performed to identify risk factors for prolonged length of hospital stay.

Results: In total, 307 cases of febrile neutropenia were evaluated. The overall median length of hospital stay was 16 days (interquartile range 18 days). According to multiple negative binomial regression analysis, hematologic neoplasms (P=0.003), high-dose chemotherapy regimens (P<0.001), duration of neutropenia (P<0.001), and bloodstream infection involving Gram-negative multi-drug-resistant bacteria (P=0.003) were positively associated with prolonged hospital length of stay in patients with febrile neutropenia. The condition index showed no evidence of multi-collinearity effect among the independent variables.

Conclusions: Hematologic neoplasms, high-dose chemotherapy regimens, prolonged periods of neutropenia, and bloodstream infection with Gram-negative multi-drug-resistant bacteria are predictors of prolonged length hospital of stay among adult cancer patients with febrile neutropenia.

Keywords: Febrile neutropenia; Length of hospital stay; Risk factors.

INTRODUCTION

Febrile neutropenia (FN) is a common complication of cancer treatment. The absolute neutropenia caused by intensive cytotoxic chemotherapy increases the risk of severe infections, which frequently require hospitalization for administration of broad-spectrum antibiotics to minimize morbidity and mortality [1,2].

Hospital length of stay (LOS) is an important marker of clinical severity and use of resources in the context of FN [3]. Neutropenic cancer patients who require prolonged LOS are at increased risk of multi-drug-resistant (MDR) infections and delays in their antineoplastic treatments [4,5], which can, in turn, have implications for cancer treatment outcomes. Moreover, given that diagnostic and treatment procedures in patients with FN are often associated with large financial expenditures, prolonged LOS has a negative impact on healthcare resource use and costs [6,7]. In specialized centers, the median cost of hospitalization per episode of FN may be as high as $24,000 USD [3] with an attributable cost excess greater than $12,000 USD [8].

Understanding the factors that prolong LOS in patients with FN may improve our ability to reduce costs and improve their quality of care. Therefore, we performed this study with the aim of evaluating the factors associated with increased LOS in hospitalized adult cancer patients with FN.

METHODS

Study design, patients, and settings

A prospective cohort study was conducted in the hematology ward of the Hospital de Clínicas de Porto Alegre, Rio Grande do Sul, a tertiary referral center for bone marrow transplantation in southern Brazil. All patients admitted between October 2009 and August 2011 and fitting the eligibility criteria were enrolled in this study. Inclusion criteria comprised age ≥18 years, neutropenia (absolute neutrophil count <500 cells/mm³ or <1000 cells/mm^3 with an expectation of a decrease to <500 cells/mm³ during the ensuing 48 h), and fever (a single axillary temperature measurement ≥38.5 °C or ≥38.0 °C sustained for 1 h). Exclusion criteria comprised individuals receiving only palliative treatment, an indication for outpatient treatment, or neutropenia caused by something other than

manifestations of hematological malignancy, bone marrow or peripheral blood stem cell transplantation**,** or adverse reaction to chemotherapy. Subjects were eligible to re-enter the study with a second or subsequent episode of FN if they had been discharged from hospital after completing treatment for a prior episode of FN.

Treatment protocol

Febrile neutropenic patients were treated according to the 2010 updated guidelines of the Infectious Diseases Society of America [9]. Initial antimicrobial treatment was β-lactam monotherapy with anti-pseudomonal activity (i.e., cefepime, piperacillin–tazobactam, or a carbapenem); a glycopeptide (i.e., vancomycin) was added to this initial empiric regimen only in patients with hemodynamic instability, suspected catheter-related infection, or infection of skin and soft tissue. Empiric antifungal therapy with amphotericin B deoxycholate was administered in patients with persistent fever after 4 days of treatment with broad-spectrum antibiotics. No patients received antibacterial prophylaxis. Antifungal prophylaxis with fluconazole was routinely administered to patients in whom the anticipated duration of neutropenia was >7 days. Acyclovir antiviral prophylaxis was administered to herpes simplex virus seropositive patients undergoing allogeneic hematopoietic stem-cell transplantation or leukemia induction chemotherapy.

Independent variables

The independent variables to be examined in this study were selected based on previously reported associations with prognosis in patients with FN [10-13]. All baseline characteristics were verified at the onset of fever by a medical research team not associated with patient care. Clinical comorbidity was defined as the presence of heart failure, diabetes mellitus, chronic pulmonary disease, chronic liver disease, or chronic renal failure. The patients were allocated to two groups based on their chemotherapy regimens: a high-dose chemotherapy group that included patients undergoing hematopoietic stem cell transplantation or induction chemotherapy and a standard-dose chemotherapy group that included patients undergoing consolidation or maintenance chemotherapy. Profound neutropenia was defined as an absolute neutrophil count <100 cells/mm^3 at the onset of FN. Prolonged neutropenia was defined as duration of neutropenia >7 days after the onset of FN. Nosocomial-

acquired FN was defined as FN developing 48 h or more after hospitalization. Microbiological studies were performed at the onset of fever according to standard practice and included two separate blood samples from two different sites. In the absence of an indwelling central venous catheter, these blood sets were obtained from two distinct peripheral veins. When an indwelling central venous catheter was present, one sample for blood culture was obtained through that catheter and the other from a peripheral vein. The susceptibilities of the isolated pathogens to antibiotics were evaluated according to the recommendations of the Clinical and Laboratory Standards Institute [14]. Polymicrobial bloodstream infection was defined as a bacteremic episode in which at least two different pathogens were isolated from the same blood sample. For Gram-positive bacteria, MDR bacteremia was defined as bloodstream infection (BSI) with methicillin-resistant staphylococci or vancomycin-resistant enterococci, whereas for Gram-negative bacteria it was defined as resistance to three or more classes of antimicrobial agents. Proven and probable invasive fungal infections (IFIs) were defined according to the criteria of the European Organization for Research and Treatment of Cancer-Invasive Fungal Infections Cooperative Group [15].

Outcome and follow-up

The primary outcome of the present study was the LOS after the onset of FN. Patient follow-up was performed by researchers who were not associated with the assistant physician's team through interviews and medical record reviews using a standardized data collection instrument. Follow-up was maintained throughout each hospitalization.

Statistical analysis

Independence could not be assumed because some patients had more than one episode of FN and were therefore evaluated more than once. Accordingly, stepwise random-effects negative binomial regression analysis was performed: this is a validated strategy for dealing with clustered data (that is, when observations in one cluster tend to be more similar to each other than to individuals in the rest of sample) [16]. All clinical and microbiological variables with a P value <0.10 in the univariate analysis were included. In the multivariate model, independent variables were eliminated from the highest to the lowest P value but remained in the model if the P value was <0.05. Incidence rate ratios (IRR) were estimated with 95% confidence intervals (95% CI). Multi-collinearity was assessed according to the

condition index of the multivariate model: a condition index <10 denotes weak collinearity, 10–30 denotes moderate collinearity, and >30 denotes strong collinearity [17]. The statistical analysis was performed using STATA version 12 (Stata Corp LP, USA).

Ethical considerations

Written informed consent was obtained from all study participants. The institutional review board of Hospital de Clínicas de Porto Alegre approved the study protocol and consent form (GPPG 09282). A copy of each written consent obtained is available for review from the Editor-in-Chief of this journal if necessary.

RESULTS

Three hundred and seven cases of FN (in 169 patients) were evaluated during the study period. Seventy-one patients (42% of the study cohort) had two or more episodes of FN; the maximum number of episodes in an individual patient was four. Relevant characteristics of all episodes of FN are shown in Table 1. Most of the cancers were hematological malignancies (78.8%); the most common being acute myeloid leukemia (48.5%), lymphoma (16.6%), and acute lymphoblastic leukemia (14.6%); in 53.4% of the cases, high-dose chemotherapy regimens were being administered.

During the study period, 115 BSIs were documented. The predominant isolates from blood were *Escherichia coli* (41.7%), coagulase-negative staphylococci (31.3%), *Klebsiella pneumoniae* (11.3%), *Pseudomonas aeruginosa* (9.5%), viridans streptococci (6.9%), and *Enterococcus* spp (3.4%). Among all BSIs evaluated, 38 episodes (33.0%) were caused by MDR bacteria; of these, 68.4% were caused by Gram-positive bacteria, 29.0% by Gram-negative bacteria, and 2.6% by both Gram-positive and Gram-negative bacteria. Methicillin resistance and production of extended-spectrum beta-lactamase were the most frequent types of antimicrobial resistance, occurring in 96.2% of BSIs involving Gram-positive MDR bacteria and 83.3% of BSIs involving Gram-negative MDR bacteria. The overall *in vitro* rate of resistance of blood isolates to the initial antibiotics administered was 12.7%. The incidence of proven or probable IFI was 7.1%.

The median LOS of the all episodes of FN was 16 days (interquartile range [IQR] 18 days). Sixty-nine percent of the cases were hospitalized for longer than 10 days. The median LOS for those

admitted for 10 days or less was 8 days (IQR 3 days). The median LOS for those admitted for longer than 10 days was 22 days (IQR 17 days). The median LOS according to case characteristics are shown in Figure; the greatest differences in median LOS according to the presence or absence of certain clinical features were found in the following categories: IFI, BSI involving Gram-negative MDR bacteria, and prolonged neutropenia.

According to the univariate analysis (Table 2), hematologic neoplasms (P<0.001), high-dose chemotherapy regimens (P<0.001), duration of neutropenia (P<0.001), MDR BSI (P=0.04), BSI involving Gram-negative MDR bacteria (P=0.009), and proven or probable IFI (P=0.002) were statistically associated with LOS. Interestingly, variables related to antimicrobial treatment, such as *in vitro* sensitivity of blood isolates to initial antibiotic treatment (P=0.07) and time to initial antibiotic (P=0.24) were not significant predictors of LOS. According to multivariate analysis (Table 2), hematologic neoplasms (P=0.003), treatment with high-dose chemotherapy regimens (P<0.001), duration of neutropenia (P<0.001), and BSI by MDR Gram-negative bacteria (P=0.006) were positively associated with LOS. The condition index of the final multivariate negative binomial regression was 5.5, indicating little collinearity among the explanatory variables in the model. In cases with hematologic neoplasms and those receiving high-dose chemotherapy before the episode of FN, the median LOS was 30% and 46%, respectively, longer than in cases without these risk factors. Each additional day of neutropenia was associated with a 2% increase in the total LOS. In cases with BSI caused by MDR Gram-negative bacteria, the median LOS was 62% longer than in other patients.

DISCUSSION

In the present cohort of patients with one or more episodes of FN, hematologic neoplasms, high-dose chemotherapy regimens, duration of neutropenia, and BSI with Gram-negative MDR bacteria were positively associated with prolonged LOS among hospitalized adult cancer patients with FN.

Reported median LOS in the context of FN varies according to the category of patient studied. In the study by Kuderer et al., LOS among cancer patients with FN had a range from 8.1 days (for patients with solid tumors) to 19.7 days (for patients with leukemia) [18]. Basu et al. reported a median LOS of 5 days in pediatric cancer patients with both high- and low-risk episodes of FN; specifically,

the median LOS for patients admitted for longer than 5 days was 12 days [19]. In addition, Weycker et al. reported a mean LOS of 8.4 days for adult patients with FN who were receiving myelosuppressive chemotherapy for solid tumors or non-Hodgkin lymphomas [20]. The prolonged median LOS found in our study (16 days) is consistent with the characteristics of our study sample, which included a large proportion of high-risk hematologic patients receiving high-dose chemotherapy regimens. Moreover, we evaluated only patients receiving intravenous chemotherapy; this fact also contributed to the prolonged LOS seen in our study population.

The factors we identified as associated with LOS are supported by findings of previous studies. Consistent with our findings, Haeusler et al. [21] showed a correlation between MDR Gram-negative bacteremia and prolonged hospital and intensive care unit length of stay in pediatric oncology patients. Interestingly, the relationship between BSI with MDR bacteria and LOS can become a vicious cycle because these two variables are reciprocal risk factors: prolonged LOS increases the risk of MDR bacteremia, which in turn increases the risk of prolonged hospitalization. Hematological malignancies are also reportedly risk factors for complications during episodes of FN; Taccone et al. [22] showed that, in an intensive care setting, patients with hematological cancer were more seriously ill and more commonly had sepsis, acute respiratory distress syndrome, and renal failure than did patients with solid cancers. The impact of prolonged neutropenia caused by high-dose chemotherapeutic regimens on LOS has also been well documented. Previously validated strategies have focused on reducing the duration of neutropenia through interventions such as prophylactic administration of granulocyte colony-stimulating factors, which is often associated with a decrease in the incidence of infections and shorter hospitalizations in neutropenic patients, without an impact on mortality [23-25].

The major limitation of our study is the observational design; we cannot be certain that we have identified all potential confounding factors. However, both assessment of independent variables by a research group not involved in patient care and the use of a prospective design with an objective endpoint contributed to the methodological strength of this study.

Identifying risk factors for prolonged LOS in patients with FN is of paramount importance to clinicians and healthcare administrators: this knowledge may guide preventative measures focused on decreasing LOS to both improve care (avoiding nosocomial infections and delays in cancer treatment) and optimize resource consumption (the duration of hospital stay is directly related to cost). Future

trials are needed to evaluate the impact on LOS of directed measures focused on prevention and management of the factors associated with prolonged LOS among cancer patients with FN.

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Table 1. Clinical characteristics in 307 cases of febrile neutropenia

Age, mean years ± SD	40.7 ± 14.2
Female sex	148 (48.2)
Type of cancer	
Acute myeloid leukemia	149 (48.5)
Acute lymphoblastic leukemia	45 (14.6)
Chronic myeloid leukemia	18 (5.8)
Multiple myeloma	30 (9.7)
Lymphoma	51 (16.6)
Other solid tumors	14 (4.5)
Relapsing underlying disease	155 (50.4)
Clinical comorbidity	76 (24.7)
Phase of chemotherapy	
Induction	76 (24.7)
Consolidation	86 (28.0)
Maintenance	57 (18.6)
HSCT	88 (28.7)
ANC at the time of diagnosis of FN, median cells/mm³ (IQR)	130 (260)
Duration of neutropenia, median days (IQR)	9 (12)

Nosocomial-acquired episodes of FN	250 (81.7)
Bloodstream infection	115 (37.4)
BSI involving Gram-positive bacteria	46 (14.9)
BSI involving Gram-negative bacteria	74 (24.1)
Polymicrobial BSI	12 (3.9)
BSI involving Gram-positive MDR bacteria	27 (8.7)
BSI involving Gram-negative MDR bacteria	12 (3.9)
Proven or probable IFI	22 (7.1)

Data presented as n (%) unless otherwise indicated. SD = standard deviation; HSCT = hematopoietic stem cell transplantation; ANC = absolute neutrophil count; FN = febrile neutropenia; IQR = interquartile range (P75–P25); BSI = bloodstream infection; MDR = multi-drug-resistant; IFI = invasive fungal infection.

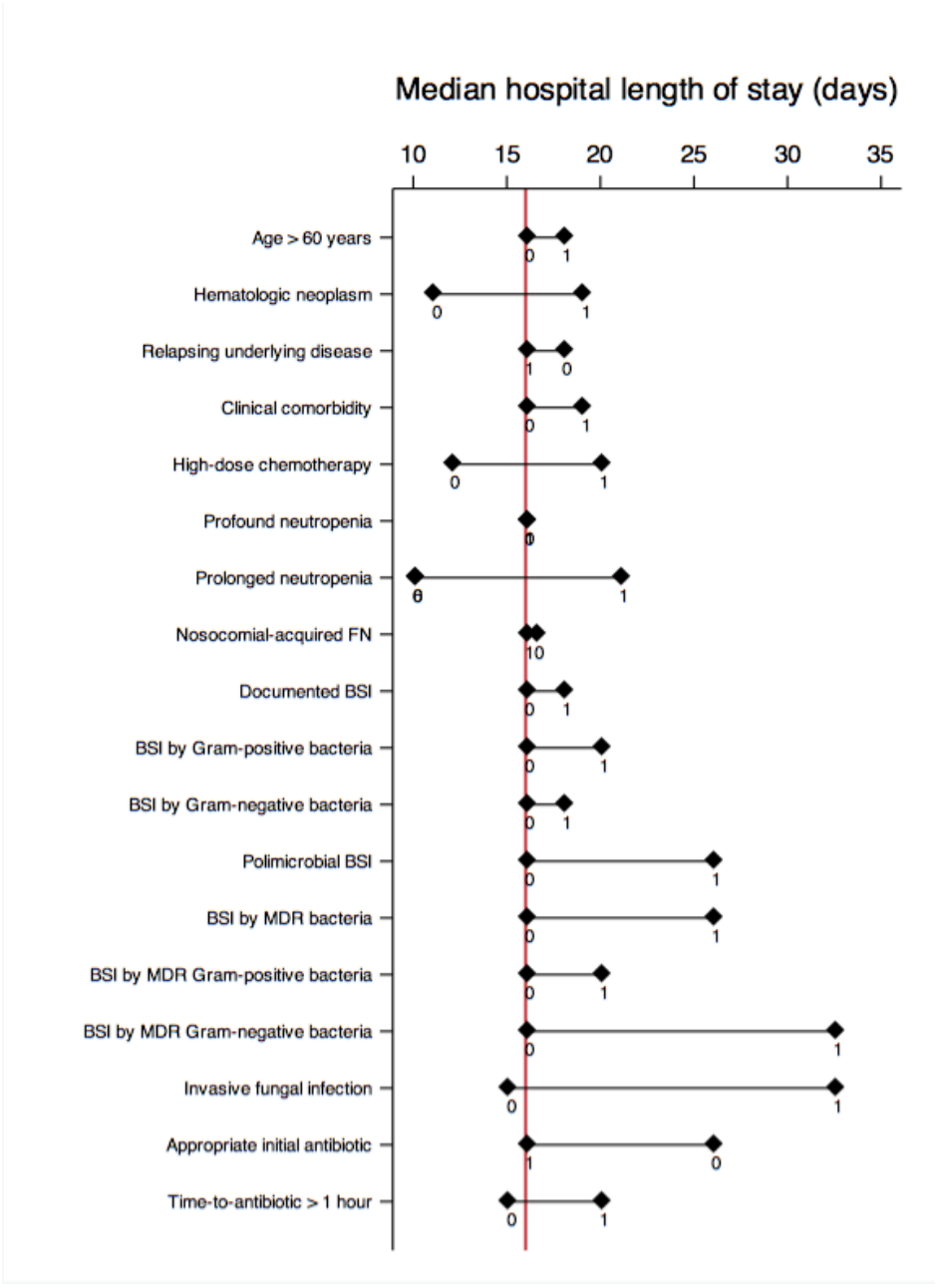
Table 2. Negative binomial regression of factors associated with hospital length of stay among cases of febrile neutropenia in cancer patients.

Variables	**Univariate analysis**		**Multivariate analysis**	
	IRR (95% CI)	***P* value**	**IRR (95% CI)**	***P* value**
Age, years	0.99 (0.98-1.00)	0.10	-	-
Hematologic neoplasm	1.64 (1.35-2.00)	<0.001	1.30 (1.09-1.55)	0.003
Relapsing underlying disease status	0.87 (0.74 – 1.03)	0.11	-	-
Clinical comorbidity	1.02 (0.84-1.23)	0.79	-	-
High-dose chemotherapy regimens	1.48 (1.26-1.73)	<0.001	1.43 (1.24-1.64)	<0.001
ANC at the time of the diagnosis of FN, cells/mm³	1.0003 (0.99 - 1.00)	0.05	-	-
Duration of neutropenia, median days	1.02 (1.01-1.03)	<0.001	1.02 (1.01-1.02)	<0.001
Nosocomial-acquired episode of FN	0.91 (0.74-1.12)	0.40	-	-
Bloodstream infection	1.007 (0.85-1.19	0.93	-	-
BSI involving Gram-positive bacteria	1.08 (0.86-1.36)	0.47	-	-
BSI involving Gram-negative bacteria	1.009 (0.83-1.22)	0.92	-	-
Polymicrobial BSI	1.46 (0.97-2.21)	0.06	-	-
MDR BSI	1.28 (1.00-1.63)	0.04	-	-
BSI involving Gram-positive MDR bacteria	1.09 (0.82-1.46)	0.51	-	-
BSI involving Gram-negative MDR bacteria	1.72 (1.14-2.58)	0.009	1.62 (1.15-2.29)	0.006
Proven or probable IFI	1.63 (1.20-2.22)	0.002	-	-

In vitro sensitivity of blood isolates to initial antibiotic treatment	0.79 (0.62-1.01)	0.07	-	-
Time to initial antibiotic, hours	1.01 (0.98-1.04)	0.24	-	-

Note. The incidence rate ratio (IRR) represents the change in the dependent variable (days of hospitalization) in terms of percentage (determined by the amount the IRR is above or below 1) per unit increase of continuous independent variables or in the yes versus no group for binary independent variables. ANC = absolute neutrophil count; FN = febrile neutropenia; BSI = bloodstream infection; MDR = multi-drug-resistant; IFI = invasive fungal infection.

Figure. Median hospital length of stay among cases of febrile neutropenia according to clinical characteristics



The red line represents the median length of hospital stay of the entire cohort. For each variable, 1 and 0 represent, respectively, the median LOS for cases with and without the clinical characteristic described in the corresponding row; BSI = bloodstream infection; MDR = multi-drug-resistant.

Aetiology of bacteraemia as a risk factor for septic shock at the onset of febrile neutropaenia in adult cancer patients

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Running Title: Septic shock and febrile neutropaenia

ABSTRACT

Background: Septic shock (SS) at the onset of febrile neutropaenia (FN) is an emergency situation that is associated with high morbidity and mortality. The impact of the specific aetiology of bloodstream infections (BSIs) in the development of SS at the time of FN is not well established. The aim of this study was to evaluate the association between the aetiology of BSIs and SS at the time of FN in hospitalised adult cancer patients.

Methods: This prospective cohort study was performed at a single tertiary hospital from October 2009 to August 2011. All adult cancer patients admitted consecutively to the haematology ward with FN were evaluated. A stepwise logistic regression was conducted to verify the association between the microbiological characteristics of BSIs and SS at the onset of FN.

Results: In total, 307 cases of FN in adult cancer patients were evaluated. There were 115 cases with documented BSI. A multivariate analysis showed that polymicrobial bacteraemia (P=0.01) was associated with SS. The specific blood isolates independently associated with SS were viridans streptococci (P=0.02) and *Escherichia coli* (P=0.01).

Conclusions: Neutropaenic cancer patients with polymicrobial bacteraemia or BSI by viridans streptococci or *Escherichia coli* are at increased risk for SS at the time of FN.

Keywords: Febrile neutropaenia, Septic shock, Risk factors, Aetiology, Bacteraemia.

INTRODUCTION

Despite improvements in treating febrile neutropaenia (FN) and sepsis over the past decade, septic shock (SS) continues to be associated with substantial morbidity and mortality among cancer patients undergoing intensive cytotoxic chemotherapy [1]. The unpredictable clinical course of infections in neutropaenic patients because of the lack of an adequate inflammatory response makes managing FN a significant challenge because clinically stable patients may suddenly progress to severe sepsis or SS [2].

SS is a result of the host response to the pathogen and is dependent on the virulence of the microorganism and the infection site [3]. The known risk factors for SS in immunocompetent patients include advanced age, low functional status, and the presence of cancer, clinical comorbidities, nosocomial infections, and infection that does not originate in the urinary tract [4-6]. Infection with certain bacteria, such as *Staphylococcus aureus* and *Pseudomonas aeruginosa*, is also associated with an increased risk for SS, as the expression of certain proteins or molecules (virulence factors) contributes to pathogen replication and dissemination by subverting or eluding the host's defences [7]. Unfortunately, data regarding the influence of microbiological factors on the development of SS in cancer patients with FN are scarce. Therefore, we conducted a study with the aim of evaluating the association between microbiological aspects of bloodstream infections (BSIs) and SS development at the onset of FN in hospitalised adult cancer patients.

METHODS

Study design and participants

A prospective cohort study was conducted at a single referral centre for adult bone marrow transplantation in Southern Brazil from October 2009 to August 2011. This study followed all consecutive haemodynamically stabile cancer patients older than 18 years of age who were admitted to the haematology ward of the Hospital de Clínicas de Porto Alegre (Porto Alegre, Brazil) with neutropaenia (i.e., an absolute neutrophil count [ANC] <500 cells/mm³ or <1000 cells/mm^3 with an expectation of a decrease to <500 cells/mm³ during the ensuing 48 h). The subjects who developed fever (i.e., a single axillary temperature measurement ≥38.5°C or sustained temperature ≥38.0°C over a

1 h period) during the course of neutropaenia were entered into the study. Outpatients, patients who had neutropaenia caused by a specific aetiology other than an adverse reaction to chemotherapy, and patients who had episodes of FN without documented bacteraemia were excluded. Subjects were allowed to re-enter the study after an initial episode of FN if they remained free of signs or symptoms of infection for at least 7 days after completing the treatment for the first episode and if all causative organisms, if any, were eradicated.

Definitions

Microbiological studies, which included 2 separate blood samples that were obtained from 2 different anatomical sites for culture, were performed at the onset of fever, according to standard practice. In the absence of an indwelling central venous catheter, 2 blood samples were obtained from 2 distinct peripheral veins. When an indwelling central venous catheter was present, 1 blood sample was obtained through this catheter, and a second sample was obtained from a peripheral vein. The susceptibilities of the isolated pathogens to antibiotics were evaluated according to the recommendations of the Clinical and Laboratory Standards Institute [8]. Bacteraemia caused by coagulase-negative *Staphylococcus* spp. was diagnosed after 2 positive results from 2 independent cultures. Bacteraemia indicated by 1 positive culture was considered to be diagnostic for the other microorganisms. Polymicrobial BSI was characterised as a bacteraemic episode due to at least two different pathogens isolated from the same blood sample. Multidrug-resistant (MDR) bacteraemia was defined as a BSI with methicillin-resistant staphylococci or vancomycin-resistant enterococci for Gram-positive bacteria or as resistance to ≥3 classes of antimicrobial agents for Gram-negative bacteria. Clinical comorbidity was determined by the presence of heart failure, diabetes mellitus, chronic pulmonary disease, chronic liver disease, or chronic renal failure. Profound neutropaenia was characterised by an ANC <100 cells/mm³. The patients were divided into 2 groups based on their chemotherapy regimens: a high-dose chemotherapy group that included patients who underwent haematopoietic stem cell transplantation or induction chemotherapy and a standard-dose chemotherapy group that included patients who underwent consolidation or maintenance chemotherapy. Nosocomial-acquired FN was defined as the onset of FN after 48 hours of hospitalisation. The oral mucositis grade was classified according to the World Health Organisation's oral toxicity scale [9].

Outcomes and follow-up

The primary outcome measure of the present study was SS at the onset of fever in neutropaenic patients. SS was defined as persistent haemodynamic instability (systolic arterial pressure <90 mmHg or a reduction in systolic blood pressure >40 mmHg from baseline) despite adequate fluid resuscitation (30 ml per Kg of crystalloid) with at least 2 systemic inflammatory response syndrome criteria [10]. The secondary outcome was mortality by day 28. Researchers who were not associated with the assistant physician's team conducted the patient follow-ups through interviews and medical record reviews using a standardised data collection instrument. The follow-up was maintained for 28 days after the onset of fever in the neutropaenic patients. For the subjects who were discharged before 28 days, follow-up telephone calls were made on the 28th day after the onset of FN to determine whether they remained alive; if a patient was deceased at the time of the phone call, the survival time was calculated based on the date of death reported by the family.

Statistical analysis

Stepwise logistic regression analysis was performed to determine whether the microbiological characteristics of BSIs were risk factors for SS at the time of FN. All clinical and microbiological variables that had a *P* value <0.10 in the univariate analysis were included. In the multivariate model, independent variables were eliminated from the highest to the lowest *P* value but remained in the model if the *P* value was <0.05. Odds ratios (OR) were estimated with 95% confidence intervals (95% CI). Kaplan-Meier curves were utilised to evaluate the time-dependent occurrence of death; the log-rank test was applied for between-group comparisons. The statistical analysis was performed using STATA version 12 (Stata Corp LP, USA).

Ethics statement

Written informed consent was obtained from all study participants. The institutional review board of the Hospital de Clínicas de Porto Alegre approved the study.

RESULTS

In total, 307 episodes of FN (in 169 patients) were evaluated; a total of 115 BSIs were documented (37.4% of all episodes). Antibiotic prophylaxis was not administered to any patient. The incidence of SS was 14.7% (17 episodes).

The characteristics of the study population and the specific pathogens responsible for all BSIs in the present cohort are shown in Table 1. Subjects with haematological malignancies comprised 83.5% of the study population; haematopoietic stem cell transplantation was performed in 21.7% of the cases. Forty-eight per cent of the study sample had some degree of chemotherapy-induced mucositis. The proportion of nosocomial episodes of FN was 88.7%. In descending order, the predominant blood isolates were *Escherichia coli*, coagulase-negative staphylococci, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, viridans streptococci, and *Enterococcus* spp. Among all BSIs evaluated, 38 cases were due to MDR bacteria (table 2): 4 cases in the SS group (23.5%) and 34 cases in the non-SS shock group (34.6%). Methicillin resistance and the production of extended-spectrum beta-lactamase were the most frequent types of antimicrobial resistance, occurring in 96.2% of BSIs involving Gram-positive MDR bacteria and 83.3% of BSIs involving Gram-negative MDR bacteria, respectively.

A univariate analysis revealed that polymicrobial BSI (P=0.01) and bacteraemia by *Escherichia coli* (P=0.04) were associated with the main outcome (Table 3). Multidrug-resistant (MDR) bacteraemia was not associated with SS at the onset of FN with either the Gram-positive MDR or Gram-negative MDR bacteria.

After multiple logistic regression analyses were performed (Table 4, model 1), the only variable that constituted an independent risk factor for SS at the time of FN was polymicrobial BSI (OR, 5.41, 95% CI, 1.48 – 19.79). A second logistic regression model was used to assess the effect of specific pathogens on the development of SS without the inclusion of other microbiological variables (Table 4, model 2). This model was conducted to avoid the dilution of the effect of specific pathogens by other microbiological factors in the multivariate analysis. The specific blood isolates that were independently associated with the main outcome were viridans streptococci (OR, 7.58, 95% CI, 1.34 – 42.80) and *Escherichia coli* (OR, 4.30, 95% CI, 1.34 – 14.48). The percentage of the polymicrobial samples that included *E. coli* and viridans streptococci was 58.3% (7 cases) and 25% (3 cases), respectively.

As expected, the 28-day mortality rate of the patients who presented with SS at the time of FN was greater than that of the patients who did not present with SS (35.2% versus 14.2%, log-rank *P*=0.01) (Figure 1).

DISCUSSION

The present prospective cohort study demonstrated that cancer patients with polymicrobial bacteraemia were more likely to develop SS at the onset of FN. In particular, BSIs involving *E. coli* and viridans streptococci were independently associated with SS at the time of FN. The 28-day survival rate of the patients with SS at the time of FN was significantly lower than that of the patients who did not present with SS.

Previous observational studies involving distinct populations have confirmed the influence of microbiological aspects of BSIs on the hazards of SS. Consistent with the results of our study, Leibovici et al. conducted a retrospective study involving more than 4000 episodes of bacteraemia in a general population and found that the polymicrobial aetiology was predictive of SS [11]. Moreover, the association of specific BSI by *E. coli* and viridans streptococci with SS in FN patients is feasible because invasive infections by *E. coli* and viridans streptococci are often associated with significant morbidity and mortality [12-15]. For example, the study of Marron et al. [15] reported an association between viridans streptococcal bacteraemia and serious complications, such as SS and acute respiratory distress syndrome, in neutropaenic patients receiving high-dose chemotherapy with cyclophosphamide before allogeneic bone marrow transplantation.

Interestingly, none of the studied clinical characteristics was significantly associated with SS at the time of FN in the multiple logistic regression analysis. These findings differ from the immunocompetent patient studies in which the early development of SS was more frequent in the subjects with advanced age and multiple comorbidities [4-6]. One possible explanation is the relative homogeneity of our study population, which consisted of a large proportion of young patients with haematological malignancies and a relatively low prevalence of associated comorbidities. This fact highlights the need to identify the rapidly available clinical diagnostic features that can predict septic shock in this setting.

This study had some limitations. For example, we found a low incidence of bacteraemia by *Staphylococcus aureus* and *Pseudomonas aeruginosa*, which are often associated with a poorer prognosis in septic patients; therefore, our results should be interpreted with caution, as distinct virulent bacteria may be found in other centres. Furthermore, this study was susceptible to biases that are inherent to observational studies; however, the following factors minimised the possibility of systematic errors: the proper measurement of variables and outcomes with previously defined objective criteria, the use of standardised data collection, the implementation of a follow-up by a research team that was not related to the care provided, and the use of multivariate analyses.

CONCLUSIONS

The aetiology of BSIs is an important risk factor for SS at the onset of FN in adult cancer patients. Polymicrobial BSI, particularly bacteraemia by *E. coli* and viridans streptococci, are the risk factors for SS at the onset of FN.

Identifying the microbiological factors associated with SS in FN is of paramount importance to clinicians, as this knowledge can determine the preventative measures to avoid BSI by specific highly virulent pathogens and the best choice of empiric antimicrobial therapy.

Future studies are required to assess other possible risk factors for the early onset of SS in the context of FN and to determine whether specific interventions based on the early identification of highly virulent bacteria could result in an effective method to prevent SS and its characteristically pronounced mortality rates.

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CONFLICT OF INTERESTS

The authors declare no conflict of interests. This work was partialy supported by CNPq (Brazilian National Council of Research).

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Table 1. Study population characteristics and microorganisms isolated in 115 cases of febrile neutropenia (FN) in hospitalised cancer patients with documented bloodstream infection.

Age, mean years ± SD	42.9 ± 14.1
Female sex	52 (45.2)
Type of cancer	
Acute myeloid leukaemia	59 (51.3)
Acute lymphoblastic leukaemia	19 (16.5)
Chronic myeloid leukaemia	7 (6.1)
Multiple myeloma	11 (9.6)
Lymphoma	15 (13.0)
Other solid tumours	4 (3.5)
Relapsing underlying disease	59 (51.3)
Clinical comorbidity	36 (31.3)
Phase of chemotherapy	
Induction	27 (23.5)
Consolidation	37 (32.2)
Maintenance	26 (22.6)
HSCT	25 (21.7)
Oral mucositis	
Without oral mucositis	59 (51.3)
Grade I	33 (28.7)

Grade II Grade III Grade IV	10 (8.7) 6 (5.2) 7 (6.1)
ANC at the time of diagnosis of FN, mean cells/mm³ ± SD	206.1 ± 218.5
Profound neutropenia at the time of diagnosis of FN *	52 (45.2)
Nosocomial-acquired episodes of FN	102 (88.7)
Bloodstream isolates †	
Escherichia coli	48 (41.7)
Coagulase-negative staphylococci	36 (31.3)
Klebsiella pneumonia	13 (11.3)
Pseudomonas aeruginosa	11 (9.5)
Viridans strepcococci	8 (6.9)
Enterococcus spp	4 (3.4)
Serratia spp	2 (1.7)
Enterobacter spp	2 (1.7)
Candida spp	2 (1.7)
Salmonella spp	1 (0.8)
Staphylococcus aureus	1 (0.8)
Kocuria varians	1 (0.8)

Data presented as n (%) unless otherwise indicated. SD = Standard deviation; ANC = Absolute neutrophil count; HSCT = Hematopoietic stem cell transplantation; * ANC < 100 cells/mm³; † There were 12 cases of polymicrobial bloodstream infections.

Table 2. Multidrug-resistant bacteria isolated in 38 cases of bacteraemia in febrile neutropaenic patients.

Microorganism	**No. isolated (%)**
Gram-positive	
MR Coagulase-negative staphylococci	25 (65.7)
MR *Staphylococcus aureus*	1 (2.6)
VR *Enterococcus faecalis*	1 (2.6)
Gram-negative	
Escherichia coli ESBL	7 (18.4)
Klebsiella pneumoniae ESBL	3 (7.8)
Enterobacter spp.	1 (2.6)
Serratia spp.	1 (2.6)

MR = methicillin resistant, VR = vancomycin resistant, ESBL = extended-spectrum beta-lactamase.

There was 1 case of polymicrobial multidrug-resistant bacteraemia.

Table 3. Univariate analysis of the risk factors for septic shock (SS) at the time of febrile neutropenia (FN) in hospitalised cancer patients.

Variable	SS group (n=17)	Non-SS group (n=98)	OR (95% CI)	*P* value
Age, years, mean ± SD	43.4 ± 16.0	42.8 ± 13.8	1.00 (0.96 – 1.04)	0.87
Female sex	10 (58.8)	42 (42.8)	1.90 (0.66 – 5.41)	0.22
Haematological neoplasm	13 (76.4)	83 (84.6)	0.58 (0.16 – 2.04)	0.40
Relapsing underlying disease	10 (58.8)	49 (50.0)	1.42 (0.50 – 4.05)	0.50
Clinical comorbidity	2 (11.7)	34 (34.6)	0.25 (0.05 – 1.16)	0.07
High-dose chemotherapy regimens *	5 (29.4)	47 (47.9)	0.45 (0.14 – 1.38)	0.16
Oral mucositis				
Grade I	4 (23.5)	29 (29.5)	0.76 (0.21 – 2.71)	0.68
Grade II	2 (11.7)	8 (8.1)	1.38 (0.25 – 7.63)	0.70
Grade III	1 (5.8)	5 (5.1)	1.11 (0.11 – 10.66)	0.92
Grade IV	1 (5.8)	6 (6.1)	0.92 (0.09 – 8.63)	0.94
ANC at the time of diagnosis of FN, mean ± SD	161.7 ± 219.0	213.8 ± 218.7	0.99 (0.99 – 1.00)	0.36
Profound neutropenia at the time of diagnosis of FN †	9 (52.9)	43 (43.8)	1.43 (0.51 – 4.04)	0.49
BSI involving Gram-positive bacteria	6 (39.2)	40 (40.8)	0.79 (0.27 – 2.31)	0.66
BSI involving Gram-negative bacteria	14 (82.3)	60 (61.2)	2.96 (0.79 – 10.97)	0.10
Polymicrobial BSI	5 (29.4)	7 (7.1)	5.41 (1.48 – 19.79)	0.01
MDR BSI	4 (23.5)	34 (34.6)	0.57 (0.17 – 1.91)	0.37

BSI involving Gram-positive MDR bacteria	3 (17.6)	24 (24.4)	0.66 (0.17 – 2.49)	0.54
BSI involving Gram-negative MDR bacteria	1 (5.8)	11 (11.2)	0.49 (0.05 – 4.09)	0.51
BSI by *Escherichia coli*	11 (64.7)	37 (37.7)	3.02 (1.03 – 8.85)	0.04
BSI by coagulase-negative staphylococci	4 (23.5)	32 (32.6)	0.63 (0.19 – 2.10)	0.45
BSI by *Klebsiella pneumoniae*	3 (17.6)	10 (10.2)	1.88 (0.46 – 7.70)	0.37
BSI by *Pseudomonas aeruginosa*	2 (11.7)	9 (9.1)	1.31 (0.25 – 6.70)	0.73
BSI by viridans streptococci	3 (17.6)	5 (5.1)	3.98 (0.85 – 18.54)	0.07

Data presented as n (%) unless otherwise indicated. ANC = Absolute neutrophil count; BSI = Bloodstream infection; HSCT = Haematopoietic stem cell transplantation; MDR = Multidrug-resistant; OR = Odds ratio; 95%CI = 95% confidence interval; SD = Standard deviation. * Induction chemotherapy or HSCT; † ANC < 100 cells/mm³.

Table 4. Multiple logistic regression analysis of the risk factors for septic shock (SS) at the time of febrile neutropenia (FN) in hospitalised adult cancer patients.

Model 1			
Risk factor	**Adjusted OR**	**95% CI**	***P* value**
Polymicrobial BSI	5.41	1.48 – 19.79	0.01
Model 2			
Risk factor	**Adjusted OR**	**95% CI**	***P* value**
BSI by *Escherichia coli*	4.30	1.27 – 14.48	0.01
BSI by viridans streptococci	7.58	1.34 – 42.80	0.02

OR = odds ratio; 95%CI = 95% confidence interval; BSI = Bloodstream infection.

Risk Factors for Multidrug-Resistant Bacteraemia in Hospitalised Cancer Patients with Febrile Neutropaenia: A Cohort Study

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Running Title: Febrile neutropaenia and multidrug resistance

ABSTRACT

We conducted a prospective cohort study in a single tertiary hospital with the aim of assessing predictors of multidrug-resistant bacteraemia in 307 cases of febrile neutropaenia in adult patients with cancer. After multivariate analysis using the stepwise logistic regression, age (P = 0.009), duration of neutropaenia (P = 0.022), and the presence of an indwelling central venous catheter (P = 0.022) were associated with bloodstream infection by MDR bacteria.

Keywords: Immunocompromised host; drug resistance, bacterial; bacteraemia; risk factors; fever; neutropaenia.

INTRODUCTION

The aetiology of bloodstream infections (BSIs) in patients with cancer and febrile neutropaenia (FN) has changed over the past 40 years (1). Recently, a notable increase in antimicrobial resistance among gram-negative and gram-positive bacteria has been reported (2). Methicillin resistance and the production of extended-spectrum beta-lactamase (ESBL) have emerged as the most frequent mechanisms of antimicrobial resistance in this setting; however, other types of multidrug resistance, such as vancomycin resistance and the production of carbapenemases, have also been described (2-4). Unfortunately, few data are available concerning the risk factors for multidrug-resistant bacteraemia in the context of FN. To this end, we investigated the predictors of MDR bacteraemia in adult cancer patients with FN admitted to a tertiary hospital.

METHODS

A prospective cohort study was conducted in the haematology ward of Hospital de Clínicas de Porto Alegre, which is a tertiary referral centre for bone marrow transplantation in southern Brazil. We screened all consecutive subjects admitted from October 2009 to August 2011. Patients aged ≥ 18 years with neutropaenia secondary to cytotoxic chemotherapy (absolute neutrophil count [ANC] < 500 cells/mm³ or < 1000 cells/mm^3 with an expectation of decreasing to < 500 cells/mm³ during the next 48 hours) and fever (a single axillary temperature measurement ≥ 38.5°C or temperature of ≥ 38.0°C sustained over a 1-hour period) were eligible for this study.

Microbiological studies were performed at the onset of fever according to standards of practice and included two separate blood samples from two different sites. In the absence of an indwelling central venous catheter, the two blood sets were obtained from two distinct peripheral veins. When an indwelling central venous catheter was present, one set of samples for blood culture was obtained through an indwelling central venous catheter and another set was collected from a peripheral vein. The susceptibilities of the isolated pathogens to antibiotics were evaluated according to the recommendations of the Clinical and Laboratory Standards Institute (CLSI) (5). Bacteraemia resulting from coagulase-negative *Staphylococcus* spp. was diagnosed after 2 positive results from 2 independent cultures. Bacteraemia with one positive culture was considered diagnostic for other

microorganisms. Nosocomial-acquired FN was defined as the onset of FN after 48 hours of hospitalisation. Clinical comorbidity was defined by the presence of heart failure, diabetes mellitus, chronic pulmonary disease, chronic liver disease, or chronic renal failure. The grade of oral mucositis was classified according to the World Health Organization's oral toxicity scale (6).

The primary outcome of the study was MDR bacteraemia, which was defined as a BSI that was the result of methicillin-resistant staphylococci or vancomycin-resistant enterococci for gram-positive bacteria or as resistance to ≥ 3 classes of antimicrobial agents for gram-negative bacteria.
A stepwise backward logistic regression analysis with a limit of 0.10 was performed to determine if the characteristics related to the host or FN episode were risk factors for BSIs caused by MDR bacteria.

RESULTS

Three hundred and seven episodes of FN were evaluated. Antibiotic prophylaxis with fluoroquinolones was not administered to any patient. During the study period, 115 BSIs were documented. The predominant pathogens were *Escherichia coli* (38.2%), coagulase-negative *Staphylococcus* spp. (31.3%), *Klebsiella pneumoniae* (11.3%), *Pseudomonas aeruginosa* (9.5%), and *Streptococcus* spp. (6.0%).

Among all BSIs evaluated, 38 episodes (33.0%) were caused by MDR bacteria; of these, 68.4% were caused by gram-positive bacteria, 29.0% were caused by gram-negative bacteria, and 2.6% were caused by both gram-positive and gram-negative bacteria. All of the MDR bacteria isolated in this study are listed in Table 1. Methicillin resistance and the production of ESBL were the most frequent types of antimicrobial resistance, occurring in 70.2% of staphylococci and 13.5% of all gram-negative isolates, respectively.

After logistic regression analysis was performed, age (P=0.009), the duration of neutropaenia (P=0.022), and the presence of an indwelling central venous catheter (P=0.022) were significantly associated with a BSI caused by MDR bacteria (Table 2). Each increase of one year in age and one day in the duration of neutropaenia raised the risk of MDR bacteraemia by 3% and 2%, respectively.
The sub-analysis of the main outcome revealed that age (OR, 1.04; 95%CI, 1.01-1.08) and the presence of an indwelling central venous catheter (OR, 8.05; 95%CI, 1.05-61.26) were independently associated with bacteraemia caused by MDR gram-positive bacteria. In addition, the duration of neutropaenia

(OR, 1.04; 95%CI, 1.01-1.07) was independently associated with bacteraemia caused by MDR gram-negative bacteria.

DISCUSSION

This study showed that older patients with prolonged neutropaenia and patients with an indwelling central venous catheter were more likely to develop a BSI caused by MDR bacteria. In particular, age and the presence of an indwelling central venous catheter were associated with gram-positive MDR bacteraemia, while prolonged neutropaenia was associated with gram-negative MDR bacteraemia.

Although our results seem to differ from those of previous publications, studies on the risk factors for MDR bacteraemia in patients with FN are heterogeneous, and these differences may reflect the influence of local epidemiology. In a prospective multicenter study in 91 hematopoietic stem cell transplant recipients with bacteremia, Oliveira et al. (7) found that previous exposure to third-generation cephalosporins was associated with an increased risk of MDR gram-negative bacteraemia. In our institution, there is a restriction policy for third-generation cephalosporin use that became effective in 2003. In addition, El-Mahallawy et al. (8) found that a reduced ANC, , and previous exposure to antibiotics, and in particular prolonged duration of neutropaenia extending for more than 7 days were associated with a BSI due to a MDR gram-negative bacteria among 239 episodes of bacteremia (75% gram-positive organisms versus 25% gram-negative organisms) in children with cancer and FN. In contrast to these previous studies, our study has shown that the presence of an indwelling central venous catheter was a risk factor for a BSI due to MDR gram-positive bacteria, which may be explained by the high incidence of methicillin-resistant coagulase-negative staphylococci in our institution. Additionally, the finding that age and prolonged neutropaenia were risk factors for a BSI due to MDR gram-negative bacteria has scientific plausibility, as both factors are associated with a decreased host's response to infection.

The improvement of preventative measures to avoid catheter-related infections and the appropriate use of less cytotoxic chemotherapy regimens with short periods of neutropenia could result in effective ways to prevent MDR bacteraemia in patients with FN.

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Table 1. Multidrug-resistant bacteria isolated in 38 cases of bacteraemia in febrile neutropaenic patients.

Microorganism	No. isolated (%)
Gram-positive	
MR Coagulase-negative staphylococci	25 (65.7)
MR *Staphylococcus aureus*	1 (2.6)
VR *Enterococcus faecalis*	1 (2.6)
Gram-negative	
Escherichia coli ESBL	7 (18.4)
Klebsiella pneumoniae ESBL	3 (7.8)
Enterobacter spp.	1 (2.6)
Serratia spp.	1 (2.6)

Note. MR = methicillin resistant, VR = vancomycin resistant, ESBL = extended-spectrum beta-lactamase.

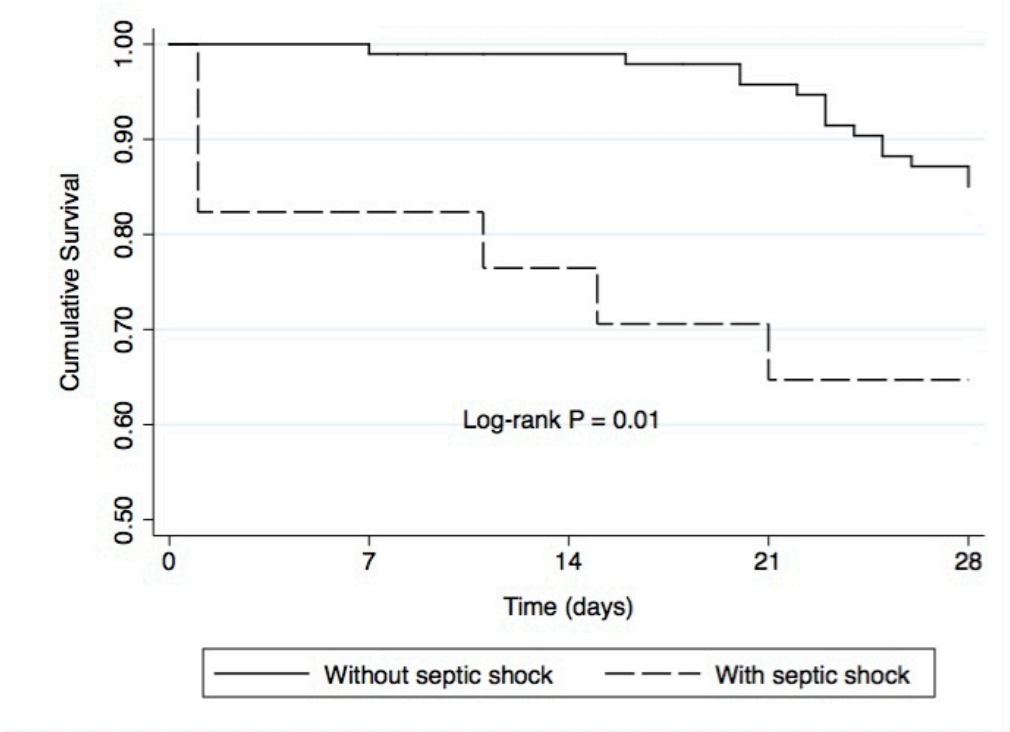
There was 1 case of polymicrobial multidrug-resistant bacteraemia.

Table 2. Logistic regression analysis of the risk factors for multidrug-resistant bacteraemia in hospitalised cancer patients with febrile neutropaenia.

Variables	Cases of MDR bacteraemia (n =38)	Other cases (n= 269)	Univariate analysis		Multivariate analysis	
			OR (95%CI)	*P*	OR (95%CI)	*P*
Age, mean years (SD)	46.21 (13.0)	39,97 (14,2)	1.03 (1.006-1.05)	0.013	1.03 (1.008-1.06)	0.009
Female sex (%)	18 (47.3)	131 (48.6)	0.94 (0.48-1.87)	0.878	...	
Clinical comorbidity (%)	15 (39.4)	61 (22,6)	2.20 (1.08-4.48)	0.027	...	
Relapsing underlying disease (%)	18 (47.3)	137 (50.9)	0.86 (0.43-1.71)	0.681	...	
Median ANC at the time of diagnosis of FN (IQR)	170.0 (320.0)	130 (250.0)	1.0002 (0.99-1.001)	0.788	...	
Duration of neutropaenia, median days (IQR)	16.5 (15.0)	8 (10)	1.02 (1.005-1.05)	0.012	1.02 (1.003-1.05)	0.022
Nosocomial-acquired episode (%)	35 (92.1)	216 (80.2)	2.86 (0.84-9.66)	0.090	...	
Antimicrobial treatment in the last 30 days (%)	12 (31.5)	98 (36.4)	0.80 (0.38-1.66)	0.560	...	
Previous hospitalisation in the last 30 days (%)	12 (31.5)	108 (40.1)	0.68 (0.33-1.42)	0.313	...	
Presence of an indwelling central venous catheter (%)	36 (94.7)	207 (76.9)	5.39 (1.26-23.02)	0.023	5.56 (1.28-24.18)	0.022
Presence of mucositis* (%) - Grade I - Grade II - Grade III - Grade IV	 9 (23.6) 1 (2.6) 1 (2.6) 1 (2.6)	 73 (27.5) 27 (10.0) 15 (5.5) 11 (4.0)	 0.65 (0.29-1.48) 0.19 (0.02-1.48) 0.36 (0.04-2.85) 0.49 (0.06-3.98)	 0.313 0.114 0.335 0.507		

Note. MDR = multidrug-resistant, OR= odds ratio, 95% CI = 95% confidence interval, SD = standard deviation, IQR = interquartile range, ANC = absolute neutrophil count (cells/mm^3), FN = febrile neutropaenia. * According to the WHO's oral toxicity scale (7).

Figure 1. Survival curves according to the presence of septic shock at the time of febrile neutropenia in hospitalised adult cancer patients.



MORTALITY RELATED TO COAGULASE-NEGATIVE STAPHYLOCOCCAL BACTEREMIA IN FEBRILE NEUTROPENIA: A COHORT STUDY

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Running title: Coagulase-negative Staphylococci and Mortality

ABSTRACT

Objectives: Coagulase-negative staphylococci (CoNS) are currently the most common isolates from the blood of patients with cancer and febrile neutropenia (FN). The present study sought to assess the mortality associated with bloodstream infections (BSIs) by CoNS in cancer patients with FN.

Methods: We conducted a prospective cohort study in a single tertiary hospital from October 2009 to August 2011. Follow-ups were performed on all of the adult patients who were admitted to the hematology ward with cancer and FN. Bacteraemia by CoNS was defined as 2 positive results of 2 independent cultures. Twenty-eight days after the onset of FN, the mortality rates of the patients with BSIs by CoNS were compared to those of patients with BSIs by other pathogens.

Results: In total, 169 subjects were evaluated. During the study period, 78 cases with BSIs were documented. Twenty-three BSIs (29.4%) were a result of CoNS. CoNS-induced bacteremia resulted in lower 28-day mortality compared with bacteraemia by other pathogens (4.3% vs. 32.7%; log-rank P = 0.009). In a Cox proportional hazards regression analysis, BSIs by CoNS were independently associated with lower mortality (HR, 0.09; 95% CI, 0.01 to 0.74).

Conclusions: In adult patients with cancer and FN, BSIs by CoNS are associated with lower mortality compared to BSIs by other pathogens.

Keywords: Immunocompromised host*, Staphylococcus*, bacteremia, fever, neutropenia, mortality

Introduction

INTRODUCTION

Coagulase-negative staphylococci (CoNS) are currently the most common isolates from the blood of patients with cancer and febrile neutropenia (FN) (1-3). Although bloodstream infections (BSIs) by CoNS are often considered indolent (4), their impact on the mortality of immunocompromised patients is not well established, particularly for patients with neutropenia secondary to cytotoxic chemotherapy.

Nosocomial isolates of CoNS tend to be multidrug resistant, and many are only susceptible to vancomycin (5,6). In an era of increasing antibiotic resistance, determining the actual virulence of BSIs by CoNS in the context of FN is of paramount importance for the appropriate administration of vancomycin, particularly in centres in which the prevalence of methicillin-resistant *Staphylococcus aureus* is low. The aim of this study was to evaluate the relevance of BSIs by CoNS in the mortality of adult patients with cancer and FN.

METHODS

Study design and participants

A prospective cohort study was conducted in the haematology ward of Hospital de Clínicas de Porto Alegre, Rio Grande do Sul, a teaching hospital and tertiary referral centre for bone marrow transplantation in southern Brazil. We screened all consecutive subjects admitted between October 2009 and August 2011. Patients aged ≥ 18 years, with neutropenia (absolute neutrophil count < 500 cells/mm³ or < 1000 cells/mm^3 with an expectation of decreasing to < 500 cells/mm³ during the next 48 h) and fever (a single axillary temperature measurement ≥ 38.5°C or temperature of ≥ 38.0°C sustained over a 1-h period) were eligible for this study. We excluded subjects who were only receiving palliative treatment, had an indication of outpatient treatment and had neutropenia due to an etiology in addition to the manifestation of hematological malignancies or an adverse reaction to chemotherapy. Patients were not allowed to reenter the study after a first episode of FN with documented BSI.

Definitions

Microbiological studies were performed at the onset of fever according to standards of practice and included two separate blood samples from two different sites. In the absence of an indwelling central venous catheter, the two blood sets were obtained from two distinct peripheral veins. When an indwelling central venous catheter was present, one set of samples for blood culture was obtained through an indwelling central venous catheter and another set was collected from a peripheral vein. ***S. aureus*** **was identified using** agar (blood agar and mannitol salt) via catalase and coagulase tests. CoNS were identified by Gram stain, the presence of catalase, bacitracin resistance, and the absence of free coagulase. The susceptibilities of the isolated pathogens to antibiotics were evaluated according to the recommendations of the Clinical and Laboratory Standards Institute (CLSI) (7). Bacteremia by CoNS was defined as 2 positive results of 2 independent cultures. Bacteremia in one positive culture was considered diagnostic for other pathogens. Multidrug-resistant bacteremia was defined as a BSI that was a result of methicillin-resistant *Staphylococcus* or vancomycin-resistant *Enterococcus* for gram-positive bacteria or resistance to ≥ 3 classes of antimicrobial agents for gram-negative bacteria. The Multinational Association for Supportive Care in Cancer (MASCC) Risk Index score was applied at the onset of fever to determine the risk of serious complications during FN (8); episodes were classified as high risk if the score was less than 21 points. Clinical comorbidity was defined as the presence of heart failure, diabetes mellitus, chronic pulmonary disease, chronic liver disease, or chronic renal failure. Nosocomial-acquired FN was defined as the onset of FN after 48 hours of hospitalization. Patients with FN were treated according to the 2002 guidelines of the Infectious Diseases Society of America (9). The initial antimicrobial treatment scheme was performed with β-lactam monotherapy with antipseudomonal activity; vancomycin was recommended as part of the initial empiric regimen only in cases with haemodynamic instability, suspected catheter-related infection, or infection of the skin and soft tissue. Antibiotic prophylaxis with fluoroquinolones was not administered to any patient.

Outcome and follow-up

The primary outcome of the study was mortality 28 days after the onset of FN. Patients were followed up through interviews and medical record review with a standardised data collection instrument by researchers who were not associated with the assistant physician's team. Follow-up was maintained for 28 days after fever began in neutropenic patients. Regarding patients who were

discharged before completing 28 days, follow-up phone calls were made on the 28th day after the onset of FN to determine whether they were still alive.

Statistical analysis

The chi-square and Fisher tests were used to compare categorical variables, and the Mann-Whitney U test was used to compare continuous variables. Kaplan-Meier curves were used to calculate the time-dependent occurrence of death. The log-rank test was used for comparisons between groups. We used the multivariate Cox proportional hazards model to assess mortality, and all variables that had a *P* value < 0.15 in a univariate analysis were included. In the multivariate model, independent variables were eliminated from the highest to the lowest *P* value but remained in the model if the *P* value was less than 0.05. Hazard ratios were estimated along with 95% confidence intervals. The software used for the statistical analysis was STATA version 12 (Stata Corp LP, USA).

Ethical issues

Written informed consent was obtained from all study participants. The institutional review board of Hospital de Clínicas de Porto Alegre approved the study.

RESULTS

In total, 169 patients were evaluated during the study period. During this time, 78 cases with BSIs were documented: 96.1% secondary to cytotoxic chemotherapy (75 subjects) and 89.7% occurring after 48 h of hospitalization (70 subjects). Patients with hematological malignancies comprised 82% (64 subjects) of the study population. The proportion of patients who underwent high-dose chemotherapy (induction chemotherapy or hematopoietic stem cell transplantation) was 53.8% (42 subjects). The overall 28-day mortality associated with BSIs was 24.3% (19 subjects).

Of the total number of BSIs, 23 cases (29.5%) were caused by CoNS, of which 65.2% (15 cases) were due to methicillin-resistant isolates. Other pathogens accounted for 70.5% of all BSIs (55 cases), and the predominant microorganisms were *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and *Streptococcus* spp (Table 1). The rate of BSIs caused by other multidrug-resistant

pathogens was 18.1% (10 cases), and the production of extended-spectrum beta-lactamase was the most frequent type of antimicrobial resistance (80.0%).

The characteristics of the groups of patients with BSIs by CoNS and BSIs by other pathogens are shown in Table 2. Patients with BSIs by CoNS had a higher proportion of *in vitro* resistance of blood isolates to initial antibiotic treatment compared to patients with BSIs by other pathogens. There were no differences between the two study arms with respect to age, gender, presence of clinical comorbidity, type of cancer, relapsing underlying disease status, phase of chemotherapy, absolute neutrophill count at the time of diagnosis of FN, duration of neutropenia, proportion of nosocomial-acquired episodes of FN, presence of indwelling central venous cateter, or MASCC score.

The 28-day mortality rate was significantly lower in the BSIs by CoNS group in comparison with the BSIs by other pathogens group (4.3% vs. 32.7%; log-rank $P = 0.009$) (Figure 1).

In the univariate Cox proportional hazards model, some characteristics were associated with 28-day mortality during FN (Table 3). Patients who survived were more likely to have BSIs by CoNS ($P = 0.03$) or to receive a regimen of high dose chemotherapy (0.01). Presenting with relapsing disease stages ($P = 0.01$) was significantly higher among nonsurvivors.

After the multivariate analysis was performed, the variables that constituted independent predictors for mortality were presentation with relapsing disease stages ($P = 0.008$) and high-risk MASCC score ($P = 0.02$). BSIs by CoNS were independently associated with higher survival rates ($P = 0.02$). The assessment of whether mortality was attributable to infection was concordant in all 19 patients who died.

DISCUSSION

Despite a high incidence of methicillin resistance among CoNS isolates and the lack of vancomycin during routine initial antibiotic treatment, this study demonstrated a lower 28-day mortality rate for cancer patients with FN and BSIs by CoNS compared to BSIs by other pathogens.
The analysis of the characteristics of patients with FN showed a conservative bias with regard to the hypothesis of the lower virulence of BSIs by CoNS. Both the rate of multidrug-resistance and the *in vitro* resistance of blood isolates to the initial antibiotic administered were higher in the group of

patients with BSIs by CoNS. Even so, bacteremia by CoNS was independently associated with higher survival rates.

Although some publications have demonstrated concern in relation to a trend of increasing methicillin resistance among CoNS isolates in FN (10,11), our study suggests a low virulence of CoNS, even in the context of a high prevalence of methicillin resistance and the omission of a glycopeptide from the initial empiric antimicrobial treatment. These findings are comparable with previous studies that demonstrated a relatively benign clinical course of CoNS infections related to central vein catheter infection in bone marrow transplantation recipients (12) and a lack of increase in mortality attributable to CoNS bacteraemia in noncritical patients (13). Moreover, our study results may provide a possible explanation for why randomised trials did not demonstrate a significant impact on mortality with the empiric association of glycopeptides in the initial treatment for FN (14) because CoNS represents the majority of gram-positive isolates in FN (1-3).

There are limitations to this study. Neither the initiation time of antibiotic therapy nor antimicrobial modifications during the course of FN was controlled. Furthermore, this study is susceptible to biases inherent to observational studies (selection, assessment, and confounding); however, the appropriate measurement of variables and outcomes with previously defined objective criteria, the use of standardised data collection, follow-up by a research team that was not related to care, and multivariate analysis minimised the possibility of systematic errors.

Future studies are required to assess markers of virulence of BSIs by CoNS in patients with FN and determine which patients would benefit from treatment with glycopeptides.

The appropriate use of vancomycin in patients with FN and BSIs by CoNS could be an important strategy to avoid the horizontal spread of antibiotic resistance genes to more virulent bacteria, such as *Staphylococcus aureus*.

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Conflict of Interests: The authors declare that they have no conflict of interests.

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Table 1. Microorganisms isolated in 78 patients with febrile neutropenia and bloodstream infection.

Microorganism	**No. isolated**
Coagulase-negative *Staphylococcus* spp	23
Other pathogens*	
Escherichia coli	27
Pseudomonas aeruginosa	9
Klebsiella pneumoniae	7
Streptococcus spp	5
Enterococcus faecalis	4
Enterobacter spp	2
Serratia spp	2
Candida spp	2
Salmonella spp	1
Staphylococcus aureus	1
Kocuria spp	1

Note. * There were 6 cases of polymicrobial bacteremia.

Table 2. Comparison of variables between patients with bloodstream infection (BSI) by coagulase-negative *Staphylococcus* spp and patients with BSI by other pathogens.

variables	BSIs by CoNS (n=23)	BSIs by other pathogens (n=55)	*P*
Age, mean years (SD)	47.0 (10.8)	41.4 (15.0)	0.08
Female sex (%)	10 (43.4)	27 (49.1)	0.65
Clinical comorbidity (%)	8 (34.7)	12 (21.8)	0.23
Type of Cancer			0.66 *
Acute myeloid leukemia (%)	12 (52.2)	23 (41.8)	
Acute linfoblastic leukemia (%)	3 (13.0)	9 (16.4)	
Chronic myeloid leukemia (%)	1 (4.3)	5 (9.1)	
Multiple myeloma (%)	3 (13.0)	8 (14.5)	
Lymphoma (%)	4 (17.4)	6 (10.9)	
Other solid tumors (%)	0 (0)	4 (7.3)	
Relapsing underlying disease (%)	13 (56.5)	31 (56.3)	0.99
Phase of Chemotherapy			0.39 *
Induction (%)	8 (34.8)	10 (18.2)	
Consolidation (%)	3 (13.0)	14 (25.4)	
Maintenance (%)	3 (13.0)	16 (29.1)	
HSCT (%)	9 (39.1)	15 (27.3)	
ANC at the time of diagnosis of FN, median cells/mm³ (IQR)	170 (260)	160 (290)	0.28
Median time in days to neutropenia recovery (IQR)	16 (17)	9 (11)	0.20
Nosocomial-acquired episode of FN (%)	23 (100)	47 (85.4)	0.09
Presence of an indwelling central venous cateter (%)	22 (95.6)	44 (80.0)	0.09
High risk MASCC score † (%)	8 (34.7)	21 (38.1)	0.77
In vitro resistance of blood isolates to initial antibiotic treatment (%)	15 (65.2)	14 (25.4)	0.001

Note. CoNS = coagulase-negative *Staphylococcus* spp; SD = standard deviation; HSCT = hematopoietic stem cell transplantation; ANC = absolute neutrophill count; FN = febrile neutropenia; IQR = interquartile range (P75 - P25); * chi-square test for goodness of fit; † score < 21 points.

Table 3. Univariate analysis of risk factors for 28-day mortality in febrile neutropenic patients with bloodstream infection.

variables	Survival group (n=59)	Mortality group (n=19)	HR (95%CI)	*P*
Age, mean years (SD)	43.3 (13.9)	42.2 (14.9)	0.99 (0.96 - 1.03)	0.95
Female sex (%)	29 (49.1)	8 (42.1)	0.76 (0.30 - 1.91)	0.57
Clinical comorbidity (%)	14 (23.7)	6 (31.5)	1.39 (0.53 - 3.66)	0.50
Hematological neoplasm (%)	49 (83.0)	15 (78.9)	0.68 (0.22 - 2.06)	0.50
High dose chemotherapy regimens * (%)	37 (62.7)	5 (26.3)	0.28 (0.10 - 0.79)	0.01
Relapsing underlying disease (%)	29 (49.1)	15 (78.9)	3.82 (1.26 - 11.53)	0.01
ANC at the time of diagnosis of FN, median cells/ mm^3 (IQR)	160 (260)	190 (360)	1.00 (0.99 - 1.002)	0.47
Median time in days to neutropenia recovery (IQR)	11 (13)	10 (19)	0.97 (0.92 - 1.02)	0.31
Nosocomial-acquired episode of FN (%)	55 (93.2)	15 (78.9)	0.36 (0.12 - 1.10)	0.07
High risk MASCC score † (%)	19 (32.2)	10 (52.6)	2.31 (0.94 - 5.70)	0.06
In vitro resistance of blood isolates to initial antibiotic treatment (%)	21 (35.5)	8 (42.1)	1.10 (0.44 - 2.73)	0.83
Bloodstream infection by CoNS (%)	22 (37.2)	1 (5.2)	0.11 (0.01 - 0.83)	0.03

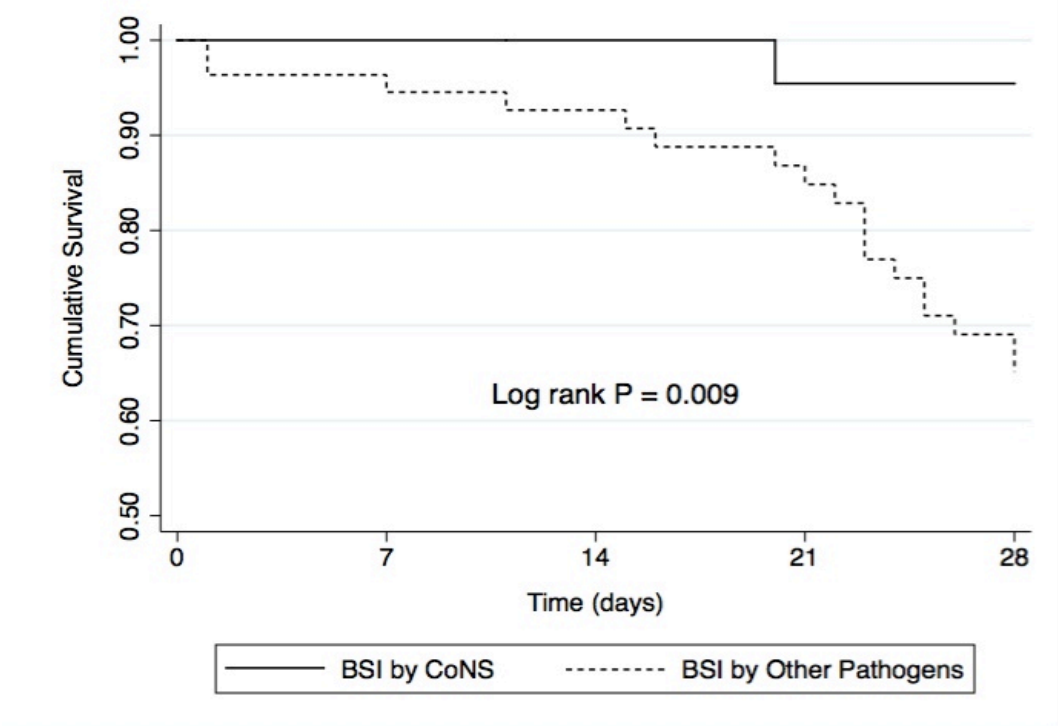
Note. HR = hazard ratio; 95% CI = 95% confidence interval; SD = standard deviation; ANC = absolute neutrophill count; FN = febrile neutropenia; IQR = interquartile range (P75 - P25); CoNS = coagulase-negative *Staphylococcus* spp; * induction or hematopoietic stem cell transplantation; † score < 21 points.

Table 4. Multivariate analysis of risk factors for 28-day mortality in febrile neutropenic patients with bloodstream infection.

variables	Adjusted HR (95% CI)	*P*
High risk MASCC score*	2.84 (1.14 - 7.06)	0.02
Relapsing underlying disease	4.46 (1.47 - 13.53)	0.008
Bloodstream infection by CoNS	0.09 (0.01 - 0.74)	0.02

Note. CoNS = coagulase-negative *Staphylococcus* spp; HR = hazard ratio; 95% CI = 95% confidence interval; * score < 21 points.

Figure 1. Survival curves of febrile neutropenic patients with bloodstream infection (BSI) by coagulase-negative Staphylococcus spp (CoNS) and BSIs by other pathogens.



7. CONSIDERAÇÕES FINAIS

As 5 publicações abordadas nesta tese trazem resultados relevantes para a prática clínica dos profissionais envolvidos no manejo de pacientes com NF.

Assim como em pacientes criticamente enfermos, o tempo de início de antibioticoterapia eficaz configura importante preditor de mortalidade em pacientes com NF secundária à quimioterapia citotóxica. A maior taxa de sobrevida dos pacientes que receberam antibioticoterapia nos primeiros 30 minutos após início da febre comparativamente com aqueles que receberam antibioticoterapia entre 30 e 60 minutos reforça a necessidade de início imediato de antibioticoterapia empírica eficaz nesta população.

Os achados de associação de períodos prolongados de internação hospitalar com neoplasia hematológica, regimes quimioterápicos de altas doses, duração da neutropenia e bacteremia por Gram-negativos também são relevantes uma vez em que estratégias voltadas para a prevenção de períodos prolongados de neutropenia e de infecção por patógenos multirresistentes podem ter impacto na redução do tempo de hospitalização e, consequentemente, na redução de custos assistenciais em pacientes com NF.

A associação de bacteremia por *Escherichia coli* e *Streptococcus* viridans com choque séptico no início da do quadro de NF ressalta a virulência destes patógenos e a importância da adequada cobertura antimicrobiana contra *Escherichia coli* e *Streptococcus* viridans nos esquemas de antibioticoterapia empírica de instituições com elevada incidência de infecções por estes patógenos.

O risco aumentado de bacteremia por patógenos multirresistentes em pacientes neutropênicos com idade avançada, períodos prolongados de neutropenia e presença de cateteres venosos centrais sugere que o uso de esquemas de quimioterapia menos tóxicos bem como a minimização do tempo de uso de cateteres venosos centrais e a intensificação de medidas de prevenção de infecções relacionadas a dispositivos venosos possam diminuir o risco de bacteremia por patógenos multirresistentes.

Por fim, cabe ressaltar que bacteremia por *Staphylococcus* coagulase-negativo, apesar de ser muito frequente em pacientes com NF, associa-se com um menor risco de morte quando comparado à bacteremia por outros patógenos, confirmando que o *Staphylococcus* coagulase-negativo possui baixa virulência mesmo em um contexto de imunossupressão.