ALESSANDRO COMARÚ PASQUALOTTO

EPIDEMIOLOGIA DAS INFECÇÕES POR *Candida* spp. NA CORRENTE SANGUÍNEA:

coorte retrospectiva em hospital terciário brasileiro

Tese apresentada ao Programa de Pós-Graduação em Medicina: Pneumologia da Universidade Federal do Rio Grande do Sul, para obtenção do grau de Doutor.

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Orientador:

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Porto Alegre

2004

Pasqualotto, Alessando Comarú
Epidemiologia das infecções por *Candida* spp. na corrente sanguínea: coorte retrospectiva em hospital terciário brasileiro/Alessandro Comarú Pasqualotto. -- Porto Alegre, 2004.
xii, 144f.

Tese (Doutorado) – Universidade Federal do Rio Grande do Sul. Faculdade de Medicina. Programa de Pós-graduação em Pneumologia.

Título em inglês: Epidemiology of bloodstream *Candida* spp. infections: retrospective cohort in a Brazilian tertiary care hospital.

1. *Candida*. 2. *Candida albicans*. 3. Candidíase. 4. Candidemia. 5. Controle de infecção. 6. Infecção hospitalar. 7. Estudo de coorte. 8. Epidemiologia.

UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL

PÓS-GRADUAÇÃO EM MEDICINA: PNEUMOLOGIA

Coordenador do Curso de Pós-Graduação: Prof. Dr. João Carlos Prolla

Dedicatória

À minha mulher, Daniela,

por sua incomparável doçura, leveza, carinho, companheirismo,

motivação e compreensão.

A meus pais, Álvaro e Clarice, por serem pais exemplares,

sempre incentivando nossa educação.

A meu irmão, Beto,

a quem sempre estive ligado por mútua admiração.

A minha nova família, Beto, Ety e Gui,

meus segundos pais e irmão.

A meu orientador, Severo,

por sua constante busca do conhecimento científico.

Agradecimentos

Ao Wagner e ao Tiago,

pelo auxílio na árdua revisão dos prontuários.

À Ana Graciela, por sua parceria na identificação das espécies de *Candida*

e nos testes de suscetibilidade aos antifúngicos.

Aos funcionários do CEDOP da Santa Casa de Porto Alegre,

em especial Jéssica e Ricardo, pela preciosa ajuda na seleção dos prontuários.

Aos colegas do Serviço de Controle de Infecção Hospitalar,

em especial a Teresa Sukiennik,

pelos ensinamentos e companheirismo na árdua tarefa de “controlar infecções”.

Sumário

Resumo

Objetivos: definir os dados demográficos, as doenças de base e os fatores de risco associados aos episódios de candidemia ocorridos na Santa Casa Complexo Hospitalar entre 17/02/1995 e 31/12/2003; identificar as espécies envolvidas nestes episódios de candidemia e determinar a mortalidade global entre estes pacientes.

Métodos: estudo de coorte retrospectivo não-controlado com inclusão de todos os casos consecutivos de candidemia diagnosticados na instituição entre 17/02/1995 e 31/12/2003. Como critério de inclusão no estudo, foi exigida a presença de sinais ou sintomas temporalmente relacionados ao isolamento de *Candida* em hemocultivo coletado de veia periférica.

Resultados: 210 pacientes com candidemia foram incluídos (infecção nosocomial em 91,0%). O sexo feminino foi mais prevalente (51,4%) e a idade mediana foi de 41,0 anos. A doença de base mais prevalente foi câncer (neoplasias sólidas 30,5% e hematológicas 9,0%). *Candida albicans* foi a espécie mais freqüente (38,1%), seguida de *Candida parapsilosis* (27,6%) e *Candida tropicalis* (15,7%); candidemia por *Candida glabrata* ocorreu em 3,8%, e por *Candida krusei*, em 2,4%. Procedimentos cirúrgicos foram realizados em 43,8%, cateter venoso central estava presente em 74,8%, cateter urinário em 57,1%, ventilação mecânica em 48,6% e nutrição parenteral em 33,8%; o número mediano de antimicrobianos foi 4,0 por paciente (glicopeptídeos 54,3%, carbapenêmicos 25,7%). A maioria dos pacientes com candidemia comunitária (52,6%) havia sido hospitalizada nos 60 dias anteriores à candidemia; em 21,1%, *Candida* foi isolada de cateter; insuficiência renal crônica ($p<0,001$) e hemodiálise ($p=0,027$) foram mais freqüentes no grupo de candidemia comunitária do que no nosocomial; a distribuição das espécies de *Candida* foi semelhante entre os grupos.

Comparadas aos adultos, as crianças com candidemia nosocomial foram mais expostas a antimicrobianos de amplo espectro (p<0,001), ventilação mecânica invasiva (p=0,002) e nutrição parenteral (p<0,001). Candidemia nosocomial por *Candida parapsilosis* foi mais freqüente em crianças (p=0,002), bem como o isolamento de *Candida* de cateteres (p=0,019); crianças foram mais freqüentemente tratadas com anfotericina B do que adultos (p<0,001), os quais receberam mais fluconazol (p=0,013). Entre os pacientes com câncer e candidemia nosocomial, tratamento prévio com corticosteróides (p=0,004), quimioterapia (p<0,001) e cefepima (p=0,004) foram mais comuns naqueles com malignidades hematológicas; cirurgias foram mais comuns em pacientes com tumores sólidos (p<0,001), principalmente do trato gastrointestinal (p=0,016); a distribuição das espécies de *Candida* foi semelhante entre os grupos. Candidemia *breakthrough* (“de escape”) ocorreu em 10,5% dos pacientes com candidemia nosocomial; a maioria destes vinha em uso de anfotericina B em doses terapêuticas, por período mediano de 6,5 dias; o isolamento de *Candida* de sítios outros que o sangue foi mais freqüente nestes pacientes (p=0,028). A mortalidade dos pacientes com candidemia foi 50,5%, sem diferenças estatisticamente significativas entre pacientes com candidemia comunitária ou nosocomial, com câncer ou outros diagnósticos e com infecção *breakthrough* ou não-*breakthrough*; a mortalidade foi maior em adultos do que em crianças (p=0,005).

Conclusões: espécies não-*Candida albicans* foram os principais agentes de candidemia; assim como em outros estudos brasileiros, a prevalência de espécies como *Candida glabrata* e *Candida krusei* foi baixa. Fatores de risco já descritos na literatura foram freqüentemente encontrados, e a distribuição dos mesmos variou de acordo com as diferentes características dos pacientes estudados. A mortalidade em pacientes com candidemia foi semelhante \à descrita na literatura.

1 INTRODUÇÃO

Espécies de *Candida* são as principais agentes de infecção fúngica, levando a um amplo espectro de manifestações clínicas, que variam desde doença mucocutânea até infecções invasivas, associadas com elevada letalidade. Os mecanismos de defesa do hospedeiro têm papel crucial na epidemiologia destas infecções; embora candidose ocorra com maior freqüência no indivíduo imunocomprometido, como exemplificado por infecções mucocutâneas recorrentes em indivíduos infectados pelo vírus da imunodeficiência humana (HIV), candidose invasiva tem sido claramente associada nas últimas décadas ao uso de múltiplos procedimentos invasivos e terapia antimicrobiana de largo espectro em pacientes imunocompetentes criticamente enfermos, muitos deles admitidos em unidades de terapia intensiva.

O termo candidemia implica a presença de *Candida* na corrente sangüínea. Historicamente, *Candida albicans* tem sido o principal agente etiológico da candidose invasiva; com base nesta observação, pouca discussão havia na literatura sobre a importância de identificar-se precisamente as espécies dos agentes da candidemia. A epidemiologia da candidemia tem, no entanto, sofrido grandes modificações nas últimas três décadas, com particular aumento na proporção de espécies não-*Candida albicans* e emergência de espécies com reduzida suscetibilidade aos antifúngicos. Embora as causas deste fenômeno sejam ainda motivo de discussão, importante papel parece ser reservado ao incremento na proporção de imunodeprimidos e ao uso disseminado de triazólicos, em especial fluconazol.

A distribuição global de espécies com reduzida suscetibilidade a imidazólicos, particularmente *Candida glabrata*, tem mostrado marcada variação entre as

diferentes regiões do mundo, reforçando a importância de estudos epidemiológicos locais. Enquanto nos Estados Unidos da América *Candida glabrata* costuma ser a segunda espécie mais prevalente, na América Latina esta tem sido pouco freqüente, ao contrário de espécies como *Candida parapsilosis e Candida tropicalis*. No Brasil, *Candida albicans* tem sido o principal agente de candidemia, seguida de *Candida parapsilosis* e *Candida tropicalis*. *Candida krusei* tem sido causa infreqüente de candidemia em todo o mundo.

O diagnóstico de candidemia é limitado pela falta de especificidade das manifestações clínicas, pela baixa sensibilidade dos métodos de hemocultivo, pela falta de utilidade dos testes sorológicos e pela indisponibilidade de testes moleculares que permitam diagnóstico precoce. Assim, torna-se especialmente importante identificar as populações mais vulneráveis à infecção e quais os fatores de risco para candidemia presentes em populações específicas. Embora estudos de caso-controle tenham definido que pacientes imunodeprimidos e aqueles admitidos em unidades de terapia intensiva estejam em maior risco de desenvolver candidemia, muitos possuem casuística limitada; além disso, há carência de estudos brasileiros abordando esta questão.

1.1 O patógeno

Embora tenham sido reconhecidas mais de 200 espécies de *Candida*, muitas destas são parte da microbiota humana habitual, e apenas cerca de 10% destas são consideradas patogênicas. [1] As principais espécies de interesse clínico são: *Candida albicans*, *Candida parapsilosis*, *Candida tropicalis*, *Candida glabrata* (anteriormente classificada como *Torulopsis glabrata*), *Candida krusei*, *Candida guilliermondii* e *Candida lusitaniae*. Entretanto, um número progressivo de casos de doenças superficiais e invasivas relacionadas a espécies emergentes de *Candida* tem sido descrito, envolvendo amostras de *Candida dubliniensis* (que pode ser confundida com *Candida albicans*), *Candida kefyr*, *Candida rugosa*, *Candida famata*, *Candida utilis*, *Candida lipolytica*, *Candida norvegensis* e *Candida inconspicua*, entre outras. [2]

As diferentes espécies de *Candida* têm sido isoladas do solo, de superfícies hospitalares, de objetos inanimados e de alimentos. Os microorganismos são parasitas habituais de humanos, e são comumente encontrados na pele e nos tratos gastrointestinal, genitourinário e respiratório. *Candida albicans* é a mais abundante espécie em humanos. [1]

1.2 Aspectos históricos

Embora os primeiros relatos escritos de lesões orais compatíveis com candidose datem da época de Hipócrates e Galeno, a história das infecções por *Candida* é relativamente recente: apenas em 1861 foi descrito o primeiro caso de infecção invasiva por *Candida*, e endocardite por *Candida* foi descrita em 1940. [3] Até as décadas de 60-80, candidose disseminada era considerada uma doença rara, [4,5] ocorrendo predominantemente em pacientes cirúrgicos, com queimaduras graves ou vítimas de trauma, [6,7] e em pacientes gravemente neutropênicos, com leucemia ou linfoma. [8]

O grande marco na história das infecções por *Candida* ocorreu com a introdução do uso disseminado de antibacterianos; desde então, têm sido descritas manifestações previamente não documentadas de candidose, e a incidência de praticamente todas as formas de infecção por *Candida* tem se elevado.

1.3 O aumento na incidência de candidemia

Em estudo de bacteremia e fungemia realizado no *Boston City Hospital* em sete anos selecionados entre os períodos de 1935 a 1972, não foi detectada infecção por *Candida* spp. nos primeiros 3 anos de estudo (1935, 1941 e 1947). Nos três anos seguintes (1953, 1961 e 1969), a taxa de infecção por *Candida* permaneceu estável entre 3,5-3,9% dos microorganismos isolados em hemocultivo; no último ano de estudo (1972), a freqüência se elevou para 9%. [9]

Entre o período de 1970 a 1979, dados do sistema norte-americano NNIS (*National Nosocomial Infections Surveillance*) [10] documentaram ter havido aumento persistente nas taxas de infecções na corrente sanguínea. Enquanto *Candida* spp. não figurava entre os dez agentes etiológicos mais freqüentes dessas infecções em 1975, em 1983 elas apareceram em sexto lugar (5,6%). Em adição, dados do programa de vigilânca epidemiológica de infecções hospitalares do estado norte-americano da Virgínia, abrangendo 112 hospitais, documentaram ter havido aumento significativo na incidência de candidemia entre os anos de 1978 e 1984. [11]

Entre os anos de 1980 e 1982, dados de 60 hospitais norte-americanos mostravam que as espécies de *Candida* representavam 4,5% das etiologias de infecções hospitalares e 4,7% das infecções hospitalares na corrente sanguínea. Os microorganismos do gênero foram apontados como a nona causa de infecções na corrente sanguínea nos hospitais de ensino. [12] Dados do NNIS de 1983 mostraram que 5,6% das infecções na corrente sanguínea foram causadas por *Candida* spp.; a taxa de candidemia hospitalar aumentou mais de duas vezes entre os anos de 1980 e 1984. [13] Em meados da década de 80, muitas Instituições, incluindo unidades de oncologia, hospitais universitários e comunitários relataram que os fungos estavam se tornando patógenos comuns em infecções nosocomiais. [14-17]

Entre 1980 a 1990, foi descrito nos Estados Unidos da América um constante aumento na taxa de infecções fúngicas nosocomiais. A proporção de infecções nosocomiais devidas a fungos aumentou de 6,0% em 1980 para 10,4% em 1990 em todos os principais sítios de infecção nosocomial: infecção de síto cirúrgico, pneumonia, infecção do trato urinário e infecção na corrente sangüínea. [18] A maioria das infecções fúngicas nosocomiais foram causadas por espécies de *Candida*. [18,19] A taxa de infecção fúngica variou entre os diferentes serviços de hospitais pertencentes ao sistema NNIS, tendo sido maior em unidades de queimados e de pacientes vítimas de trauma, cirurgia cardíaca, oncologia, berçários de alto risco e cirurgia geral. Vale salientar que os hospitais participantes do sistema NNIS são amiúde hospitais de grande porte e universitários, em geral atendendo a pacientes com risco maior de infecções nosocomiais quando comparados à média dos hospitais norte-americanos. Entretando, os dados sugerem que, embora as infecções fúngicas possam ser mais comuns em hospitais universitários, o aumento na incidência destas infecções pôde ser evidente em todos os tipos de hospitais. [20]

O programa SCOPE (*Surveillance and Control of Pathogens of Epidemiologic Importance*) [21,22] foi desenvolvido para avaliar os patógenos predominantes e os padrões de suscetibilidade destes em amostras de sangue de aproximadamente 50 centros médicos nos Estados Unidos da América. Os hospitais participantes incluíam Instituições de vários tamanhos (de 60 a 1200 leitos), pertencentes a regiões geográficas diversas. Durante os 14 meses de estudo (abril de 1995 a junho de 1996), um total de 4.725 infecções na corrente sangüínea foram relatadas pelos participantes do SCOPE. C*andida* spp. foi o quarto patógeno mais comumente isolado, correspondendo a 8% de todas as infecções na corrente sangüínea. [21,22] Em muitos grandes hospitais norte-americanos, as espécies de *Candida* tornaram-se responsáveis por 8-15% de todas estas infecções. [23,24]

Embora as taxas de infecções na corrente sanguínea causadas por *Candida* tenham se elevado na década de 1980, recentes evidências sugerem que esta tendência pode estar sendo revertida. Na avaliação de 2.759 episódios de candidemia (dados do sistema NNIS referentes a candidemia em pacientes internados em unidade de terapia intensiva entre os anos de 1989 e 1999), [25] *Candida albicans* foi a espécie mais comum (59%), seguida de *Candida glabrata* (12%), *Candida parapsilosis* (11%), *Candida tropicalis* (10%) e *Candida krusei* (1,2%). O estudo mostrou ter havido uma significativa diminuição na incidência de infecções causadas por *Candida albicans*, possivelmente devido ao maior uso de fluconazol e à melhora nas práticas de controle de infecção (visto que as taxas de infecção bacteriana isolada na corrente sanguínea também diminuíram). No mesmo período, a incidência de candidemia por espécies não-*Candida albicans* permaneceu estável, com aumento significativo na incidência de infecções por *Candida glabrata*.

Embora grande volume de publicações tenha sido gerado sobre as mudanças epidemiológicas ocorridas nos Estados Unidos da América, as alterações não ficaram restritas a este país. No Canadá, por exemplo, foi realizado um estudo em um hospital-escola terciário entre os anos de 1976 e 1996. [26] Enquanto nos primeiros 15 anos o percentual de isolados de *Candida* spp. na corrente sangüínea manteve média inferior a 2%, após 1991 houve um marcado aumento na incidência de candidemia, de modo que o gênero *Candida* passou a ser a quarta etiologia mais freqüente destas infecções (6% do total). Na Europa, a realidade é semelhante. [27,28] Na Eslováquia, um estudo nacional realizado em 71 hospitais [29] entre 1989 e 1998 mostrou um aumento considerável na incidência das infecções por *Candida* spp.: nos três primeiros anos, foram relatados menos de 10 casos por ano, passando a 22-27 casos nos próximos quatro anos e a 41, 66 e 65 casos, respectivamente, nos anos de 1996, 1997 e 1998. Na Noruega, os dados indicam que a incidência de

candidemia tem aumentado desde o final dos anos 70, permanecendo estável após o início da década de 90. [30] Estudos asiáticos têm também demonstrado aumento na incidência de infecções disseminadas por *Candida*. Na Índia, um estudo realizado em um hospital terciário (1981-1990) [31] mostrou que, nos cinco últimos anos do estudo, houve um aumento de 11 vezes na taxa de candidemia, quando comparado aos anos iniciais. Em Taiwan, houve um aumento de 27 vezes na taxa de candidemia entre 1980 e 1994 no *National Taiwan University Hospital*; desde 1993, *Candida* spp. tem se tornado uma causa muito comum de infecção nosocomial associada à corrente sangüínea.[32]

1.4 A emergência de espécies não-*Candida albicans*

Entre as espécies do gênero *Candida* associadas a candidemia, historicamente *Candida albicans* tem sido a mais prevalente, responsável por 51-70% dos casos. [33-35] Entretanto, em adição ao aumento na incidência da candidemia, observou-se, nas últimas décadas, marcado aumento na freqüência de infecções causadas por espécies não-*Candida albicans*, particularmente *Candida glabrata*. [30,36-40] Uma possível explicação para a emergência dessas espécies é a seleção de populações menos suscetíveis por pressão exercida pelo uso de antifúngicos; o uso disseminado de imidazólicos, em especial fluconazol, tem sido implicado por vários autores como o principal responsável por estas mudanças. [36,37,41-43] Esta associação é, no entanto, controversa, não parecendo ser a única explicação para o fenômeno; em dois grandes estudos multi-institucionais, o uso profilático de fluconazol não levou a um aumento na colonização nem na infecção por espécies não-*Candida albicans*. [44,45] Ainda, a emergência de *Candida glabrata* foi também descrita em hospitais públicos brasileiros onde o uso de fluconazol é pouco acentuado. [46,47]

As três espécies não-*Candida albicans* mais prevalentes costumam ser *Candida glabrata*, *Candida tropicalis* e *Candida parapsilosis*. [10] Nos estudos norte-americanos, *Candida glabrata* tem sido a segunda espécie mais prevalente, responsável por 20-25% dos episódios de candidemia, [24,38,48,49] enquanto que *Candida tropicalis* costuma ter prevalência menor, em média 10%; [49-52] poucos hospitais têm relatado taxas de infecção por *Candida tropicalis* entre 15-20%. [36-38,53] Enquanto a prevalência de cepas de *Candida parapsilosis* tem sido entre 10-20%, a de *Candida krusei* tem sido mais baixa (menor que 4%). [30]

Dados do programa norte-americano SCOPE [22] (1995-1996) mostraram que *Candida albicans* foi responsáveis por 52% dos isolados de *Candida* em

hemocultivo; entre as infecções por espécies não-*Candida albicans*, cita-se *Candida glabrata* (20%), *Candida tropicalis* (11%), *Candida pasapsilosis* (8%), *Candida krusei* (5%) e *Candida* spp. (4%).

Em estudo multicêntrico europeu sobre candidemia, [28] embora *Candida albicans* tenha sido a espéce predominante, outras espécies foram responsáveis por 43,6% dos episódios; entre estas, *Candida parapsilosis* foi freqüentemente isolada de crianças prematuras, enquanto *Candida glabrata* foi mais freqüente em pacientes cirúrgicos e indivíduos com tumores sólidos. *Candida tropicalis* foi prevalente em pacientes com malignidades hematológicas. Como um grupo, espécies não-*Candida albicans* predominaram em pacientes com malignidades hematológicas (2/3 dos casos).

Em estudo prospectivo sueco, realizado entre janeiro de 1998 e dezembro de 1999, [54] *Candida albicans* foi o agente de 67,0% dos 191 casos de candidemia, seguida por *Candida glabrata* (15,7%), *Candida parapsilosis* (7,3%) e *Candida tropicalis* (2,1%). Candidemia por espécies não-*Candida albicans* foi mais freqüente em pacientes com malignidades hematológicas (56%), comparado com pacientes cirúrgicos (30%) ou admitidos em unidade de terapia intensiva (19%).

O declínio na prevalência de *Candida albicans* tem também sido notado em relatos de algumas Instituições individuais. Entre 1992 e 1998, em um hospital australiano, ocorreu progressivo declínio na incidência de infecções na corrente sanguínea por *Candida albicans*, com concomitante aumento na incidência de candidemia por outras espécies. [55] De modo geral, a freqüência de infecções corrente sanguínea permaneceu inalterada. Este achado foi confirmado em estudo multicêntrico australiano conduzido entre 1995 e 1998.[56]

Estudo analisando 6.082 amostras de *Candida* enviadas para a Universidade de Iowa mostrou haver grandes diferenças geográficas na distribuição das espécies

de *Candida* causadoras de candidemia. [57] A freqüência de *Candida albicans* variou de 46,6% na América Latina a 73,5% na região da Ásia-Pacífico. Dentro de cada principal região geográfica, houve também grandes variações na freqüência de infecções por *Candida albicans*: na região da Ásia-Pacífico, variou de 28,6% (Malásia) a 81,3% (África do Sul); na Europa, de 45,2% (Alemanha) a 79,3% (Suíça); na América Latina, de 33,3% (Colômbia) a 61,0% (Chile). *Candida glabrata* foi menos comum na América Latina (7,5%, variando de 0,0% a 12,2%) e mais comum no Canadá (20,1%) e nos Estados Unidos da América (18,3%). *Candida parapsilosis* foi mais comum do que *Candida glabrata* como causa de candidemia na Europa e na América Latina, e foi a terceira espécie mais comum nas regiões da Ásia-Pacífico, Canadá e Estados Unidos da América.

Desta forma, a freqüência de candidemia devida a espécies não-*Candida albicans* tem variado amplamente entre as diferentes Instituições (de 14 a 100%), [37] o que pode ser reflexo de múltiplos fatores, como população estudada (em especial a presença de malignidades hematológicas) e uso prévio de antimicrobianos, quimioterapia citotóxica e antifúngicos. Deve-se reforçar a importância da adequada identificação das espécies de *Candida* isoladas, além de regularmente montitorar os padrões de suscetibilidade das mesmas.[22,58]

1.5 Estudos multicêntricos realizados na América Latina

Em estudo multicêntrico randomizado, [59] originário de estudo clínico desenhado para avaliar a eficácia de caspofungina versus anfotericina B desoxicolato, [60] descreveu-se a distribuição global das espécies de *Candida* em pacientes com candidose invasiva. Houve diferença significativa na distribuição dos patógenos em diferentes áreas do mundo (p=0,002). *Candida albicans* foi a espécie mais comumente identificada em todas as regiões, embora menos de metade dos casos tenham sido causadas por esta espécie. *Candida parapsilosis* e *Candida tropicalis* foram responsáveis, respectivamente, por 30% e 25% dos isolados na América Latina, mas apenas 11% e 14% dos isolados na América Anglo-Saxônica. Por outro lado, *Candida glabrata* foi mais comumente isolada nos Estados Unidos da América e no Canadá (18%) do que na América Latina (3%) ou na Europa e na Rússia (8%). Neste estudo, *Candida parapsilosis* foi a segunda espécie mais freqüente na América Latina.

Dados do SENTRY [49,61] – estudo multicêntrico de vigilância de infecções na corrente sanguínea causadas por espécies de *Candida* – revelaram que, em contraste com os Estados Unidos da América, *Candida glabrata* foi muito incomum na América Latina (6% dos isolados; $p \leq 0,01$ em comparação com os dados norte-americanos), enquanto *Candida parapsilosis* foi a segunda espécie mais freqüente nesta região ($p \leq 0,001$, comparado com dados norte-americanos). *Candida krusei* foi uma espécie pouco encontrada em todas as áreas geográficas (1-2%). Os dados do SENTRY mostraram que isolados obtidos da América Latina e do Canadá foram geralmente mais suscetíveis aos triazólicos do que os isolados obtidos dos Estados Unidos da América, [49] reforçando a importância de se documentar dados epidemiológicos locais.

Em estudo prospectivo multicêntrico envolvendo cinco hospitais terciários de quatro países latino-americanos, *Candida albicans* foi responsável por 41,7% dos episódios de candidemia, seguida de *Candida tropicalis* (24,2%), *Candida parapsilosis* (21,3%) e *Candida glabrata* (7,7%). A maioria dos isolados de *Candida* foi sensível a todos os antifúngicos testados. [63]

1.6 Estudos realizados no Brasil

Os estudos brasileiros sobre candidemia são pouco numerosos. O primeiro estudo multicêntrico realizado no Brasil envolveu 145 casos de candidemia em seis hospitais-escola de atendimento terciário entre 1995 e 1996. [47] Neste estudo os autores observaram que, embora *Candida albicans* tenha sido a espécie mais comum, houve predomínio de espécies não-*Candida albicans* que, como um grupo, foram responsáveis por 63,4% dos casos (*Candida parapsilosis* 24,8% e *Candida tropicalis* 24,1%). A mortalidade foi de 50,0%. Em outro estudo epidemiológico reunindo dados sobre infecções na corrente sanguínea em quatro hospitais da cidade de São Paulo durante período de 12 meses (março de 2002 a fevereiro de 2003), *Candida* spp. respondeu por 4,3% do total das infecções na corrente sanguínea, de um total de 7.038 episódios de bacteremias e fungemias avaliados. [64]

Em um estudo realizado em três hospitais na cidade do Rio de Janeiro envolvendo 33 pacientes com câncer e candidemia, [65] *Candida tropicalis* foi o agente etiológico em 48,5% dos casos de fungemia, seguida de *Candida parapsilosis* (18,2%) e *Candida albicans* (15,2%). Nenhum paciente teve fungemia por *Candida glabrata* neste estudo, onde a mortalidade foi de 36,4%.

Em outro estudo, avaliando o perfil de sensibilidade aos antifúngicos de 200 isolados de *Candida* spp. seqüencialmente obtidos de pacientes com candidemia admitidos em cinco hospitais terciários brasileiros, [66] *Candida albicans* foi a espécie mais freqüente (41,5%), seguida de *Candida tropicalis* (24,0%) e *Candida parapsilosis* (20,5%). *Candida glabrata* e *Candida krusei* foram espécies infreqüentes (4,5% e 1,0%, respectivamente). Apenas três cepas foram resistentes ao fluconazol (duas cepas de *Candida krusei* e uma de *Candida glabrata*), novamente reforçando a idéia de que os episódios de candidemia em hospitais

públicos brasileiros são representados principalmente por espécies não-*Candida albicans* sensíveis a fluconazol.

Uma série prospectiva realizada no Hospital de Clínicas de São Paulo entre 1994 e 1996 incluiu 86 pacientes consecutivos com fungemia nosocomial. [67] *Candida albicans* foi o principal agente neste estudo (50,0%), seguida de *Candida parapsilosis* (17,4%), *Candida tropicalis* (11,6%) e *Candida guilliermondii* (9,3%). *Candida glabrata* e *Candida krusei* foram responsáveis por 2,3% e 1,2% dos casos, respectivamente. Neste estudo, a mortalidade foi maior em pacientes infectados por *Candida tropicalis* (70,0%) que em pacientes com fungemia por outras leveduras (41,0%).

No período de junho de 1994 e junho de 1998, foram identificados 185 episódios de candidemia nosocomial no Hospital São Paulo e no Hospital Universitário Clementino Fraga Filho, Rio de Janeiro. [68] Entre os adultos incluídos no estudo (n=121), *Candida albicans* foi a principal espécie (35,5%), seguida de *Candida tropicalis* (24,8%), *Candida parapsilosis* (19,0%) e *Candida glabrata* (5,8%); entre as crianças (n=64), as espécies mais prevalentes foram *Candida albicans* (35,9%), *Candida parapsilosis* (28,1%), *Candida tropicalis* (15,6%) e *Candida guilliermondii* (14,1%). A mortalidade foi de 45,0%, maior entre os pacientes não tratados com antifúngicos e naqueles onde o cateter venoso central não foi removido; menor mortalidade foi observada nas infecções por *Candida parapsilosis*.

Durante período de 21 meses, um estudo avaliou através de hemocultura (lisecentrifugação) a etiologia de síndromes febris durando mais de três dias em 111 pacientes adultos com síndrome da imunodeficiência adquirida avançada (definida como contagem de células CD4 $\leq$ 200 células/mm^3) hospitalizados em três hospitais terciários da cidade de São Paulo. [69] Entre as etiologias identificadas de infecção

relacionada à corrente sanguínea, apenas 19,6% deveram-se a fungos (6,5% *Candida albicans*, 6,5% *Cryptococcus neoformans* e 6,5% *Histoplasma capsulatum*).

Pouca informação é também disponível sobre candidemia em crianças brasileiras. Avaliando as leveduras isoladas do sangue (n=59) e de cateteres (n=21) de crianças com idades entre 0-7 anos admitidas em hospital público pediátrico na cidade de São Paulo, no período de 1998 e 1999, [70] os autores documentaram que *Candida parapsilosis* foi a espécie mais prevalente (35,0%), seguida de *Candida albicans* (20,0%), *Candida tropicalis* (13,8%), *Candida glabrata* (13,8%), *Candida guilliermondii* (8,8%), *Trichosporon cutaneum* (6,2%) e *Candida krusei* (2,5%).

A mortalidade em estudo que avaliou 40 crianças com candidemia nosocomial admitidas no Hospital Infantil Darcy Vargas, São Paulo, foi de 57,5%. [71] Neste estudo, *Candida albicans* foi a espécie mais comumente isolada (60,0%), seguida de *Candida tropicalis* (22,5%), *Candida parapsilosis* (10,0%), *Candida krusei* (5,0%) e *Candida guilliermondii* (2,5%). Foi selecionado um controle para cada paciente com candidemia. À análise multivariada, obteve-se duas variáveis preditoras de infecção fúngica: a presença de candidose oral e/ou perineal (razão de chances 4,3) e a utilização de cinco ou mais antimicrobianos (razão de chances 11,3). Comparando-se com estudo anteriormente realizado na mesma Instituição, [70] os autores documentaram ter havido aumento significativo na incidência de candidemia. Em outro estudo retrospectivo, realizado entre 1991 e 1994 em unidade de terapia intensiva neonatal de São Paulo, [72] documentou-se aumento na incidência das infecções por *Candida* de 1,3% (1991) para 3,2% (1994). A mortalidade em recém-nascidos com candidemia foi de 71,4%, superior à mortalidade de 50,0% encontrada em pacientes com sepse bacteriana.

Os estudos realizados no estado do Rio Grande do Sul são também escassos. Em estudo retrospectivo conduzido entre 1996 e 1999 no Hospital de

Clínicas de Porto Alegre (n=101), [73] *Candida albicans* foi responsável por 32,6% dos episódios de candidemia, seguida de *Candida tropicalis* (26,7%), *Candida parapsilosis* (23,7%), *Candida glabrata* (8,9%), *Candida lusitaniae* (2,9%), *Candida krusei* (1,9%), *Candida famata* (1,9%) e *Candida rugosa* (0,8%). Na Santa Casa de Porto Alegre, estudou-se a etiologia da candidemia e a sensibilidade aos antifúngicos durante o período de agosto de 2002 a agosto de 2003. [46] Neste estudo (n=120), espécies não-*Candida albicans* foram responsáveis por 51,6% dos episódios, principalmente *Candida parapsilosis* (25,8%) e *Candida tropicalis* (13,3%). Espécies menos freqüentes foram *Candida glabrata* (3,3%), *Candida krusei* (1,7%), *Candida famata* (1,7%), *Candida sake* (1,7%), *Candida guilliermondii* (1,7%), *Candida lusitaniae* (0,8%), *Candida dubliniensis* (0,8%) e *Candida lipolytica* (0,8%). Resistência aos antifúngicos não foi encontrada neste estudo.

1.7 Dificuldades diagnósticas

O diagnóstico de candidemia é difícil. Embora o isolamento da *Candida* no sangue de pacientes com sinais e sintomas temporalmente relacionados ao evento estabeleça o diagnóstico, [48,74,75] a hemocultura é um marcador de baixa sensibilidade, [75] com elevada taxa de resultados falso-negativos. [76] Os microorganismos crescem bem em frascos de hemocultura de rotina e em placas de ágar, não requerendo meio especial para cultivo. Entre os métodos de hemocultivo, embora alguns estudos tenham mostrado haver sensibilidade semelhante entre os métodos automatizados bifásicos e a lisecentrifugação no diagnóstico de candidema, [77,78] outros demonstraram a superioridade da lisecentrifugação. [79,80] O diagnóstico definitivo de infecção disseminada por *Candida* pode também ser estabelecido através da demonstração histopatológia de invasão tecidual pelos microorganismos. [75]

Com base no exame clínico, biópsia de lesões cutâneas suspeitas pode facilitar o dianóstico de candidose disseminada. O exame de fundo de olho é também muito importante em pacientes com candidemia, podendo mostrar alterações sugestivas de endoftalmite endógena por *Candida* em até metade dos casos. [81]

Na busca de um diagnóstico precoce de candidemia, métodos não baseados em cultura estão sendo desenvolvidos, incluindo dosagem de D-arabinitol, razão de D-arabinitol para L- arabinitol, detecção de antígenos, teste G e teste de reação em cadeia da polimerase (PCR); [77,82] nenhum destes, no entanto, é no momento aplicável na prática clínica. Esforços para a detecção de anticorpos em pacientes com candidose são limitados por dois motivos principais: primeiro, a colonização por espécies de *Candida* do trato gastrointestinal ou de outros sítios pode levar a

resposta sorológica no indivíduo não infectado; segundo, pacientes imunocomprometidos podem não demonstrar resposta detectável de anticorpos, mesmo em infecções invasivas por *Candida*. [82]

Devido à elevada letalidade da candidemia, que usualmente ocorre em pacientes criticamente enfermos, o início do tratamento não deve aguardar pela identificação definitiva do fungo nos exames culturais. Para tanto, é muito importante que se caracterize adequadamente as populações e as situações de maior risco para candidemia.

1.8 Fatores de risco

A fonte da infecção sistêmica por *Candida* tem sido motivo de considerável debate: enquantos muitos dados favorecem que a aquisição do fungo possa ser exógena, a partir da pele, [83-85] outros sugerem que o trato gastrointestinal seja a principal fonte da infecção. [86] Argumentos favorecendo a aquisição exógena incluem a freqüente associação de candidemia com o uso de cateteres intravenosos, particularmente com cateteres muito manipulados ou em pacientes sob tratamento com nutrição parenteral, e a associação entre o uso de cateteres intravenosos e infecções por *Candida parapsilosis*. [87,88] Estima-se que 25-80% das candidemias sejam relacionadas a cateteres venosos centrais. [1] Em uma revisão da literatura, [89] os autores concluíram que, apesar da carência de estudos para definir a questão, os dados disponíveis (estudos experimentais, clínicos e de base molecular) sugerem que o trato gastrointestinal seja a principal origem da infecção disseminada. É possível que a perda da integridade do trato gastrointestinal devida a cirurgias, doenças ou a quimioterapia citotóxica crie uma porta de entrada por onde o fungo possa atingir a corrente sangüínea. [86] Disseminação sistêmica de *Candida* a partir de infecção do trato urinário baixo é evento raro, ocorrendo amiúde em pacientes com obstruções na via urinária. [90,91] Assim, é possível que ambas as vias contribuam para a gênese da candidemia; casos individuais podem estar relacionados a uma ou outra fonte.

Numerosos estudos têm identificado fatores de risco para o desenvolvimento de infecções sistêmicas por *Candida*. A maioria destes fatores foram identificados em pacientes imunocompetentes criticamente enfermos; [1] muitos deles são fatores comuns a pacientes hospitalizados, sendo assim difícil determinar quais os indivíduos se encontram em maior risco para o desenvolvimento da infecção. A

população de pacientes mais comumente afetados são aqueles com doenças neoplásicas malignas, pacientes com cursos pós-operatórios complicados e pacientes queimados; entre os pacientes com câncer, a associação mais comum tem sido com leucemia aguda. [8,27] Estudos indicam que 10-40% dos pacientes que morrem com leucemia aguda têm evidência de doença fúngica disseminada à autopsia, e que os fungos são a causa de morte em cerca de um quinto destes pacientes. [8,92-94]

Em estudo clássico de fatores de risco para candidemia nosocomial, publicado em 1989, [95] foram identificados 28 potenciais fatores de risco à análise univariada; após regressão logística múltipla, foram identificadas 4 variáveis que melhor prediziam candidemia: número de antimicrobianos prescritos (razão de chances 1,7), uso prévio de cateter de Hickman (razão de 7,2), isolamento de *Candida* em outro sítio (razão de chances 10,3) e hemodiálise prévia (razão de chances 18,3). Este estudo, no entanto, pareou casos e controles por procedimentos cirúrgicos, de modo que esta variável não pôde ser identificada como fator de risco.

Os principais fatores de risco para candidemia são apresentados a seguir. Alguns destes fatores foram identificados apenas na análise univariada, e muitos deles são fatores comuns às infecções hospitalares por outros agentes, como bacilos gram-negativos multi-resistentes, *Staphylococcus aureus* meticilino-resistentes, enterococos resistentes a glicopeptídeos e *Clostridium difficile*: [96]

Colonização

Prévia colonização por *Candida* spp. é um dos principais fatores de risco para candidemia na maioria das séries que estudaram esta variável. [17,95,97-107] Vários elementos suportam a colonização como importante fator para subseqüente infecção: o crescimento acentuado de *Candida* spp. em espécimes obtidos da cavidade peritoneal pode predizer infecção subseqüente; [106,108] grande quantidade de *Candida* spp. nas fezes em pacientes com câncer e em neonatos de baixo peso foi também identificado como fator de risco significativo para candidemia, [1,101] assim como colonização de múltiplos sítios corporais é fator de risco independente para infecção invasiva. [1,95,99,101] Embora apenas 5-15% dos pacientes hospitalizados estejam colonizados por *Candida* à admissão, [1] a proporção de indivíduos colonizados pode chegar a mais de 80% durante permanência prolongada em unidade de terapia intensiva. [109] Por outro lado, mesmo que a taxa de colonização seja elevada em nestes indivíduos, a freqüência de infecção fúngica invasiva é bastante baixa, [109-111] reforçando a importância de outros fatores de risco.

Uso de antimicrobianos

Exposição prévia ou concomitante a antimicrobianos é um dos principais fatores de risco para candidemia. [95,97,99,101,112-114] Embora potencialmente associado com qualquer agente, a pressão de seleção parece ser mais pronunciada com o uso de cefalosporinas e com o uso de drogas com atividade contra anaeróbios. Quanto maior o espectro e duração da terapia antimicrobiana, maior parece ser o risco. [1,104]

Neutropenia

Como adequada função dos neutrófilos é um componente essencial da defesa do hospedeiro contra fungos, quimioterapia e neutropenia são fatores de risco constantemente identificados. O risco de infecção fúngica parece ser maior com neutopenia prolongada ou muito acentuada. [41,97-101,103]

Cateter venoso central

Como anteriormente referido, há forte associação entre candidemia e uso de cateteres venosos centrais, especialmente nas infecções por *Candida parapsilosis*. [83-85,87,88,95,97,99,114] Em alguns estudos, nutrição parenteral foi associada com aumento significativo no risco de candidemia, particularmente no contexto de surtos. [41,42,97,99,114-117]

Corticoterapia

O uso de corticosteróides tem sido associado com o desenvolvimento de candidemia. [41,95,97,103,118] Corticoterapia pode também predispor o paciente a candidemia *breakthrough* (“de escape”), possivelmente por supressão da função de neutrófilos e macrófagos ou por aumentar a colonização fúngica no tubo digestivo, como demonstrado em modelos experimentais. [103] Ainda, em modelos animais, a administração de corticosteróides pode elevar a freqüência de disseminação hematogênica de espécies de *Candida*. [103]

Procedimentos cirúrgicos

Cirurgias, especialmente aquelas envolvendo o trato gastrointestinal, foram associadas em vários estudos a maior risco de candidemia. [1,41,99,102,111,115,119,120] Em uma série, mais de metade dos episódios de candidemia ocorrem em pacientes cirúrgicos criticamente enfermos. [121]

Outros fatores

Outros fatores de risco para candidemia incluem queimadura extensa, [99] presença de cateter urinário, [95,97] diarréia, [97] íleo, [97] baixo peso ao nascimento, [102] múltiplas transfusões, [95] sangramento gastrointestinal, [97] uso de antiácidos ou bloqueadores H2, [97,102] insuficiência renal ou hemodiálise, [95,97,115,119] dieta enteral, [101,113,122] idade, [1,99,123] insuficiência hepática, [113,122] transplante, [119] transferência de casa geriátrica, [97] cateter arterial, [124] ventilação mecânica [95,97,99,101,102,114,122] duração da internação (especialmente permanência prolongada em unidade de terapia intensiva), [95,97,102,125] escores de gravidade elevados, [41,97,100,102,104,123] bacteremia prévia [126] e diabete melito. [126]

1.9 Mortalidade em pacientes com candidemia

1.9.1 Mortalidade geral

Em diferentes estudos, a taxa global de mortalidade em pacientes com candidemia (mortalidade crua) tem variado de 40 a 75%, o que parece ser importantemente influenciado pela doença de base do paciente. [16,17,24,42,47,48,53,127-134] Preditores de pior desfecho em pacientes com candidemia incluem presença de choque séptico, [135] disfunção multi-orgânica, [134] escores elevados de gravidade no momento da candidemia (como APACHE II ou APACHE III), [117,126,136-138] neutropenia, [117,136,138,139] doença disseminada, [117,138] permanência em unidade de terapia intensiva, [133,138] corticoterapia, [136] longa duração da candidemia, [133] idade avançada, [133,139,140] terapia antifúngica inadequada (atraso, inadequação ou ausência de tratamento), [133,136,137,140,141] não remoção do cateter venoso central [133,136,140] e candidemia por espécie outra que *Candida parapsilosis*. [140,142]

Ainda, é importante comentar que a mortalidade encontrada na prática clínica costuma ser maior do que aquela relatada em estudos clínicos, onde taxas de resposta superiores a 70% têm sido documentadas; [35,60] estas diferenças podem ser explicadas pela seleção natural de pacientes incluídos em estudos clínicos.

1.9.2 Mortalidade atribuível

Investigadores da Universidade de Iowa previamente estimaram a mortalidade atribuível à candidemia em 38%, em estudo de pacientes hospitalizados entre 1983 e 1986, [3,143] um estudo clássico amplamente citado na literatura médica. Mortalidade atribuível à candidemia foi definida como o excesso de óbitos devido à candidemia, expresso pela subtração da mortalidade global em pacientes com candidemia e de controles pareados. No entanto, o uso de antifúngicos e a epidemiologia das infecções por *Candida* em hospitais terciários tiveram grandes mudanças desde esta publicação. Em recente estudo retrospectivo, usando a mesma metodologia do anterior, [130] a mortalidade atribuível à candidemia foi de 49%, com um intervalo de confiança de 95% de 38-60%. Desta forma, a despeito de vários avanços ocorridos nas últimas duas décadas, esses parâmetros não parecem ter mudado significativamente nesse período.

2. OBJETIVOS

2.1 Objetivos gerais

2.1.1 Descrever os dados demográficos, as doenças de base e os fatores associados aos episódios de candidemia ocorridos na Santa Casa Complexo Hospitalar entre o período de 17/02/1995 e 31/12/2003;

2.1.2 Identificar as espécies de *Candida* envolvidas nesses episódios de candidemia;

2.1.3 Determinar a mortalidade global entre os pacientes com candidemia nessa Instituição.

2.2 Objetivos específicos

2.2.1 Candidemia comunitária

2.2.1.a Determinar, nos pacientes com candidemia, o percentual de episódios que ocorreram na comunidade e no ambiente hospitalar;

2.2.1.b Descrever as doenças de base e a presença de fatores de risco no grupo de pacientes com candidemia comunitária e nosocomial;

2.2.1.c Comparar a distribuição dos fatores de risco, das doenças de base, das espécies de *Candida* relacionadas aos episódios de candidemia e o desfecho da infecção entre os pacientes com candidemia nosocomial e aqueles com candidemia comunitária;

2.2.2 Candidemia em crianças

2.2.2.a Determinar o percentual de crianças entre os pacientes com candidemia nosocomial;

2.2.2.b Comparar a distribuição dos fatores de risco e as espécies de *Candida* relacionadas aos episódios de candidemia nosocomial em crianças e adultos;

2.2.2.c Comparar as modalidades terapêuticas e o desfecho da candidemia nosocomial em crianças e adultos;

2.2.3 Candidemia em pacientes com câncer

2.2.3.a Determinar o percentual de pacientes com diagnóstico de câncer entre aqueles com candidemia nosocomial;

2.2.3.b Avaliar os tipos de neoplasias e o estágio das mesmas nos pacientes com candidemia nosocomial e câncer;

2.2.3.c Comparar a distribuição dos fatores de risco e as espécies de *Candida* relacionadas aos episódios de candidemia nosocomial em pacientes com câncer e pacientes com outras doenças de base e em pacientes com tumores sólidos e malignidades hematológicas;

2.2.3.d Comparar a mortalidade geral entre pacientes com candidemia nosocomial e câncer e pacientes com candidemia nosocomial e outras doenças de base;

2.2.3.e Comparar a mortalidade geral entre pacientes com candidemia nosocomial e tumores malignos sólidos e pacientes com candidemia nosocomial e malignidades hematológicas;

2.2.4 Candidemia “de escape” (*breakthrough*)

2.2.4.a Determinar, entre os pacientes com candidemia nosocomial, o percentual de infecções que ocorreram em pacientes em uso de antifúngicos (candidemia “de escape” ou *breakthrough*);

2.2.4.b Demonstrar quais os antifúngicos em uso no momento da candidemia nosocomial *breakthrough*, e quais as mudanças terapêuticas realizadas nestes pacientes após o diagnóstico de candidemia;

2.2.4.c Determinar as espécies de *Candida* relacionadas aos episódios de candidemia nosocomial *breakthrough*, e comparar a distribuição destas espécies com aquela encontrada em pacientes com candidemia nosocomial não-*breakthrough*;

2.2.4.d Comparar a distribuição dos fatores de risco entre os pacientes com candidemia nosocomial e infecção *breakthrough* e não-*breakthrough*;

2.2.4.e Comparar a mortalidade geral entre pacientes com candidemia nosocomial estratificados por infecção *breakthrough* ou não-*breakthrough*.

3 MÉTODOS

3.1 Delineamento do estudo

Estudo de coorte retrospectivo.

3.2 População do estudo

A população do estudo foram todos os casos consecutivos de candidemia diagnosticados na Santa Casa Complexo Hospitalar no período de 17 de fevereiro de 1995 (data do primeiro isolado de *Candida* em hemocultivo na Instituição, com identificação da espécie) a 31 de dezembro de 2003.

3.3 A Instituição

A Santa Casa de Porto Alegre é um complexo hospitalar de atendimento terciário composto por sete hospitais, que ao todo somam mais de 1.100 leitos, 133 dos quais são de terapia intensiva. Ocorrem na Instituição 52.000 internações e 708.000 consultas ambulatoriais por ano. É uma Instituição com mais de 200 anos de existência, servindo como hospital-escola à Faculdade de Medicina da Fundação Faculdade Federal de Ciências Médicas de Porto Alegre. Cerca de 60% dos leitos do hospital são destinados a pacientes do Sistema Único de Saúde, e 40% a pacientes particulares ou conveniados.

3.4 Critérios de inclusão

Para inclusão no estudo, foi requerido o diagnóstico de sepse temporalmente relacionado à data da coleta da hemocultura positiva para *Candida*. Ainda, a hemocultura que revelou o crescimento de *Candida* deveria ter sido coletada de veia periférica. Embora o conceito de infecção na corrente sanguínea englobe infecção na corrente sanguínea laboratorialmente confirmada e sepse clínica, esta última sem confirmação laboratorial, incluímos neste estudo apenas pacientes pertencentes à primeira categoria. Para o diagnóstico de sepse, foi necessário haver resposta inflamatória sistêmica à infecção, clinicamente reconhecida por dois ou mais das seguintes manifestações: [144]

- Temperatura maior que 38º C ou menor que 36º C;

- Freqüência cardíaca maior que 90 batimentos por minuto;

- Freqüência respiratória maior que 20 movimentos por minuto ou $PaCO_2$ (pressão arterial de dióxido de carbono) menor que 32 mm Hg;

- Leucocitose (leucócitos acima de 12.000 células/mm^3), leucopenia (leucócitos abaixo de 4.000 células/mm^3) ou presença de formas granulocíticas imaturas (acima de 10%) no sangue periférico.

3.5 Critérios de exclusão

3.5.1 Pacientes cuja única hemocultura positiva para *Candida* foi colhida através de cateter

Esta medida visou não incluir no estudo pacientes com cateter colonizado, sem candidemia.

3.5.2 Ausência de identificação de *Candida* ao nível de espécie

Todos os pacientes cuja hemocultura tenha revelado crescimento de estruturas leveduriformes, mas que, por qualquer motivo, não foi possível se identificar a espécie, foram excluídos do estudo. Esta decisão visou não incluir no estudo pacientes com fungemia por leveduras outras que as do gênero *Candida*.

3.6 Definições

3.6.1 Candidemia

Presença de ao menos uma hemocultura positiva para *Candida* obtida de veia periférica em associação com sinais e sintomas temporalmente relacionados;

3.6.2 Candidemia nosocomial

Candidemia em paciente admitido há mais de 72 horas, ou candidemia ocorrendo em período de 30 dias após procedimento cirúrgico ou 1 ano após inserção de prótese;

3.6.3 Candidemia comunitária

Candidemia em paciente ambulatorial ou admitido em período igual ou inferior a 72 horas;

3.6.4 Candidemia *breakthrough* ou “de escape”

Ocorrência de candidemia em paciente recebendo ao menos 3 dias de terapia anti-fúngica sistêmica, para qualquer finalidade;

3.6.5 Paciente adulto

Aquele com idade superior a 13 anos no momento da candidemia;

3.6.6 Paciente pediátrico

Aquele com idade ≤ 13 anos no momento da candidemia;

3.6.7 Paciente neonato

Aquele com idade igual ou inferior a 28 dias no momento da candidemia;

3.6.8 Paciente prematuro

Aquele cujo nascimento ocorreu antes de 37 semanas completas de gestação;

3.6.2 Mortalidade global

Neste estudo, a mortalidade global ou “crua” foi definida como o percentual de pacientes com candidemia que foram ao óbito por qualquer causa, durante a hospitalização em que a candidemia ocorreu; para pacientes com candidemia comunitária, a mortalidade global foi definida como o percentual de óbitos durante a hospitalização que imediatamente seguiu a candidemia;

3.7 Coleta dos dados

Os casos de candidemia neste estudo foram obtidos através de revisão dos arquivos do Laboratório de Micologia Clínica e do Serviço de Controle de Infecção Hospitalar da Santa Casa Complexo Hospitalar. Rotineiramente, todas as hemoculturas com crescimento de leveduras no método automatizado BacT/Alert® são encaminhadas do Laboratório Central ao Laboratório de Micologia Clínica para identificação da espécie; diariamente, o Laboratório Central encaminha relatório ao Serviço de Controle de Infecção Hospitalar informando a relação dos pacientes com hemocultivo positivo para leveduras. Alternativamente, os frascos de hemocultivo encaminhados diretamente ao Laboratório de Micologia Clínica para cultivo em lisecentrifugação (Isolator®) são sistematicamente processados, uma vez positivos, para identificação da espécie. A escolha de um ou outro método de hemocultivo é decisão do médico assistente.

Os prontuários dos pacientes com candidemia foram obtidos junto ao Arquivo Médico da Instituição (CEDOP). Após criteriosa revisão, os dados de interesse foram registrados em instrumento de coleta padronizado (ver anexos – Instrumento de coleta dos dados). A coleta dos dados foi feita pelo investigador principal e por dois acadêmicos de medicina treinados para a função e supervisionados pelo primeiro.

Foram registradas no instrumento de coleta as variáveis de interesse presentes nos 30 dias que antecederam a data da candidemia, considerada como a data da coleta da primeira hemocultura positiva para *Candida*, em cada paciente incluído. Abaixo, relacionam-se as variáveis revistas no prontuário médico.

3.7.1 Variáveis demográficas

- Sexo (masculino ou feminino);

- Idade (medida em anos);

- Diagnósticos secundários (doenças de base);

3.7.2 Variáveis clínicas

- Presença de neutropenia (definida como contagens de neutrófilos no sangue periférico menores que 1.000 células/mm^3) e de neutropenia grave (definida como contagens de neutrófilos no sangue periférico menores que 100 células/mm^3);

- Mucosite, diarréia, íleo e sangramento gastrointestinal (a presença destes foi definida pela equipe assistente, de acordo com os registros obtidos no prontuário médico);

- Realização de exame de fundo de olho, após a candidemia;

3.7.3 Uso de medicamentos ou outros produtos

- Antibioticoterapia sistêmica;

- Terapia prévia com anti-fúngicos (incluído dosagem e via de uso);

- Corticoterapia sistêmica (não se registrou a dose ou o tipo de corticosteróide usado);

- Uso de antiácidos, bloqueadores H2 e inibidores da bomba de prótons;

- Quimioterapia;

- Uso de vasopressores;

- Transfusão de hemoderivados;

3.7.4 Procedimentos invasivos

- Cateteres venosos centrais (foram unidos neste grupo os cateteres de curta e longa permanência). Pacientes com flebotomia foram também incluídos como tendo cateter venoso central; não foram registrados a presença de cateter venoso periférico nem o número de vias do cateter central;

- Cateteres de longa permanência, do tipo *porth-a-cath*;

- Cateteres arteriais;

- Nutrição parenteral;

- Dieta por sonda nasogástrica ou sonda nasoentérica;

- Cateteres urinários (incluindo sondagem vesical intermitente ou “de demora”);

- Ventilação mecânica invasiva;

- Dreno de tórax;

- Hemodiálise e diálise peritoneal;

- Procedimentos cirúrgicos maiores, incluindo cirurgia gastrointestinal, neurocirurgia, cirurgia cardiotorácica ou outra (como genitourinária ou ginecológica);

3.7.5 Outras variáveis estudadas

- Internação prévia em unidade de terapia intensiva;

- Após a candidemia: tempo de hospitalização, necessidade de terapia intensiva, vasopressores ou transfusões;

- Terapia antifúngica empregada para tratamento da candemia (data de início, antifúngico empregado, dose, via e duração da terapia);

- Data da hospitalização e da alta hospitalar;

- Óbito durante a internação (desfecho primário do estudo);

3.7.6 Dados neonatais

- Prematuridade (os prematuros foram classificados de acordo com o peso ao nascimento: aqueles com peso $\leq$ 2.500 g, $\leq$ 1.500 g e $\leq$ 1.000 g foram definidos como tendo baixo peso ao nascimento, peso muito baixo ao nascimento e peso extremamente baixo ao nascimento, respectivamente);

- Escore de Apgar (medido no 5º minuto de vida);

- Peso ao nascimento;

- Devido à inconsistência nos registros, outros dados neonatais não foram coletados no prontuário;

3.7.7 Dados microbiológicos

- Data da candidemia (data do primeiro isolado positivo para *Candida*, em cada paciente incluído). Neste estudo, foi incluído apenas um isolado por paciente;

- Espécie de *Candida* isolada em hemocultivo. Neste estudo, cepas positivas ao teste do tubo germinativo foram consideradas como sendo *Candida albicans*, e cepas negativas foram identificadas com o kit ID 32 C (BioMérieux, França);

- Número de isolados positivos para Candida e duração da candidemia;

- Número de dias passados entre a admissão no hospital e a ocorrência de candidemia;

- Cultivo de *Candida* em sítios outros que sangue (nos 30 dias que antecederam a data da candidemia);

- Suspeita clinica de lesão compatível com candidose (como candidose cutânea ou oral), na ausência da realização de exame micológico (nos 30 dias que antecederam a data da candidemia);

- Método de hemocultivo (Isolator® ou BacT/Alert®) e tempo de crescimento até identificação em cultivo;

- Bacteremia prévia ou concomitante à candidemia (definida como a pesença de bactéria em hemocultivo);

3.7.8 Gravidade da doença

A gravidade da infecção foi estimada em crianças através do escore PRISM (*Pediatric Risk of Mortality Score*), [145] calculado no momento da candidemia; para adultos, foi usado o escore APACHE II (*Acute Physiology and Chronic Health Evaluation*). [146]

3.7.9 Classificação e estadiamento das doenças neoplásicas

Os tumores sólidos foram divididos em tumores localizados, localmente avançados, metastáticos ou com resposta completa ao tratamento. Os sítios anatômicos primários dessas neoplasisas foram também registrados.

Pacientes com neoplasias hematológicas foram divididos entre aqueles com leucemia (aguda ou crônica) ou linfoma (doença de Hodgkin ou linfoma não-hodkiniano); as leucemias foram também divididas em incial ou crônica e progressiva ou resistente, e os linfomas foram agrupados de acordo com o estágio da doença (de I a IV).

Pacientes com donça neoplásica avançada foram aqueles com malignidade hematológica em recidiva ou tumor sólido em múltiplas localizações.

3.8 Aspectos éticos

O projeto de pesquisa foi previamente avaliado e aprovado pelo Comitê de Ética em Pesquisa da Irmandade da Santa Casa de Misericórdia de Porto Alegre (protocolo número 547/02), através do parecer número 254/02, de 03 de dezembro de 2002.

3.9 Análise estatística

Estatística descritiva foi utilizada para a apresentação dos dados. O teste do qui-quadrado de Pearson foi utilizado para avaliar a associação entre variáveis qualitativas, e o teste exato de Fisher foi empregado quando o número esperado de observações foi < 5. Para a comparação de variáveis quantitativas, foi empregado o teste Mann Whitney, quando a normalidade dos dados não pôde ser obtida a despeito de transformação logarítmica. O nível de significância bilateral para a detecção de diferenças foi de 5%. A análise dos dados foi feita com auxílio do programa *SPSS for Windows*, versão 11.5.

4 ARTIGOS

4.1 Candidemia comunitária

A comparative study of risk factors and outcome among outpatient-acquired and nosocomial-acquired candidemia

Artigo aceito para publicação no Journal of Hospital Infection.

Trabalho parcialmente apresentado no 10th European Congress of Medical Mycology, Wrocław, Polônia, 2004, como tema livre.

Title: A comparative study of risk factors and outcome among outpatient-acquired and nosocomial-acquired candidemia

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This study was presented in the oral session of the 10th European Congress of Medical Mycology, Wrocław, Poland, 2004.

Summary

Based on the perception that candidemia is a nosocomial infection most studies have excluded patients in which candidemia occurred within 48-72 hours of hospitalization. The aim of this study was to describe all cases of candidemia that occurred in the outpatient setting and to compare risk factors and outcome among patients with outpatient-acquired and nosocomial-acquired candidemia. During 1995 and 2003, 210 patients developed candidemia at our institution, and 9.0% were outpatient-acquired. Most of these outpatients were male, median age was 51 years old, and major underlying diseases were cancer (47.4%) and chronic renal failure (36.8%). Most of the candidemias in the outpatient group occurred within 24h of hospitalization (63.2%) and 83.7% were caused by species other than *Candida albicans*, mainly *Candida parapsilosis* (36.8%). *Candida* was isolated from catheters in 21%, and most of them (52.6%) had been admitted to the hospital in the 60 days preceding candidemia. Compared to patients with nosocomial-acquired candidemia, chronic renal failure was more frequent in the outpatient group, who were also more commonly exposed to hemodyalisis. Ileus, gastrointestinal bleeding, previous bacteraemia, use of proton pump inhibitors, previous stay in the intensive care unit (ICU) and requirement for antibiotics, blood transfusion, vasopressors and invasive medical procedures were more frequent in the nosocomial group. Overall mortality rate was higher than 50% in both groups. Candidemia must be remembered as a potential etiology for sepsis in the community, and it is associated with a high mortality.

KEYWORDS: Nosocomial infection; Candidiasis; Candidemia; Community-acquired infection.

Introduction

Candida spp. has emerged in the last two decades as an increasingly important pathogen. [1] Based on the perception that candidemia is a nosocomial infection most studies have excluded patients in which candidemia occurred within 48-72 hours of hospitalization. [2-4] Recent medical advances, however, might change this scenario, with a growing number of patients being treated outside the hospital. Concerning to candidemia, few studies have described the proportion of patients in which the infection was acquired in the outpatient setting; according to these studies, 9-28% of episodes happened outside the hospital. [5-11] The aim of this study was to describe all cases of candidemia that occurred in the outpatient setting in our institution, and to compare risk factors and the outcome among patients with outpatient-acquired and nosocomial-acquired candidemia.

Materials and methods

Santa Casa Complexo Hospitalar is a 1,200-bed tertiary hospital located in Porto Alegre, southern Brazil. In the period comprising February 1995 to December 2003, we retrospectively reviewed all cases of candidemia that occurred in our institution. For inclusion in this study, patients had to have at least one positive blood culture for *Candida* obtained from a peripheral vein, in association with signs and symptoms temporarily related. We excluded patients without sepsis, patients in whom the only positive blood culture was drawn through catheter, and those cases with no *Candida* species identification. Outpatient-acquired was defined as those candidemias that occurred prior or within 72 hours of hospital admission; candidemia in patients with major surgical procedures in the last 30 days or with prosthesis insertion in the last year were considered nosocomial-acquired.

Medical charts of these patients were reviewed to record clinical and demographic characteristics presented in the period of 30 days before collection of the first blood sample positive for *Candida*. The following variables were studied: sex, age, underlying diseases, neutropenia, diarrhea, ileus, gastrointestinal bleeding, mucositis, and bacteraemia. The following invasive medical procedures were checked: central venous catheter, arterial catheter, parenteral nutrition, enteral feeding, urinary catheter, mechanical ventilation, hemodialysis, and previous stay in the intensive care unit. Prior requirement of antibiotics, antifungals, steroids, H2 blockers, proton pump inhibitors, vasopressors, chemotherapy and blood transfusion were also recorded. Breakthrough candidemia was defined as the occurrence of candidemia in a patient receiving at least 3 days of systemic antifungal therapy. Disease severity was evaluated in adults (aged ≥ 13 years-old) with APACHE II score, and the main outcome was classified as discharge or death during hospitalization. The protocol was approved by hospital ethic committee.

Statistical analysis

Pearson chi-square test was used to evaluate the association between categorical quantitative variables. Mann Whitney test was used to compare ordinal variables or continuous data where normality of data cannot be assured despite attempts at log transformation. The bilateral level of significance for the detection of differences in both tests was 5%, and data analysis was performed with SPSS software.

Results

During the period of 9-years (1995-2003), 210 cases of candidemia occurred in our institution, 19 of which (9.0%) were in the outpatient setting. Most of these outpatients were male (52.6%) and median age was 51.0 years old (range 0.3-78.1).

In 63.2% of the patients (n=12), the first positive blood culture for *Candida* was sampled prior or within 24 hours of hospitalization; in 15.8% (n=3) it occurred between 24-48 hours, and in 21.1% (n=4) within 48-72 hours. The median number of positive blood cultures for *Candida* was 1.0 (mean 1.9 ± standard deviation, sd 1.4), and median duration of candidemia was 1.0 day (mean 3.0 ± 4.2). For the inpatient group, median time elapsed between hospital admission and candidemia was 20.0 days.

C. parapsilosis was the most prevalent species in the outpatient group (36.8%, n=7), followed by *C. albicans* (26.3%, n=5), *C. glabrata* (10.5%, n=2), and *C. sake* (10.5%, n=2); *C. tropicalis*, *C. guilliermondii*, and *C. krusei* accounted for 5.3% (n=1) each. *Candida* spp. were also isolated in sites other than blood in 36.8% of patients (n=7), mainly catheters (21.1%), urine (10.6%), brochoalveolar lavage (5.3%), and aortic vegetation (5.3%). Bacteraemia concomitant to the first blood isolate of *Candida* occurred in 15.8% of patients (1 episode due to coagulase-negative staphylococci, 1 due to *Stenotrophomonas maltophilia*, and other due to *Klebsiella pneumoniae*).

Previous hospitalization in the 60 days preceding candidemia occurred in 52.6% of patients in the outpatient group. Considering 2 other patients who were in chronic hemodyalisis, and 2 more patients being treated with chemotherapy in the outpatient setting, a total amount of 73.7% (n=14) of the outpatients had been recently hospitalized or had received treatment at the hospital area. Of the 5 patients that had not been previously hospitalized, 3 had abnormalities in the genitourinary tract (1 patient had cervix cancer and a vesicovaginal fistula, 1 patient had bladder cancer and bilateral kidney stones, and 1 patient had multiple sclerosis, neurogenic bladder, and a complicated urinary tract infection due to *C. glabrata*). Except for this last patient, however, the urine of these patients with genitourinary tract abnormalities

were not cultivated for yeasts. In 2 out of the 19 patients, we found no evident predisposing condition for candidemia: a healthy 6 years-old boy admitted for aseptic meningitis (with *C. parapsilosis* in blood culture), and an also healthy 4-month girl admitted for bronchiolitis due to respiratory syncytial virus (*C. sake*); these two patients discharged without systemic antifungal treatment.

Table 1 shows the main characteristics of the outpatient group, when compared to 191 cases of nosocomial-acquired candidemia. We did not observe differences between groups related to age and sex; except for chronic renal failure, that was more common in the outpatient group, the distribution of the major underlying diseases was equal between groups. The following predisposing conditions were more frequent in the nosocomial group: ileus, gastrointestinal bleeding, use of proton pump inhibitors, previous stay in the intensive care unit and requirement for blood transfusion and vasopressors. Except for hemodyalisis, most of invasive medical procedures were more common in the nosocomial group. In the nosocomial group antibiotics were required more frequently and previous bacteraemia and surgeries were more frequent. On the other hand, there were no differences between the groups regarding *Candida* species distribution, antifungal treatment (time for initiation, mean dose of antifungals or duration of treatment) and the outcome. During candidemia, 61.1% and 71.3% of the outpatients and inpatients had fever (p=0.463), and 15.8% and 29.8% had hypotension requiring vasopressors (p=0.196), respectively. Overall mortality rate was high in both groups.

Discussion

Candidemia has increased in importance in the last years to become the 4th most frequent etiology of nosocomial bloodstream infection in the United States. [1] The changing epidemiology of candidemia has shown us that these infections do not exclusively affect patients treated in the intensive care unit [2,3,8,9,11] but, with the increasing number of patients being treated more aggressively in the outpatient setting, they can also occur in the community.

The description of candidemia in the outpatient setting is not a new subject. In a series of 37 HIV-infected patients with candidemia, Tumbarello et al. reported that 16% of episodes were community-acquired. [5] Colombo et al. reported in Brazil that 9% of all candidemias represented community-acquired infections [8] and Viscoli et al. described in the EORTC study that 10% of candidemias in cancer patients occurred outside the hospital. [6] Weinstein et al. also described that 16.7% of patients with candidemia acquired this infection outside the hospital. [7] Two interesting population-based studies were recently published by the Centers of Disease Control and Prevention. [10,11] In the first study, Kao et al. showed that 20.2% of patients with candidemia developed this infection in the outpatient setting, [10] and they also showed that species other than *C. albicans* were more prevalent in the community, mainly *C. parapsilosis*. In the second study, Hajjeh et al. published that 28% of all patients with candidemia and 38% of patients with *C. parapsilosis* blood stream infection had the blood culture sampled prior or on the first day of hospital admission, and that infections with fluconazole-resistant strains were more frequent among patients with outpatient-acquired candidemia. [11] Although these studies lack details about the population of patients with community-acquired candidemia, they concluded that these patients still shared health care-related risk factors, since most had indwelling vascular catheters at the time of diagnosis and had a history of recent

hospitalizations. In accordance to these data, we have shown that most of our patients had recent hospitalizations and they were frequently submitted to invasive procedures such as central venous catheters.

Different criteria, however, has been used for the definition of a community-acquired episode. While most of the studies have used the criteria of 48 hours of hospital admission, [1,3,4,9] other have chosen 72 hours [2] or even 24 hours. [10,11] According to the guidelines published by the Centers for Disease Control and Prevention (CDC), [12] nosocomial infections are those that result from adverse reaction to the presence of an infectious agent(s) or its toxin(s) and that was not present or incubating at the time of admission to the hospital. For most bacterial nosocomial infections, this means that the infection usually becomes evident 48 hours (i.e., the typical incubation period) or more after admission. However, because the incubation period varies with the type of pathogen and to some extent with the patient's underlying condition, each infection must be assessed individually for evidence that links it to the hospitalization. Considering to candidemia, it seems to us that 24 hours is a very short cut-off for this definition, while 48-72 hours seems to be more appropriated.

As we have shown in this paper, patients in which candidemia occurred in the outpatient setting were frequently submitted to invasive procedures and received large spectrum antimicrobial treatment. In the comparison of patients with outpatient-acquired and nosocomial-acquired candidemia, we observed that they differed in various aspects, usually because patients with nosocomial candidemia were more frequently submitted to invasive medical procedures and antibiotics. As we did not have other control group, however, it is possible that those differences observed just reflected natural differences among patients treated inside the hospital or in the outpatient setting. By the other hand, the severity of candidemia and the mortality

rate were similar between groups. As far as we are concerned, this was the first study to address details about candidemia in the outpatient setting.

In the SENTRY study, [9] Pfaller et al. observed no difference in susceptibility to six different antifungal agents between nosocomial and community-acquired blood stream infection isolates of *Candida* species. This observation was distinctly different from the experience with bacterial infections, where nosocomial strains were almost always more resistant to antimicrobial agents than community-acquired strains. The absence of susceptibility tests to compare outpatient-acquired and nosocomial-acquired candidemia is one of the main limitations of our study.

In accordance to a previous study, [11] most of episodes in the outpatient group were caused by species other than *C. albicans*, mainly *C. parapsilosis*. Patients with outpatient-acquired candidemia in our study were frequently submitted to central venous catheters, and *Candida* was isolated from catheters in 21% of patients. Furthermore, the relationship between *C. parapsilosis* fungemia and intravascular catheters is well appreciated. [13]

Chronic renal failure was also common in the outpatient group. As previously shown, [2,14] chronic renal failure and hemodialysis are important risk factors for candidemia. Three patients in our series had complicated genitourinary diseases, and one can suppose that the candidemia could have emerged from the urinary tract in these patients. As previously shown, candiduria rarely resulted in candidemia unless upper urinary tract obstruction was present. [15] Unfortunately, only one of these 3 patients had the urine cultivated for yeasts. Only two out of the 19 outpatients had no underlying conditions predisposing to candidemia. Based on the fact that these patients were dismissed without antifungal treatment, it is possible that these cases represented transitory candidemia, or even contamination.

Most of outpatients in this study had been admitted to hospital in the 60 days preceding candidemia. It is well known that colonisation is a prerequisite for the development of candidiasis. Although *Candida* spp. are part of the normal endogenous microbiota, this colonisation increases highly during hospitalization. [16] It is possible that these patients could have been colonised during previous hospitalizations, and that their underlying conditions, the use of antibiotics and invasive medical procedures could have facilitated *Candida* spp. blood stream infection.

Concluding, candidemia must be remembered as a potential etiology for sepsis in the community, and it is associated with a high mortality. *C. parapsilosis* was the main species in this population, composed in our study mainly of patients with cancer and chronic renal failure. Recent hospitalizations occurred in most of these patients, and it is possible that some of them, in fact, may have hospital-acquired candidemia. New population-based studies are necessary to better clarify the changing epidemiology of candidemia.

Acknowledgments

We would like to thank Dr. Arnaldo L. Colombo for reviewing this manuscript.

References

1. Edmond MB, Wallace SE, McClish DK, Pfaller MA, Jones RN, Wenzel RP. Nosocomial Bloodstream Infections in United States Hospitals: A Three-Year Analysis. *Clin Infect Dis* 1999; **29:** 239-244.

2. Wey SB, Mori M, Pfaller MA, Woolson RF, Wenzel RP. Risk factors for hospital-acquired candidemia. A matched case-control study. *Arch Intern Med* 1989; **149:** 2349-2353.

3. Lark RL, Chenoweth C, Saint S, Zemencuk JK, Lipsky BA, Plorde JJ. Four year prospective evaluation of nosocomial bacteremia: epidemiology, microbiology, and patient outcome. *Diagn Microbiol Infect Dis* 2000; **38:** 131-140.

4. Gudlaugsson O, Gillespie S, Lee K, Berg JV, Hu J, Messer S, et al. Attributable Mortality of Nosocomial Candidemia, Revisited. *Clin Infect Dis* 2003; **37:** 1172-1177.

5. Tumbarello M, Tacconelli E, de Gaetano Donati K, Morace G, Fadda G, Cauda R. Candidemia in HIV-infected subjects. *Eur J Clin Microbiol Infect Dis* 1999; **18:** 478-483.

6. Viscoli C, Girmenia C, Marinus A, Collette L, Martino P, Vandercam B, et al. Candidemia in cancer patients: a prospective, multicenter surveillance study by the Invasive Fungal Infection Group (IFIG) of the European Organization for Research and Treatment of Cancer (EORTC). Clin Infect Dis 1999; **28:** 1071-1079.

7. Weinstein MP, Towns ML, Quartey SM, Mirrett S, Reimer LG, Parmigiani G, et al. The clinical significance of positive blood cultures in the 1990s: a prospective comprehensive evaluation of the microbiology, epidemiology, and outcome of bacteremia and fungemia in adults. *Clin Infect Dis* 1997; **24:** 584-602.

8. Colombo AL, Nucci M, Salomao R, Branchini ML, Richtmann R, Derossi A, et al. High rate of non-albicans candidemia in Brazilian tertiary care hospitals. *Diagn Microbiol Infect Dis* 1999; **34:** 281-286.

9. Pfaller MA, Diekema DJ, Jones RN, Sader HS, Fluit AC, Hollis RJ, et al. International surveillance of bloodstream infections due to *Candida* species: frequency of occurrence and in vitro susceptibilities to fluconazole, ravuconazole, and voriconazole of isolates collected from 1997 through 1999 in the SENTRY antimicrobial surveillance program. *J Clin Microbiol* 2001; **39:** 3254-3259.

10. Kao AS, Brandt ME, Pruitt WR, Conn LA, Perkins BA, Stephens DS, et al. The epidemiology of candidemia in two United States cities: results of a population-based active surveillance. *Clin Infect Dis* 1999; **29:** 1164-1170.

11. Hajjeh RA, Sofair AN, Harrison LH, Lyon GM, Arthington-Skaggs BA, Mirza SA, et al. Incidence of bloodstream infections due to *Candida* species and in vitro susceptibilities of isolates collected from 1998 to 2000 in a population-based active surveillance program. *J Clin Microbiol* 2004; **42:** 1519-1527.

12. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections. In: Olmsted RN, ed.: APIC Infection Control and Applied Epidemiology: Principles and Practice. St. Louis: Mosby; 1996: pp. A-1--A-20.

13. Abi-Said D, Anaissie E, Uzun O, Pinzcowski H, Vartivarian S. The epidemiology of hematogenous candidiasis caused by different *Candida* species. *Clin Infect Dis* 1997; **24:** 1122-1128.

14. Bross J, Talbot GH, Maislin G, Hurwitz S, Strom BL. Risk factors for nosocomial candidemia: a case-control study in adults without leukemia. *Am J Med* 1989; **87:** 614-620.

15. Ang BS, Telenti A, King B, Steckelberg JM, Wilson WR. Candidemia from a urinary tract source: microbiological aspects and clinical significance. *Clin Infect Dis* 1993; **17:** 662-666.

16. Eggimann P, Garbino J, Pittet D. Epidemiology of *Candida* species infections in critically ill non-immunosuppressed patients. *Lancet Infect Dis* 2003; **3:** 685-702.

Table I. Major demographic features, underlying diseases, predisposing conditions, antifungal treatment and outcome between patients with outpatient-acquired and nosocomial-acquired candidemia.

Variables			Outpatient (%)	Nosocomial (%)	p value
Demographics	Age (years)	1st quartile	27.8	0.7	
		2nd quartile (median)	51.0	36.5	0.117 [b]
		3rd quartile	69.6	63.9	
	Sex (male)		52.6	48.2	0.710 [a]
Major underlying diseases	Diabetes mellitus		15.8	13.1	0.741 [a]
	HIV infection		0.0	4.7	1.000 [a]
	Solid organ transplantation		5.3	2.6	0.509 [a]
	Cancer		47.4	38.7	0.463 [a]
	Chronic renal failure		36.8	5.2	< 0.001 [a]
Predisposing conditions	Neutropenia		11.1	16.9	0.524 [a]
	Mucositis		5.3	3.7	0.732 [a]
	Diarrhea		15.8	26.7	0.299 [a]
	Ileus		5.3	33.7	0.011 [a]
	Gastrointestinal bleeding		0.0	20.5	0.028 [a]
	Steroids		31.6	48.9	0.148 [a]
	H2 blockers		31.6	54.5	0.057 [a]
	Proton pump inhibitors		15.8	40.0	0.038 [a]
	Chemotherapy		15.8	16.8	0.914 [a]
	Previous intensive care unit stay		0.0	66.5	< 0.001 [a]
	Previous blood transfusion		10.5	71.2	< 0.001 [a]
	Previous vasopressors requirement		0.0	43.5	< 0.001 [a]
Invasive medical procedures	Central venous catheter		36.8	78.5	< 0.001 [a]
	Port-a-cath		15.8	10.5	0.479 [a]
	Mechanical ventilation		0.0	53.4	< 0.001 [a]
	Urinary catheter		10.5	61.8	< 0.001 [a]

	Arterial catheter	0.0	23.0	0.015 [a]
	Enteral feeding	10.5	56.5	< 0.001 [a]
	Chest tube	0.0	18.3	0.048 [a]
	Parenteral nutrition	5.3	36.6	0.006 [a]
	Hemodialysis	21.1	5.2	0.008 [a]
	Percentual of antibiotic use	47.4	96.9	< 0.001 [a]
	Median duration of antibiotic treatment (days)	3.0	16.0	< 0.001 [b]
	Median number of antibiotic used	2.0	4.0	0.014 [b]
Antibiotics use	2^{nd} or 3^{rd} gen. cephalosporins	5.3	40.3	0.003 [a]
	4^{th} gen. cephalosporins	10.5	30.4	0.068 [a]
	Glycopeptides	21.1	57.6	0.002 [a]
	Carbapenems	5.3	27.7	0.032 [a]
	Aminoglycosides	10.5	53.4	< 0.001 [a]
	Quinolones	21.1	26.2	0.626 [a]
Previous bacteraemia		10.5	33.5	0.040 [a]
Major surgery		0.0	48.2	< 0.001 [a]
Breakthrough candidemia		0.0	10.5	0.227 [a]
	No antifungal treatment	36.8	19.4	0.074 [a]
Antifungal treatment	Amphotericin B (desoxycholate)	58.3	78.1	0.120 [a]
	Fluconazole	50.0	51.0	0.948 [a]
	Flucytosine	8.3	3.9	0.457 [a]
Outcome	APACHE II score (median)	17	16	0.333 [b]
	Death during hospitalization	52.6	50.3	0.844 [a]
Total		19	191	

[a] Chi-square test or Fisher's exact test; [b] Mann-Whitney test.

4.2 Candidemia em crianças

Nosocomial candidemia in a Brazilian pediatric population: a 9-year study comparing risk factors and the outcome of pediatric and adult candidemia

Artigo aceito para publicação no periódico Mycopathologia

Trabalho parcialmente apresentado no 10th European Congress of Medical Mycology, Wrocław, Polônia, 2004 (poster 062).

Nosocomial candidemia in a Brazilian pediatric population: a 9-year study comparing risk factors and the outcome of pediatric and adult candidemia

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Abstract

Although there are numerous studies of candidemia in adults, data on pediatric population are still limited. The aim of this study was to compare risk factors, etiology, therapy, and outcome of nosocomial candidemia between pediatric and adult patients in a large Brazilian tertiary hospital (1995-2003). During this period, 78 pediatric and 113 adult patients were studied. Species other than *C. albicans* caused 78.2% of episodes of candidemia in pediatric patients. Compared to adults, pediatric patients received more frequently broad-spectrum antibiotics, H2 blockers, vasopressors, blood transfusions, arterial catheter, gastrostomy, chest tube, cardiothoracic surgery, mechanical ventilation, and parenteral nutrition. Candidemia caused by *C. parapsilosis* was more common in pediatric patients, as was the isolation of *Candida* spp. from catheters. Amphotericin B treatment was more common in pediatric patients. The 30-day mortality rate was higher in adults. We reinforce the necessity of continuous epidemiologic surveillance to follow the dynamics of candidemia.

Keywords: Candidemia, non-*albicans* species, *Candida parapsilosis*, pediatrics, neonates, children.

Introduction

Candida spp. are important hospital-acquired pathogens especially in neonatal intensive care unit (ICU) patients, critically ill patients, and those with underlying immunocompromising conditions (2, 3). Although there are numerous reports on risk factors, therapy and mortality of candidemia in adults (3, 13), data on pediatric population are still limited.

The purpose of this study was to review all cases of candidemia in pediatric patients over a 9-year period in a Brazilian large tertiary hospital, to assess demographic features, etiology, therapy, and outcome of infection. We were interested in the comparison of these variables between these patients and adults with candidemia seen in our institution in the same period.

Material and Methods

A retrospective cohort study was performed during the period comprising February 1995 to December 2003 in patients admitted at Santa Casa Complexo Hospitalar, a 1,200-bed Brazilian tertiary hospital. All consecutive patients with nosocomial candidemia were studied, including pediatric and adult patients. Nosocomial candidemia was defined as the presence of at least one blood culture positive for *Candida* obtained from a peripheral vein in a patient admitted for more than 72 hours, in association with signs and symptoms temporarily related. Patients were considered pediatric if their age was $\leq$ 13 years-old. Breakthrough candidemia was defined as the occurrence of candidemia (the first positive blood culture) in a patient receiving at least 3 days of systemic antifungal therapy.

Medical charts of these patients were reviewed to record on a standardized case report form clinical and demographic characteristics presented in the period of 30 days before collection of the first blood sample positive for *Candida*. The following

variables were studied: sex, age, underlying diseases, neutropenia (< 1000 cells/mm^3), diarrhea, ileus, gastrointestinal bleeding, mucositis, and previous bacteremia. The following invasive procedures were studied: central venous catheter, arterial catheter, parenteral nutrition, nasogastric tube, urinary catheter, mechanical ventilation, chest tube, hemodialysis, and major surgical procedures. Prior therapy with antibiotics, steroids, H2 blockers, proton pump inhibitors, cytotoxic drugs, vasopressors, and blood transfusion were also recorded. Length and type of antifungal therapy were recorded, and outcome was defined as discharge or death while hospitalized. The mortality rate within 48h of blood sample, 7 days, 15 days and 30 days was also analyzed. Disease severity was estimated in pediatric patients using Pediatric Risk of Mortality Score (PRISM) (15), calculated at the moment of candidemia. The protocol was approved by hospital ethic committee.

Neonates were defined as those patients with age ≤ 28 days at candidemia, and preterm birth defines those births that occurred before 37 completed weeks of gestation. Because of the inconstancy in registers, other maternal data were not collected. Neonatal data studied included prematurity, Apgar score at 5 minutes, birth weight, and prevalence of small-for-gestational-age infants. Premature born infants were also classified by birth weight. Infants who weigh less then 2500 g, 1500 g and 1000 g were defined as low (LBW), very low (VLBW) and extremely low birth weight (ELBW), respectively.

Blood samples were processed with BacT/Alert™ automated system or lysis centrifugation (Isolator™). Only one isolate was included per patient (the first one). Germ tubes were performed, and negative strains were identified through kit ID 32C (BioMérieux SA, France). Other microbiological variables studied included prior colonization with *Candida* spp., number of blood cultures positive for *Candida*, and

number of days between admission and first blood culture positive. Clinical suspicion of candidosis with no mycological examination was also registered.

Statistical analysis

Mycological and epidemiological data from pediatric and adult patients were merged, and descriptive statistics were used to summarize the data. Pearson's chi-square test was used to evaluate the association between qualitative variables, and Fisher's exact test was used when the number of expected count was < 5. For the comparison of quantitative variables, Mann Whitney test was used to compare ordinal variables or continuous data where normality of data cannot be assured despite attempts at log transformation. The bilateral level of significance for the detection of differences in both tests was 5%, and data analysis was performed with SPSS software.

Results

A total of 127 pediatric patients with candidemia were seen from February 1995 to December 2003 in Santa Casa Complexo Hospitalar. Forty nine of these patients were excluded from analysis (43 due to impossibility to identify *Candida* species, 4 due to community-acquired candidemia, 1 due to absence of sepsis, and 1 because the only positive blood culture was drawn through catheter), resulting in 78 pediatric patients eligible for study. Twenty two adult patients were also excluded (15 due to community-acquired candidemia, 2 due to impossibility to identify *Candida* species, 3 due to absence of sepsis, and 2 because the only positive blood culture was drawn through catheter), resulting in 113 adults included for analysis.

Most of our pediatric patients were female (62.8%), and median age was 0.4 year-old (mean 2.0 ± standard deviation 3.1). Major underlying diseases in pediatric patients were congenital malformations (43.6%), cancer (20.5%), heart failure

(9.0%), HIV infection (3.8%), chronic renal failure (1.3%), and chronic pulmonary disease (1.3%). Most of the isolates in pediatric patients (85.9%) were cultivated in the BacT/Alert™ system, for a mean period of incubation of 30.8 ± 13.1 hours. Median number of isolates was 2.0 per patient, and median duration of candidemia was 2.0 days (mean 9.0 ± 18.0 days).

Neonates accounted for 24.4% of pediatric patients in this study (n=19). Prematurity occurred in 76.5%; among these preterm newborns, 46.2% were classified as ELBW, 23.1% as VLBW, and 23.1% as LBW infants. One third of the neonates (31.3%) were also classified as small-for-gestational-age infants. Median Apgar score was 8.0 (mean 7.7 ± 1.4). Delivery by cesarean section occurred in 56.3% of newborns. Neonates had candidemia earlier during hospital stay, compared to other non-neonates pediatric patients (median 13 days and 29 days, respectively; $p<0.001$).

Species other than *C. albicans* caused 78.2% of episodes of candidemia in pediatric patients. *C. parapsilosis* was the main species in these patients (38.5%), followed by *C. tropicalis* (21.8%), *C. humicola* (3.8%), *C. famata* (3.8%), *C. krusei* (3.8%), *C. guilliermondii* (1.3%), *C. sake* (1.3%), *C. lusitaniae* (1.3%), *C. intermedia* (1.3%), and *C. glabrata* (1.3%). *C. albicans* caused 36.8% and 16.9% of episodes in neonates and non-neonates pediatric patients, respectively (p=0.211), and *C. parapsilosis* was the etiology of 26.3% and 42.4% of candidemias in neonates and non-neonates, respectively (p=0.282). Breakthrough candidemia occurred in 15 of pediatric patients, and previous bacteremia occurred in 39.7%, mainly by gram-positive aerobic strains (77.4%).

Candida was isolated in sites other than blood in 44.9% of pediatric patients, mainly from catheters (25.6%), urine (17.9%) and wounds (6.4%). Clinical suspicion

of cutaneous candidosis without mycological examination occurred in 14.1%, and oral candidosis in 7.7%.

Comparison between pediatric and adult patients with candidemia (table 1)

Female sex and congenital anomalies were more common in pediatric patients, who also received more frequently antibiotics, particularly broad-spectrum antibiotics such as glycopeptides, carbapenems and aminoglycosides. Pediatric patients were more frequently treated with H2 blockers, vasopressors, blood transfusions and invasive procedures such as arterial catheter, gastrostomy, chest tube, and cardiothoracic surgery; mechanical ventilation and parenteral nutrition was more common in pediatric patients, mainly in neonates (89.5% and 78.9%, respectively). Previous stay in the ICU was also more common in pediatric patients than adults. Candidemia caused by species other than *C. albicans*, particularly *C. parapsilosis*, was more common in pediatric patients, as well the isolation of *Candida* spp. from catheters. Otherwise, adults with candidemia had more frequently the diagnosis of diabetes mellitus, chronic renal failure, cancer (mainly solid neoplasia), chronic lung diseases and chronic liver diseases. Requirement of proton pump inhibitors and hemodyalisis was more frequent in this group.

The proportion of patients who did not receive antifungal treatment or who received fluconazole was higher in adults. Otherwise, treatment with amphotericin B was more common in pediatric patients. After candidemia, pediatric patients required more frequently admission to ICU, mechanical ventilation and blood transfus

Central venous catheters were removed in 84.1% of pediatric and 72.1% of adult patients with catheters in place (p=0.084), and median time for catheter removal was 5.0 days in children and 4.0 days in adults (p=0.324).

Although overall mortality rate was not different between these groups, mortality was different in the period of 2 days, 7 days, 15 days and 30 days after

candidemia. Among pediatric and adult patients, mortality rate ≤ 48h after candidemia was 1.3% and 8.0% (p=0.050); ≤ 7 days was 10.3% and 27.4% (p=0.004); ≤ 15 days was 21.8% and 40.7% (p=0.006); ≤ 30 days was 26.9% and 46.9% (p=0.005); and after 30 days was 42.3% and 55.8% (p=0.068), respectively.

Discussion

Although candidemia has become an important problem in pediatric patients, data on these patients are still limited. Few series have included 70 or more patients (6-9, 11, 12, 16, 19, 21, 24), and some of these studies have focused only in neonates (6, 7, 19). The definition of a pediatric patient has been largely heterogeneous: while some studies have included patients ≤ 12 years-old (20), others have used the criteria of ≤ 13 (12), ≤ 16 (16), ≤ 17 (8, 11), ≤ 18 (21), and even ≤ 20 years-old (9). According to the MeSH Terms of the National Library of Medicine, a child is a person 6-12 years of age and an adolescent is a person 13-18 years-old; we preferred to define pediatric as those patients with age ≤ 13 years-old.

In this study, *C. parapsilosis* was the main etiology of candidemia in pediatric patients (38.5%). The growing importance of *C. parapsilosis* as agent of candidemia in pediatric patients has been previously addressed (6, 9, 12, 14). Given the known propensity of this yeast to adhere to foreign material (23), some investigators have suggested that its elevated prevalence in pediatric patients may reflect the aggressive use of intravascular devices, particularly if associated with total parenteral nutrition (9). There is also good evidence that this organism is commonly carried on the hands of health care workers (5), and, thus, that nosocomial transmission via direct contact is likely to occur. As described by others (6, 9, 13), *C. glabrata* was uncommon in our pediatric patients (1.3%). This observation remains unexplained.

Moreover, we have observed that *C. glabrata* is infrequent in Brazilian patients, even in adults (1).

The proportion of infections caused by *C. albicans* was slightly higher in neonates (36.8%) then in non-neonates pediatric patients with candidemia in this study (16.9%). Electrophoretic karyotyping and restriction endonuclease analysis of genomic DNA with pulsed field gel electrophoresis has shown that *C. albicans* is vertically transmitted from mothers to their VLBW infants but that *C. parapsilosis* is not (22). It is possible that the limited number of patients in our study could explain the similarity of *Candida* species distribution between neonates and non-neonates. Other studies, however, have shown *C. parapsilosis* as the main *Candida* species in neonates, in association with the factors described above (6, 9).

Risk factors reported for other series were frequently encountered among our pediatric patients (17). Although most studies have described risk factors that are common to pediatric and adult fungal bloodstream infections – such as central venous catheters, prior treatment with broad-spectrum antibiotics, neutropenia, corticosteroid therapy, and gastrointestinal surgery – several investigators have emphasized the particular importance of endotracheal intubation and parenteral nutrition as risk factors for candidemia in pediatric patients (12, 18, 21). Even though our study has not been designed for risk evaluation, we have described that pedi

patients were more commonly submitted to mechanical ventilation and intravenous hyperalimentation than adults.

Systemic candidosis has become an increasingly frequent cause of late-onset infection in the premature neonate (2, 6). Among VLBW infants, the reported incidence ranges from 2.6% to 12.9% (5, 18), increasing to 5.5% to 20% (18) among ELBW infants. The incidence of candidemia appears to be increasing as smaller preterm infants survive and require prolonged hospitalizations (6, 18). Prematurity

and low birth weight were common among neonates in our cohort, in whom invasive medical procedures were also frequently required. These findings were similar to those found by Krčméry et al. (7). In a recent case-control study, the most important factors associated with candidemia in neonates were the number of days of mechanical ventilation and the presence of bacterial bloodstream infection before candidemia (10). The finding that neonates had candidemia earlier during hospital stay than non-neonates pediatric patients in our study could be explained because of their immature immune system, disruptions in their cutaneous barrier and iatrogenic factors.

In our study, in-hospital crude mortality was similar between pediatric and adult patients with candidemia. However, the mortality rates within 48h, 7 days, 15 days and 30 days after blood sample were all higher in adults, which may reflect more confidently mortality due to candidemia, as we believe that late mortality may be mostly related to the prognosis of the underlying diseases themselves. In a large, prospective study of candidemia, survival rates for pediatric patients with candidemia were significantly better than survival rates for adults (76% versus 54%) (12), although there are clearly other differences in survival associated with *Candida* species, suggesting clinically important variability in virulence. Although some stu 71 showed lower mortality rates in pediatric patients with candidemia (11, 21), they included in the analysis not only patients with signs and symptoms temporarily related (sepsis), which may had selected some patients with skin colonization by *Candida* species. The evaluation of risk factors for death in patients with candidemia was not among the objectives of this study.

We have observed some differences in the antifungal treatment between pediatric and adult patients in our institution. The proportion of adults who did not receive antifungals was higher than in pediatric population, which may be related to

the higher mortality found in the former. It is not surprising, however, that patients who received no therapy had significantly higher overall mortality rates, which supports the recommendation that all patients with candidemia receive antifungal therapy (13). While adults were treated more commonly with fluconazole, pediatric patients received more frequently amphotericin B. These findings are similar to those found by Pappas et al. (12), and may reflect a traditional approach for treating a population with frequent complications associated with this disorder. In addition, differences in amphotericin B pharmacokinetics in pediatric patients, with lower volume of distribution and faster clearance rate than adults (4), could at least partially explain pediatricians' choice favoring amphotericin B.

Our study has some limitations. First, the retrospective design of this study could have led to loose of information, with the possibility of measurement bias in some particular variables. Second, our study was conducted in a single institution; since the incidence of candidemia due to resistant strains is very low in our area (1), we do not know if our results can be fully extrapolated to institutions where candidemia due to less susceptible species are more frequent. Third, 33.8% of our pediatric patients were excluded from the analysis because we were not able to identify *Candida* at the species level. Although all the yeasts identified in blood through BacT/Alert™ system had to be transported to the Mycology Laboratory for species identification, some of these became contaminated with bacteria or even lost during the period of study. However, it is possible that some of these yeasts-like organisms were not in fact *Candida* species, but other less common yeasts. Finally, this study was not designed to evaluate risk. Because of the absence of a control group without candidemia, some differences observed in underlying diseases and drugs use may have just reflected natural differences among pediatric patients and adults, independently of having or not candidemia.

In conclusion, *C. parapsilosis* was the main etiology of candidemia in this large Brazilian retrospective cohort of pediatric patients. As expected for pediatric patients, *C. glabrata* was an infrequent species. The underlying diseases, predisposing conditions, and antifungal treatment were different between pediatric and adult patients, and *Candida* spp. were more commonly isolated from catheters in pediatric patients. Treatment with amphotericin B was more common in pediatric than adult patients. Although in-hospital crude mortality was similar between these groups, the mortality rates within 48h, 7 days, 15 days and 30 days after blood sample were all higher in adults. We reinforce the necessity of continuous epidemiologic surveillance to follow the dynamics of candidemia.

References

1. Antunes AGV, et al. (2004) Candidemia in a Brazilian tertiary care hospital: species distribution and antifungal susceptibility patterns. *Rev Inst Med Trop S Paulo* 46:239-241.

2. Chapman RL (2003) *Candida* infections in the neonate. *Curr Opin Pediatr* 15:97-102.

3. Eggimann P, et al (2003) Epidemiology of *Candida* species infections in critically ill non-immunosuppressed patients. *Lancet Infect Dis* 3:685-702.

4. Goldman RD, Koren G (2004) Amphotericin B nephrotoxicity in children. *J Pediatr Hematol Oncol* 26:421-426.

5. Huang YC, et al. (1999) Outbreak of *Candida parapsilosis* fungemia in neonatal intensive care units: clinical implications and genotyping analysis. *Infection* 27:97-102.

6. Kossoff EH, et al. (1998) Candidemia in a neonatal intensive care unit: trends during fifteen years and clinical features of 111 cases. *Pediatr Infect Dis J* 17:504-508.

7. Krčméry V, et al. (2000) Fungemia in neonates: report of 80 cases from seven university hospitals. *Pediatrics* 105:913-915.

8. Krčméry V, et al. (2002) Aetiology, antifungal susceptibility, risk factors and outcome in 201 fungaemic children: data from a 12-year prospective national study from Slovakia. *J Med Microbiol* 51:110-116.

9. Levy I, et al. (1998) Emergence of *Candida parapsilosis* as the predominant species causing candidemia in children. *Clin Infect Dis* 26:1086-1088.

10. Linder N, et al. (2004) Risk factors associated with candidaemia in the neonatal intensive care unit: a case–control study. *J Hosp Infect* 57:321-324.

11. Pacheco-Rios A, et al. (1997) Mortality associated with systemic candidiasis in children. *Arch Med Res* 28:229-232.

12. Pappas PG, et al. (2003) A prospective observational study of candidemia: epidemiology, therapy, and influences on mortality in hospitalized adult and pediatric patients. *Clin Infect Dis* 37:634-643.

13. Pappas PG, et al (2004) Guidelines for treatment of candidiasis. *Clin Infect Dis* 38:161-189.

14. Pfaller MA, et al. (2002) Trends in antifungal susceptibility of *Candida* spp. isolated from pediatric and adult patients with bloodstream infections: SENTRY Antimicrobial Surveillance Program, 1997 to 2000. *J Clin Microbiol* 40:852-856.

15. Pollack MM, et al (1988) Pediatric risk of mortality (PRISM) score. *Crit Care Med* 16:1110-1116.

16. Rodrígues-Núñez A (2001) Incidence and mortality of proven invasive *Candida* infections in pediatric intensive care patients. *Infect Contr Hosp Epidemiol* 22:477-478.

17. Safdar N, Maki DG (2002) The commonality of risk factors for nosocomial colonization and infection with antimicrobial-resistant *Staphylococcus aureus*, enterococcus, gram-negative bacilli, *Clostridium difficile*, and *Candida*. *Ann Intern Med* 136:834-844.

18. Saiman L, et al. (2000) Risk factors for candidemia in neonatal intensive care unit patients. *Pediatr Infect Dis J* 19:319-324.

19. Sastre JBL, et al. (2003) Neonatal invasive candidiasis: a prospective multicenter study of 118 Cases. *Am J Perinat* 20:153-163.

20. Singhi SC, et al. (2004) Candidemia in a pediatric intensive care unit. *Pediatr Crit Care Med* 5:369-374.

21. Stamos JK, et al. (1995) Candidemia in a pediatric population. *Clin Infect Dis* 20:571-575.

22. Waggoner-Fountain LA, et al. (1996) Vertical and horizontal transmission of unique *Candida* species to premature newborns. *Clin Infect Dis* 22:803-808.

23. Weems JJ (1992) *Candida parapsilosis:* epidemiology, pathogenicity, clinical manifestations, and antimicrobial susceptibility. *Clin Infect Dis* 14:756-766.

24. Zaoutis TE, et al. (2004) Risk factors for disseminated candidiasis in children with candidemia. *Pediatr Infect Dis J* 23:635-641.

Table 1. Pediatric versus adult candidemia: demographic factors, major underlying diseases, predisposing conditions, antifungal treatment and outcome.

Variables		Children (%)	Adults (%)	p value
Sex	Female	62.8	44.2	0.012[a]
Underlying diseases	Diabetes mellitus	0.0	22.1	<0.001[a]
	Chronic renal failure	1.3	8.0	0.050[a]
	Cancer	20.5	51.3	<0.001[a]
	Solid neoplasia	10.3	43.4	<0.001[a]
	Hematological neoplasia	10.3	8.0	0.585[a]
	Chronic pulmonary disease	1.3	16.8	0.001[a]
	Chronic liver disease	0.0	7.1	0.022[b]
	Congenital malformations	43.6	0.0	<0.001[a]
Predisposing conditions	Neutropenia	19.5	15.2	0.438[a]
	Mucositis	5.2	2.7	0.444[b]
	Diarrhea	19.2	31.9	0.053[a]
	Ileus	36.4	31.9	0.519[a]
	Gastrointestinal bleeding	20.8	20.4	0.943[a]
	Steroids	53.2	46.0	0.328[a]
	H2 blockers	64.1	47.8	0.026[a]
	Proton pump inhibitors	16.9	55.8	<0.001[a]
	Chemotherapy	16.7	16.8	0.979[a]
	Previous stay in the ICU	85.9	53.1	<0.001[a]
	Previous blood transfusion	82.1	63.7	0.006[a]
	Previous vasopressors requirement	64.9	29.2	<0.001[a]
	Previous bacteremia	39.7	29.2	0.129[a]
Invasive medical procedures	Central venous catheter	83.3	75.2	0.180[a]
	Port-a-cath	10.3	10.6	0.936[a]
	Mechanical ventilation	66.7	44.2	0.002[a]
	Urinary catheter	60.3	62.8	0.719[a]
	Arterial catheter	33.3	15.9	0.005[a]

	Chest tube	28.2	11.5	0.003[a]
	Parenteral nutrition	57.7	22.1	<0.001[a]
	Hemodialysis	0.0	8.8	0.006[b]
	Nasogastric tube	57.7	55.8	0.790[a]
	Gastrostomy	5.1	0.0	0.027[b]
	Major surgery	56.5	42.5	0.058[a]
	Gastrointestinal surgery	19.2	21.2	0.735[a]
	Cardiothoracic surgery	30.8	8.0	<0.001[a]
	Median duration of antibiotic treatment	19.0	14.0	0.003[c]
	Number of antibiotic used (median)	5.0	3.0	<0.001[c]
Antibiotic use	Glycopeptides use	84.6	38.9	<0.001[a]
	Aminoglycosides use	71.8	40.7	<0.001[a]
	Carbapenems use	37.2	21.2	0.016[a]
Median time between admission and candidemia (days)		17.0	16.0	0.830[c]
	Species other than *Candida albicans*	78.2	47.8	<0.001[a]
	Candida parapsilosis	38.5	18.6	0.002[a]
Microbiological	*Candida* isolation in other sites	44.9	37.2	0.286[a]
data	Catheter	25.6	12.4	0.019[a]
	Urine	6.4	11.5	0.236[a]
	Breakthrough candidemia	15.4	7.1	0.065[a]
	No antifungal treatment	7.7	27.4	0.001[a]
Antifungal treatment	Amphotericin B (desoxycholate)	97.2	61.4	<0.001[a]
	Fluconazole	40.3	60.2	0.013[a]
	Intensive care unit after candidemia	83.3	60.2	0.001[a]
Outcome	Mechanical ventilation after candidemia	66.7	48.7	0.014[a]
	Death during hospitalization	42.3	55.8	0.068[a]
Total (n)		78	113	191

[a] Chi-square test; [b] Fisher's exact test; [c] Non-parametric Mann-Whitney test.

4.3 Candidemia em pacientes com câncer

Candidemia in Brazilian cancer patients

Artigo submetido ao Scandinavian Journal of Infectious Diseases.

Trabalho parcialmente apresentado no 10th European Congress of Medical Mycology, Wrocław, Polônia, 2004 (posters 024 e 152).

CANDIDEMIA IN BRAZILIAN CANCER PATIENTS

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This study was partially presented at the 10th European Congress of Medical Mycology, Wrocław, Poland, 2004 (posters 024 and 152). This study was funded by the researchers. The authors declare no conflict of interests to write this manuscript.

Key words: candidemia, fungemia, cancer, hematological malignancies, solid tumors.

ABSTRACT

OBJECTIVE: To review all cases of candidemia that affected cancer patients in our medical center over a 9-year period to assess demographic features, etiology, therapy, and outcome of the infection.

DESIGN: Retrospective cohort study.

METHODS: Medical charts were reviewed to record clinical and demographic characteristics presented in the period of 30 days before collection of the first blood sample positive for *Candida*.

RESULTS: During the period of study, 74 patients (38.7%) with nosocomial candidemia had cancer. Solid tumors occurred in 77.0% and most of them were non-metastatic cancers (63.8%). Species other than *C. albicans* caused 59.1% of episodes of candidemia in cancer patients. In comparison with other patients, candidemia in cancer patients was more frequently associated with neutropenia, mucositis, and port-a-cath. Patients without cancer had higher exposure to invasive procedures, large spectrum antibiotics and surgery. Previous steroids use, chemotherapy, and cefepime use were more common in patients with hematological neoplasia, in comparison with solid tumors. However, major surgeries were more common in patients with solid cancers (47.4% and 0.0%), mainly in gastrointestinal tract. Overall mortality was 50.3%.

CONCLUSIONS: Patients with candidemia may have different predisposing factors to acquire the infection when stratified according to baseline diseases. More studies are needed to emphasize specific risk factors for candidemia in patients with solid tumors. Following a worldwide trend, species other than *Candida albicans* were the main etiology of candidemia in this study. Therefore, continuous epidemiologic monitoring is necessary to follow further changes in the patterns of candidal infections.

For many years candidal infections were considered a rare event in oncology patients, mainly occurring with advanced disease.[1] The purpose of this study was to review all cases of candidemia that affected cancer patients in our medical center over a 9-year period to assess demographic features, etiology, therapy, and outcome of the infection. We were interested in the comparison of these variables between patients with and without cancer and between individuals with solid and hematological neoplasms.

METHODS

A retrospective cohort study was performed during the period comprising February 1995 to December 2003 in patients admitted at Santa Casa Complexo Hospitalar, a 1,200-bed tertiary hospital located in Porto Alegre, Brazil. Nosocomial candidemia was defined as the presence of at least one blood culture positive for *Candida* obtained from a peripheral vein in a patient admitted for more than 72h, in association with signs and symptoms temporarily related.[2] Exclusion criteria included absence of sepsis, candidemia that happened with 72 h of hospital stay, a single blood culture drawn through catheter, and lack of identification of *Candida* at species level. Breakthrough candidemia was defined as the occurrence of candidemia in a patient receiving at least 3 days of systemic antifungal therapy. Patients were considered pediatric if their age was ≤ 13 years-old and neonates were defined as those patients with age ≤ 28 days at candidemia.

Medical charts of these patients were reviewed to record on a standardized case report form clinical and demographic characteristics presented in the period of 30 days before collection of the first blood sample positive for *Candida*. The following variables were studied: sex, age, underlying diseases, neutropenia, diarrhea, ileus, gastrointestinal bleeding, mucositis, and previous bacteremia. Neutropenia was defined as an absolute neutrophil count < 1000 cells/mm^3. Severe neutropenia was defined as an absolute neutrophil count < 100 cells/mm^3. The following invasive procedures were studied: central venous catheter, arterial catheter, parenteral nutrition, enteral feeding, urinary catheter, mechanical ventilation, chest tube, hemodialysis or peritoneal dialysis, radiotherapy, and major surgical procedures. Prior therapy with antibiotics, antifungals, steroids, H2 blockers, proton pump inhibitors, cytotoxic drugs, vasopressors, and blood transfusion were also recorded. Length and type of antifungal therapy were recorded, and outcome was defined as discharge or death while hospitalized. The protocol was approved by hospital ethic committee.

Blood samples were processed with BacT/Alert™ automated system or lysis centrifugation (Isolator™). Only one isolate was included per patient (the first one). Germ tubes were performed, and negative strains were identified through kit ID 32C (BioMérieux, France). Other microbiological variables studied included prior colonization with *Candida* spp., number of blood cultures positive for *Candida*, and number of days between admission and first blood culture positive. Clinical suspicion of candidosis with no mycological examination was also registered.

Statistical analysis

Mycological and epidemiological data from patients with and without cancer and from patients with solid and hematological neoplasia were merged, and descriptive statistics were used to summarize the data. Fisher's exact test and Pearson's chi-square test were used to evaluate the association between categorical qualitative variables. Because of the limited number of cases we used Mann-Whitney test for the comparison of quantitative or ordinary qualitative variables. The bilateral level of significance for the detection of differences in both tests was 5%, and data analysis was performed with SPSS software.

RESULTS

A total of 191 patients had the diagnosis of nosocomial candidemia in the period of June 1996 until December 2003 in Santa Casa Complexo Hospitalar, and 74 of these patients had cancer (38.7%). Most of these cancer patients were male (54.1%), and median age was 50.0 year-old (mean 44.3 ± standard deviation 25.9 year-old).

Solid tumors occurred in 77.0% of these patients, mainly in the alimentary tract (38.6%). Other sites included the genitourinary tract (35.1%), the respiratory tract (10.5%), and the central nervous system (10.5%). Sarcoma occurred in 5.3% and melanoma in 1.8%. Most of solid cancers were locally advanced (37.9%), 31.0% were metastatic, 25.9% were localized, and 5.2% had had complete response to treatment.

Major diagnosis in patients with hematological neoplasia was acute leukemia (64.7%), high grade non-Hodgkin lymphoma (29.4%) and Hodgkin's disease (5.9%). Most of the patients with leukemia were receiving induction or consolidation chemotherapy (63.6%); 9.1% had their disease in remission, and 27.3% had progressive or resistant disease (27.3%). The patients with lymphoma were distributed in stage I or II disease (50.0%) and stage III or IV disease (50.00%).

Most of the isolates in cancer patients (97.3%) were cultivated in the BacT/Alert™ system, for a mean period of incubation of 37.2 ± 21.9 hours. Median time elapsed between hospitalization and the first positive blood sample was 19.0 days, median number of isolates was 2.0 per patient, and median duration of candidemia was 1.0 day (mean 1.9 ± 2.6 days). Species other than *C. albicans* caused 59.1% of episodes of candidemia in cancer patients, mainly *C. parapsilosis* (29.7%) and *C. tropicalis* (13.5%). *C. glabrata* and *C. krusei* were infrequent (2.7% each). Breakthrough candidemia occurred in 8 patients (10.8%), and previous bacteremia occurred in 25 patients (33.8%), mainly by gram-positive aerobic strains (n=15). *Candida* was isolated in sites other than blood in 36.5% of patients, mainly from

catheters (20.3%), and urine (18.2%). Clinical suspicion of cutaneous candidosis without mycological examination occurred in 4.1%, and oral candidosis in 13.5%. Central venous catheters were removed in 72.9% of patients whom had catheters at the moment of candidemia, and median time for catheter removal was 5.0 days. Bacteremia occurred concomitantly in 17.6% of cancer patients with candidemia.

Systemic antifungal treatment was used in 77.0% of cancer patients, mainly amphotericin B (55.4%) and fluconazole (43.2%). Overall mortality was 47.3%.

Comparison of patients with candidemia with and without cancer (table 1)

Patients with cancer were older than patients without cancer (median 50.0 year-old versus 7.8 year-old, respectively). As expected, the proportion of patients with neutropenia was higher in cancer patients (36.5% e 4.3%), as well the duration of neutropenia (median 7.0 days versus 1.5 d). Severe neutropenia was also more common in cancer patients (28.4% versus 0.9%). Mucositis (9.6% versus 0.0%), the presence of port-a-caths (27.0% versus 0.0%), and cefepime use (40.5% versus 23.9%) were all more common in cancer patients. *Candida* spp. was isolated from catheter in 20.3% of patients with cancer and 16.2% of patients without cancer (p=0.478). Overall mortality was equal between groups (47.3% and 52.1%).

Major underlying diseases in patients without cancer were congenital malformations (29.1%), chronic obstructive pulmonary disease (14.5%), and heart failure (10.3%). Several invasive procedures were more common in non-cancer patients versus cancer patients: mechanical ventilation (67.5% and 31.1%, respectively), urinary catheter (68.4% and 51.4%), arterial catheter (30.8% and 10.8%), enteral feeding (65.0% and 43.2%), chest tube (23.9% and 9.5%), and parenteral nutrition (47.0% versus 20.3%). Major surgical procedures (55.6% and 36.5%), mainly cardiothoracic surgery (24.8% and 5.4%) were more frequent in the non-cancer group. They also received a higher number of antibiotics (median 4.0 versus 3.5), and

had been treated more commonly with large spectrum antibiotics, such as carbapenems (35.9% and 14.9%) and glycopeptides (65.8% and 44.6%). The crude mortality and the distribution of *Candida* species were equal between groups. *C. glabrata* and *C. krusei* were infrequent in both groups. Ophtalmological examination was performed in only 1.4% of patients with cancer and 11.1% of patients without cancer (p=0.012), and endophthalmitis was not found.

Comparison of patients with candidemia in solid versus hematological neoplasia (table 2)

Patients with solid cancer were older then patients with hematological neoplasia (median age 54.3 and 14.7 years-old, respectively), and they had more frequently ileus (36.8% and 6.3%), previous stay in the intensive care unit (54.4% and 23.5%), mechanical ventilation (40.0% and 0.0%), and urinary catheter (63.2% and 11.8%). Major surgeries were more common in patients with solid cancers (47.4% and 0.0%), mainly in gastrointestinal tract (23.3% vs 0.0%). Anaerobicides antibiotics were more used in these patients (45.6% vs 11.8%), and the outcome of candidemia was the equal.

Otherwise, the proportion of children was higher in the hematological group (47.1% vs 14.0%), who also had more frequently neutropenia (76.5% versus 24.6%). The duration of neutropenia was higher in the group of patients with hematological neoplasia (median 13.0 versus 5.0 days). Previous steroids use (82.4% and 42.9%), chemotherapy (88.2% and 29.8%), and cefepime (70.6% and 31.6%) were all more common in patients with hematological neoplasia, in comparison with solid tumors, respectively.

Species other than *C. albicans* caused 76.5% of episodes of candidemia in patients with hematological malignancies and 52.6% in those with solid tumors (p=0.080).

DISCUSSION

We observed a large proportion of patients with cancer among those with candidemia in our institution. Different from other studies, which have found candidemia more frequently in patients with hematological neoplasm,[3,4] our episodes of candidemia occurred mainly in patients with solid tumors. This may have occurred because Santa Casa Complexo Hospitalar is a referral hospital for solid tumors.

Several studies have revealed risk factors for candidemia among patients with cancer.[3,5,6] The prophylactic or therapeutic use of antibiotics is recognized as an important predisposing factor, as well as the presence of central venous catheter, neutropenia, surgery, use of corticosteroids and hyperalimentation. In the comparison of risk factors for candidemia between patients with and without cancer, we found that candidemia in cancer patients was more frequently associated with neutropenia, mucositis, and the presence of port-a-cath, suggesting that both endogenous and exogenous acquisition may have been important to this group. By the other hand, patients without cancer had higher exposure to invasive procedures, large spectrum antibiotics and surgery. However, it is important to emphasize that some of the differences found could be related to the background disease, as we didn't have a control group without candidemia.

In our study, different risk factors for candidemia were observed between patients with hematologic malignancies and patients with solid tumors. According to the literature,[1] our study showed that patients with hematological malignancies and candidemia received chemotherapy more frequently than patients with solid tumors. By the other hand, major surgery was much more common among patients with solid tumors than among those with hematological disease. This condition was already described in the literature[1,6] and should be recognized as a possible predisposing factor to the development of candidemia in patients with solid tumors. Although international guidelines[7] have applied the knowledge derived from patients with hematological malignancies to patients with solid tumors in the treatment

of fever in patients with cancer, we reinforce that these populations are very heterogeneous, and specific risk factors should be addressed to patients with solid tumors. Moreover, in accordance to the findings of Viscoli et al.,[1] most of solid tumors patients with candidemia in our study did not have metastatic disease, reinforcing the concept that candidemia do not occur only in patients with advanced disease.

In accordance to previous studies, species other than *Candida albicans* caused most episodes of candidemia in cancer patients in our study, mainly in patients with hematologic malignancies.[3,8,9] The recognition of species other than *Candida albicans* as pathogens in oncology patients are supposed to be the result of widespread use of antifungal agents in the early 1990's for prophylaxis after hematopoietic stem-cell transplantation and as treatment in the setting of febrile neutropenia.[10] However, some studies[3,11] have reported low use of azoles in Brazilian patients and a previous study showed that resistance to antifungals was uncommon among patients with candidemia treated in our medical center.[11] These data suggest that the previous use of antifungals is not the main factor associated with the emergency of species other than *Candida albicans* in our institution. Although we were not able to show differences in the distribution of *Candida* species between cancer and non-cancer patients and between patients with solid tumors and hematological malignancies, this may be related to the limited number of patients in the hematological group found in our study.

Due to therapeutic implications, it is well known that all patients with candidemia should have at least one dilated retinal examination to exclude the possibility of candidal endophthalmitis.[12] Unfortunately, ophthalmologic tests were not performed for most patients with candidemia in our study, mainly for patients with cancer.

Similar to other studies[13-18] the overall mortality among patients with candidemia in our study was 50.3%. Although this study was not designed to evaluate risk factors for death or attributable mortality in patients with candidemia, we did not find differences in the

mortality rate between patients with cancer and other underlying diseases and among those infected with *Candida albicans* and other *Candida* species.

Our main conclusions are that patients with candidemia may have different predisposing factors to acquire the infection when stratified according to baseline diseases. More studies are needed to emphasize specific risk factors for candidemia in patients with solid tumors. Following a worldwide trend, species other than *Candida albicans* were the main etiology of candidemia in this study. Therefore, continuous epidemiologic monitoring is necessary to follow further changes in the patterns of candidal infections.

REFERENCES

1. Viscoli C, Girmenia C, Marinus A, Collette L, Martino P, Vandercam B, et al. Candidemia in cancer patients: a prospective, multicenter surveillance study by the Invasive Fungal Infection Group (IFIG) of the European Organization for Research and Treatment of Cancer (EORTC). *Clin Infect Dis* 1999;28:1071-1079.

2. Ascioglu S, Rex JH, de Pauw B, Bennett JE, Bille J, Crokaert F, et al. Defining Opportunistic Invasive Fungal Infections in Immunocompromised Patients with Cancer and Hematopoietic Stem Cell Transplants: An International Consensus. *Clin Infect Dis* 2002;34:7-14.

3. Nucci M, Silveira MI, Spector N, Silveira F, Velasco E, Martins CA, et al. Fungemia in cancer patients in Brazil: predominance of non-albicans species. *Mycopathologia* 1998;141:65-68.

4. Bodey GP. Candidiasis in cancer patients. Am J Med 1984;77:S13-S19.

5. Schwartz RS, Mackintosh FR, Schrier SL, Greenberg PL. Multivariate analysis of factors associated with invasive fungal disease during remission induction therapy for acute myelogenous leukemia. *Cancer* 1984;53:411-419.

6. Maksymiuk NA, Thongprasert S, Hopfer R, Luna M, Finstein V, Bodey GP. Systemic candidiasis in cancer patients. *Am J Med* 1984;77:S20-S27.

7. Hughes WT, Armstrong D, Bodey GP, Bow EJ, Brown AE, Calandra T, et al. 2002 Guidelines for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer. *Clin Infect Dis* 2002;34:730-51.

8. Bodey GP, Mardani M, Hanna HA, Boktour M, Abbas J, Girgawy E, et al. The epidemiology of *Candida glabrata* and *Candida albicans* fungemia in immunocompromised patients with cancer. *Am J Med* 2002;112:380-385.

9. Trupl J, Kunova A, Oravcova E, Pichna P, Kukuckova E, Grausova S, et al. Resistance pattern of 2816 isolates isolated from 17631 blood cultures and etiology of bacteremia and fungemia in a single cancer institution. *Acta Oncol* 1997;36:643-649.

10. Marr KA. The changing spectrum of candidemia in oncology patients: therapeutic implications. *Curr Opin Infect Dis* 2000;13:615-620.

11. Antunes AGV, Pasqualotto AC, Diaz MC, d'Azevedo PA, Severo LC. Candidemia in a Brazilian tertiary care hospital: species distribution and antifungal susceptibility patterns. *Rev Inst Med trop S Paulo* 2004;46:239-41.

12. Pappas PG, Rex JH, Sobel JD, Filler SG, Dismukes WE, Walsh TJ, et al. Guidelines for treatment of candidiasis. *Clin Infect Dis* 2004;38:161-189.

13. Richet HM, Andremont A, Tancrede C, Pico JL, Jarvis WR. Risk factors for candidemia in patients with acute lymphocytic leukemia. *Rev Infect Dis* 1991;13:211-215.

14. Kralovicova K, Spanik S, Oravcova E, Mrazova M, Morova E, Gulikova V, et al. Fungemia in cancer patients undergoing chemotherapy versus surgery: risk factors, etiology and outcome. *Scand J Infect Dis* 1997;29:301-304.

15. Bodey G, Bueltmann B, Duguid W, Hanak H, Hotchi M, Mall G, et al. Fungal infections in cancer patients. An international autopsy survey. *Eur J Clin Microbiol & Infect Dis* 1992;11:99-109.

16. Kovacicova G, Spanik S, Kunova A, Trupl J, Sabo A, Koren P, et al. Prospective study of fungaemia in a single cancer institution over a 10-y period: aetiology, risk factors, consumption of antifungals and outcome in 140 patients. *Scand J Infect Dis* 2001;33:367-374.

17. Krčméry V Jr, Mrazova M, Kunova A, Grey E, Mardiak J, Jurga L, et al. Nosomial candidaemias due to species other than *Candida albicans* in cancer patients. Aetiology, risk factors, and outcome of 45 episodes within 10 years in a single cancer institution. *Support Care Cancer* 1999;7:428-431.

18. Karabinis A, Hill C, Leclercq B, Tancrède C, Baume D, Andremont A. Risk factors for candidemia in cancer patients: a case-control study. *J Clin Microbiol* 1988;26:429-432.

Table 1. Major predisposing conditions, antifungal treatment and outcome between patients with candidemia with or without cancer.

Variables			Cancer (%)	Non-cancer (%)	p value
Demographic factors	Age	1st quartile	20.8	0.2	
		2nd quartile (median)	50.0	7.8	< 0.001[c]
		3rd quartile	67.6	59.7	
	Children		21.6	53.0	< 0.001[a]
	Neonates		0.0	16.2	< 0.001[a]
	Male sex		54.1	44.4	0.195[a]
Major underlying diseases	Diabetes mellitus		13.5	12.8	0.890[a]
	HIV infection		1.4	6.8	0.157[b]
	Transplantation		1.4	3.4	0.650[b]
	Liver disease		2.7	5.2	0.486[b]
	Chronic obstructive pulmonary disease		4.1	14.5	0.021[a]
	Heart failure		1.4	10.3	0.018[b]
	Congenital malformations		0.0	29.1	< 0.001[a]
	Chronic renal failure		1.4	7.7	0.092[b]
Predisposing conditions	Neutropenia < 1000		36.5	4.3	< 0.001[a]
	Duration < 1000	1st quartile	4.0	1.0	
		2nd quartile (median)	7.0	1.5	0.016[c]
		3rd quartile	17.0	3.5	
	Neutropenia < 100		28.4	0.9	< 0.001[a]
	Mucositis		9.6	0.0	0.001[b]
	Diarrhea		28.4	25.6	0.677[a]
	Ileus		30.1	35.9	0.414[a]
	Gastrointestinal bleeding		15.1	23.9	0.141[a]
	Steroids		52.1	47.0	0.499[a]
	H2 blockers		56.8	53.0	0.611[a]
	Proton pump inhibitors		43.8	37.6	0.394[a]

	Previous stay in the ICU	47.3	78.6	< 0.001[a]
	Previous blood transfusion	75.7	68.4	0.278[a]
	Previous vasopressors requirement	20.3	58.1	< 0.001[a]
	Central venous catheter	82.4	76.1	0.297[a]
	Porth-a-cath	27.0	0.0	< 0.001[a]
	Mechanical ventilation	31.1	67.5	< 0.001[a]
	Urinary catheter	51.4	68.4	0.018[a]
	Arterial catheter	10.8	30.8	0.001[a]
	Enteral feeding	43.2	65.0	0.003[a]
Invasive medical procedures	Chest tube	9.5	23.9	0.012[a]
	Parenteral nutrition	20.3	47.0	< 0.001[a]
	Hemodialysis	5.4	5.1	1.000[b]
	Peritoneal dialysis	0.0	4.3	0.158[b]
	Major surgery	36.5	55.6	0.010[a]
	Gastrointestinal surgery	20.3	20.5	0.968[a]
	Neurosurgery	2.7	2.6	1.000[b]
	Cardiothoracic surgery	5.4	24.8	0.001[a]
	Median duration of antibiotic treatment	15	16	0.187[c]
	Number of antibiotic used (median)	3.5	4.0	0.009[c]
	2^{nd} or 3^{rd} generation cephalosporins	28.4	47.9	0.007[a]
Antibiotic use	4^{th} generation cephalosporins	40.5	23.9	0.015[a]
	Glycopeptides	44.6	65.8	0.004[a]
	Carbapenems	14.9	35.9	0.002[a]
	Aminoglycosides	44.6	59.0	0.052[a]
	Quinolones	27.0	25.6	0.832[a]
Breakthrough candidemia		10.8	10.3	0.903[a]
Previous bacteremia		33.8	33.3	0.949[a]
	No antifungal treatment	23.0	17.1	0.317[a]
Antifungal	Amphotericin B (desoxycholate)	70.7	82.5	0.086[a]
treatment	Fluconazole	55.2	48.5	0.418[a]

	Flucytosine	1.7	5.2	0.412[b]
Outcome	Death during hospitalization	47.3	52.1	0.515[a]
Total (n)		74	117	191

[a] Chi-square test; [b] Fisher's exact test; [c] Non-parametric Mann-Whitney test.

Table 2. Major underlying diseases, predisposing conditions, antifungal treatment and outcome between patients with candidemia and solid tumors or hematological malignancies.

Variables			Solid (%)	Hematological (%)	p value
Demographic factors	Age	1st quartile	34.4	4.8	
		2nd quartile (median)	54.3	14.7	0.006[c]
		3rd quartile	68.3	51.9	
	Children		14.0	47.1	0.007[b]
	Male sex		50.9	64.7	0.315[a]
Major underlying diseases	Diabetes mellitus		14.0	11.8	1.000[b]
	HIV infection		0.0	5.9	0.230[b]
	Transplantation		0.0	5.9	0.230[b]
	Liver disease		1.8	5.9	0.409[b]
	COPD		5.3	0.0	1.000[b]
	Heart failure		1.8	0.0	1.000[b]
	Chronic renal failure		1.8	0.0	1.000[b]
Predisposing conditions	Neutropenia < 1000		24.6	76.5	< 0.001[a]
	Duration < 1000	1st quartile	3.7	7.0	
		2nd quartile (median)	5.0	13.0	0.011[c]
		3rd quartile	7.0	21.0	
	Neutropenia < 100		15.8	70.6	< 0.001[b]
	Duration < 100	1st quartile	0.0	2.0	
		2nd quartile (median)	3.0	4.0	0.164[c]
		3rd quartile	5.0	11.5	
	Mucositis		8.8	12.5	0.644[b]
	Diarrhea		31.6	17.6	0.364[b]
	Ileus		36.8	6.3	0.028[b]
	Gastrointestinal bleeding		17.5	6.3	0.437[b]
	Steroids		42.9	82.4	0.004[a]
	H2 blockers		59.6	47.1	0.358[a]
	Proton pump inhibitors		46.4	35.3	0.418[a]

	Chemotherapy	29.8	88.2	< 0.001[a]
	Previous stay in the ICU	54.4	23.5	0.025[a]
	Previous blood transfusion	71.9	88.2	0.213[b]
	Previous vasopressors requirement	22.8	11.8	0.496[b]
	Central venous catheter	78.9	94.1	0.275[b]
	Port-a-cath	24.6	35.3	0.534[b]
	Mechanical ventilation	40.4	0.0	0.002[a]
	Urinary catheter	63.2	11.8	< 0.001[a]
	Arterial catheter	14.0	0.0	0.185[b]
	Enteral feeding	49.1	23.5	0.062[a]
Invasive medical procedures	Chest tube	12.3	0.0	0.192[b]
	Parenteral nutrition	24.6	5.9	0.167[b]
	Hemodialysis	5.3	5.9	1.000[b]
	Radiotherapy	10.5	5.9	1.000[b]
	Major surgery	47.4	0.0	< 0.001[a]
	Gastrointestinal surgery	23.3	0.0	0.016[b]
	Neurosurgery	3.5	0.0	1.000[b]
	Cardiothoracic surgery	7.0	0.0	0.568[b]
	Other surgery (e.g.: genitourinary)	22.8	0.0	0.031[b]
	Median duration of antibiotic treatment	15	15	0.969[c]
	Number of antibiotic used (median)	4	3	0.515[c]
Antibiotic Use	2nd or 3rd generation cephalosporins	31.6	17.6	0.364[b]
	Metronidazole or clindamycin	45.6	11.8	0.012[a]
	4th generation cephalosporins	31.6	70.6	0.004[a]
	Glycopeptides	40.4	58.8	0.179[a]
	Carbapenems	14.0	17.6	0.707[b]
	Aminoglycosides	47.4	35.3	0.379[a]
	Quinolones	31.6	11.8	0.131[b]
Bre 96 ugh candidemia		8.8	17.6	0.374[b]
Previous bacteremia		31.6	41.2	0.463[a]

	No antifungal treatment	24.6	17.6	0.746[b]
Antifungal	Amphotericin B (desoxycholate)	65.9	85.7	0.195[b]
treatment	Fluconazole	56.8	50.0	0.655[a]
	Flucytosine	0.0	7.1	0.241[b]
Outcome	Death during hospitalization	59.3	35.3	0.259[a]
Total (n)		57	17	74

[a] Chi-square test; [b] Fisher's exact test; [c] Non-parametric Mann-Whitney test.

4.4 Candidemia “de escape” (*breakthrough*)

Nosocomial candidemia in patients using antifungals (breakthrough): comparison to non-breakthrough episodes

Artigo submetido ao Journal of Infection em 3 de novembro de 2004.

Trabalho parcialmente apresentado no 10th European Congress of Medical Mycology, Wrocław, Polônia, 2004 (poster 063).

NOSOCOMIAL CANDIDEMIA IN PATIENTS USING ANTIFUNGALS (BREAKTHROUGH): COMPARISON TO NON-BREAKTHROUGH EPISODES

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This study was partially presented at the

10th European Congress of Medical Mycology, Wrocław, Poland, 2004

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Abstract

Objectives: To describe all consecutive cases of breakthrough candidemia (BT) that occurred in a large Brazilian hospital, and to compare risk factors, etiology, and the outcome of the infection among patients with breakthrough (BT) and non-BT candidemia.

Methods: Retrospective cohort study (1995-2003). BT candidemia was defined as the occurrence of candidemia in a patient receiving at least 3 days of systemic antifungal therapy.

Results: During the period of study, 20 patients had BT candidemia. Major underlying diseases were solid tumors (25.0%) and hematological malignancies (15.0%), and 60.0% were in use of amphotericin B. Species other than *C. albicans* caused 75% of candidemias in BT patients, mainly *C. parapsilosis*. Comparing to non-BT patients with candidemia (n=171), BT patients had more frequently mucositis, longer stay in the intensive care unit, and longer periods of hyperalimentation, mechanical ventilation, urinary catheters and large spectrum antibiotics. *Candida* isolation from sites other than blood occurred more frequently in BT patients (p=0.028), as well as the *Candida* isolation from central venous catheters (p=0.057). Mortality rate and *Candida* species distribution were similar among groups

Conclusions: Based on these observations, it seems that the source of BT candidemia can be not only endogenous, but also exogenous.

Key-words: Candidemia. Fungemia. Breakthrough candidemia. Breakthrough fungemia. Candidiasis.

Introduction

Breakthrough (BT) candidemia has been reported increasingly, and suggests the possibility of an infected intravascular device, significant immunosuppression, or microbiological resistance [1,2]. The purpose of this study was to describe all BT candidemias that occurred in our institution during the last 9 years, and to compare risk factors, *Candida* species distribution and the outcome of the infection among patients with BT and non-BT (non-breakthrough) candidemia.

Patients and Methods

A retrospective cohort study of nosocomial candidemia was performed during 1995-2003 in Santa Casa Complexo Hospitalar, a 1,200-bed tertiary Brazilian hospital. Nosocomial candidemia was defined as the presence of at least one blood culture positive for *Candida* obtained from a peripheral vein in a patient admitted for more than 72h, in association with signs and symptoms temporarily related. Breakthrough candidemia was defined as the occurrence of candidemia in a patient receiving at least 3 days of systemic antifungal therapy. Patients in which the only positive blood culture was drawn through catheter were excluded.

Medical charts were reviewed to record clinical and demographic characteristics presented in the period of 30 days before first blood sample positive for *Candida*. The following variables were studied: sex, age, underlying diseases, neutropenia (< 1000 cells/mm^3 and < 100 cells/mm^3), diarrhea, ileus, gastrointestinal bleeding, mucositis, previous bacteremia, use of central venous catheter (CVC), arterial catheter, hyperalimentation, enteral feeding, urinary catheter, mechanical ventilation, chest tube, hemodialysis, and major surgical procedures. Prior therapy with antibiotics, steroids, H2 blockers, proton pump inhibitors, cytotoxic drugs, vasopressors, and blood transfusion were also recorded. Severity of infection was estimated by the presence of shock requiring vasopressors at presentation. The outcome was defined as discharge or death while hospitalized.

Blood samples were processed with BacT/Alert™ or Isolator™. Only one isolate was included per patient (the first one). Negative strains at germ tubes tests were identified through kit ID 32C (BioMérieux, France).

Statistical analysis

Descriptive statistics were used to summarize the data. Pearson's chi-square and Fisher's exact test were used to evaluate the association between qualitative variables, and Mann Whitney test was used for the comparison of quantitative variables. The bilateral level of significance was 5%, and data analysis was performed with SPSS software.

Results

During the period of study, nosocomial candidemia occurred in 191 patients, and 10.5% were BT (n=20). Most of these BT patients were female (60.0%), and median age was 5.3 year-old (table 1). Major underlying diseases were solid tumors (25.0%), hematological malignancies (15.0%), and diabetes mellitus (15.0%). Most of BT episodes (60.0%) occurred with amphotericin B (median 0.92 mg/kg/d, range, 0.1-1.2 mg/kg), and 30.0% with fluconazole (median daily 3.5 mg/kg/d, range, 1.3-10.5 mg/kg). Other regimens (5.0% each) included ketoconazole (3.1 mg/kg/d), and liposomal amphotericin B (3.5 mg/kg/d). All patients were receiving antifungal agents for prophylaxis or empirical therapy.

Species other than *Candida albicans* caused 75% of candidemias in BT group, mainly *C. parapsilosis* (30.0%) and *C. tropicalis* (25.0%). *Candida* had been isolated in sites other than blood in 65.0% of BT patients, mainly CVC (35.0%) and urine (25.0%). Overall mortality in BT group was 55.0%.

BT and non-BT patients did not differ regarding sex, age or major underlying diseases (table 2). Nosocomial candidemia occurred after a median period of 28 days of hospitalization in BT group and 20 days in non-BT group (p=0.065). Mucositis were more common in BT patients, who had been in the intensive care unit (ICU) for longer periods and had received longer courses of hyperalimentation, mechanical ventilation, urinary catheters and antibiotics, mainly glycopeptides and carbapenems. BT patients had more frequently the isolation of *Candida* from sites other than blood (65.0% and 37.4%; p=0.017), as well as the isolation of *Candida* from CVC (35.0% and 15.8%; p=0.057). The distribution of *Candida* species causing candidemia, antifungal treatment and mortality rate were similar among groups.

Discussion

In this study, the prevalence of BT candidemia was 10.5% among patients with nosocomial candidemia. Rates of BT candidemia ranging from 10-31% has been reported [1,3-6], and this variation may be related mainly to patients' underlying diseases, with the highest rates occurring in patients with leukemia [3]. In addition, the different criterion that has been used for the definition of BT candidemia [1,4-6] has created difficulties for comparative purposes. As our institution is not a referral center for hematological malignancies and antifungals prophylaxis is not a common practice, these may explain the low prevalence of BT candidemia reported.

Similar to other studies [1,4], most of our BT episodes occurred in patients using amphotericin B, a large spectrum drug. Since median daily dose of amphotericin B was in the therapeutic range, low dose was not the reason for these episodes. On the other hand, those patients in use of fluconazole were receiving a low antifungal dose, and the patient in use of ketoconazole was receiving ranitidine, which may have decreased the absorption of this antifungal.

Although species other then *C. albicans* caused 75% of episodes in BT patients and 59% of cases in non-BT group, this difference was not statistically significant, a finding similar to previous studies [1,4]. It is possible that, if a large number of patients are studied, the proportion of candidemia caused by species other than *C. albicans* may be increased in BT infections. The emergence of species other than *C. albicans* in our medical center has been previously published [7].

We have found that mucositis, isolation of *Candida* from sites other than blood, longer ICU permanence, and longer exposure antibiotics and invasive procedures were more common in the BT patients. Similar findings have been described by other authors: Krcmery et al. [8] found that mucositis, prophylaxis with quinolones and catheter-associated fungemia were more common in BT patients;

Nucci and Colombo [4] revealed that profound neutropenia (< 100/mm^3), use of corticosteroids and large exposure to antibiotics were associated with BT candidemia, and Uzun et al. [1] showed that the presence of neutropenia at the time of first blood culture, being in an ICU during candidemia and previous corticosteroid use were significant independent risk factors for BT infection.

C. parapsilosis was the main species causing BT infection in our study (30.0%), a species very frequently associated with the use of catheters [9]. Differently from other study [8], in which catheter-associated fungemia were more common in BT infections, we were not able to show a significant association between the isolation of *Candida* from catheters and BT candidemia (p=0.057), which may be explained by the limited number of BT infections in our study. Similarly, other studies [1,4] failed to identify the presence of a catheter as a risk factor, probably due to the limited number of BT patients and to the high prevalence of catheters in non-BT group. Despite these controversies, it is possible that contaminated catheters can play an important role in the etiology of BT candidemia.

Similar to other studies [1,4,8], the mortality rate was similar among patients with BT and non-BT candidemia. After the diagnosis of candidemia, most of the BT patients had the antifungal treatment changed, either by increasing dosage, changing the drug or adding a new antifungal. The CVC was usually replaced.

The absence of susceptibility tests was one of the main limitations of our study. Although BT candidemia caused by highly resistant species of *Candida* has been reported [2,5,10], other studies have not implicated antifungal resistance as the reason for BT infection [4]. In addition, we have observed no antifungal resistance in a previous study [7], which may be related to the low consumption of azoles.

Our study had some other limitations. First, the retrospective design could have led to loose of information. Second, our study was conducted in a single

institution, which is not a referral center for hematological diseases. We do not know if our results can be fully extrapolated to centers specialized in hematological malignancies or to institutions where candidemia caused by less susceptible species are more frequent. Finally, the small number of patients in the BT group (n=20) limited the use of more sophisticated statistical analysis. Although logistic regression has been used with increased frequency because of its ability to model dichotomous outcomes, guidelines [11] for its use suggests that the number of the less common of the two possible outcomes divided by the number of predictor variables should be at least 10, and preferably greater. There is only one paper in MEDLINE database that included enough patients with BT candidemia to satisfy this criterion, with an event-per-variable ratio greater than 10 [1].

In conclusion, the frequency of BT candidemia was 10.5% in our medical center. Most of these episodes were caused by species other then *C. albicans*, mainly *C. parapsilosis*, and these patients had frequently the isolation of *Candida* from sites others than blood. Common risk factors presented in patients with BT candidemia included mucositis and longer duration of large spectrum antibiotics and invasive procedures. Based on these observations, it seems that the source of BT candidemia can be not only endogenous, but also exogenous. In our opinion, the contribution of CVC in the genesis of BT candidemia is not yet resolved, and new studies will be necessary to clarify this question, with a large number of BT patients being enrolled, preferably in multicenter studies. As previously shown, the mortality rate was not different among patients with BT and non-BT candidemia.

References

1. Uzun O, Ascioglu S, Anaissie EJ, Rex JH. Risk factors and predictors of outcome in patients with cancer and breakthrough candidemia. *Clin Infect Dis* 2001; 32: 1713–1717.

2. Myoken Y, Kyo T, Fujihara M, Sugata T, Mikami Y. Clinical significance of breakthrough fungemia caused by azole-resistant *Candida tropicalis* in patients with hematologic malignancies. *Haematologica* 2004; 89: 378–380.

3. Viscoli C, Girmenia C, Marinus A, Collette L, Martino P, Vandercam B, Doyen C, Lebeau B, Spence D, Krčméry V, De Pauw B, Meunier F. Candidemia in cancer patients: a prospective, multicenter surveillance study by the Invasive Fungal Infection Group (IFIG) of the European Organization for Research and Treatment of Cancer (EORTC). *Clin Infect Dis* 1999; 28: 1071–1079.

4. Nucci M, Colombo AL. Risk Factors for Breakthrough Candidemia. *Eur J Clin Microbiol Infect Dis* 2002; 21: 209–211.

5. Nguyen MH, Peacock Jr JE, Morris AJ, Tanner DC, Nguyen LN, Snydman DR, Wagener MM, Rinaldi MG, Yu VL. The changing face of candidemia: emergence of non-*Candida albicans* species and antifungal resistance. *Am J Med* 1996; 100: 617–623.

6. Kontoyiannis DP, Reddy BT, Hanna H, Bodey GP, Tarrand J, Raad II. Breakthrough candidemia in patients with cancer differs from de novo candidemia in host factors and *Candida* species but not intensity. *Infect Control Hosp Epidemiol* 2002; 23: 542–545.

7. Antunes AGV, Pasqualotto AC, Diaz MC, d'Azevedo PA, Severo LC. Candidemia in a Brazilian tertiary care hospital: species distribution and antifungal susceptibility patterns. *Rev Inst Med trop S Paulo* 2004; 46: 239–241.

8. Krcmery V Jr, Oravcova E, Spanik S, Mrazova-Studena M, Trupl J, Kunova A, Stopkova-Grey K, Kukuckova E, Krupova I, Demitrovicova A, Kralovicova K. Nosocomial breakthrough fungaemia during antifungal prophylaxis or empirical antifungal therapy in 41 cancer patients receiving antineoplastic chemotherapy: analysis of aetiology risk factors and outcome. *J Antimicrob Chemother* 1998; 41: 373–380.

9. Anaissie EJ, Rex JH, Uzun O, Vartivarian S. Predictors of adverse outcome in cancer patients with candidemia. *Am J Med* 1998; 104: 238–245.

10. Myoken Y, Kyo T, Kohara T, Fujihara M, Sugata T, Mikami Y. Breakthrough fungemia caused by azole-resistant *Candida albicans* in neutropenic patients with acute leukemia. *Clin Infect Dis* 2003; 36: 1496–1497.

11. Bagley SC, White H, Golomb BA. Logistic regression in the medical literature: Standards for use and reporting, with particular attention to one medical domain. *J Clin Epidemiol* 2001; 54: 979–985.

Table 1. Main characteristics of patients with breakthrough (BT) candidemia (n=20).

Age (years), sex	Underlying disease	Drug in use	Mean daily dose	Duration (days)	CVC in place	CVC removal (days)	*Candida* Species	*Candida* in other site	Treatment	Death (days)
0.1, F	Neonatal sepsis	AmB	0.9 mg/kg	7	Yes	Yes (5)	*C. humicola*	-	Added Flu	Yes (12)
0.2, M	Cystic fibrosis	AmB	0.9 mg/kg	15	Yes	Yes (4)	*C. famata*	Surgical site	Added 5-FU	Yes (102)
70, M	Prostatate cancer	Flu	1.3 mg/kg	4	Yes	No	*C. albicans*	Urine	Unchanged	Yes (4)
54, M	Larynx cancer	Keto	3.1 mg/kg	3	Yes	Yes (16)	*C. tropicalis*	Catheter	Unchanged	No
49, M	Liver TX	AmB	0.6 mg/kg	8	Yes	Yes (3)	*C. parapsilosis*	-	No treatment	No
68, F	Diabetes, Creutzfeldt-Jacob	Flu	2.2 mg/kg	12	No	-	*C. albicans*	Urine	Unchanged	No
9, F	Trauma, pancreatitis	AmB	1.0 mg/kg	30	Yes	Yes (4)	*C. parapsilosis*	Surgical site	Added 5-FU	Yes (596)
0.3, M	Congenital cardiopathy	Flu	10.0 mg/kg	27	Yes	Yes (2)	*C. tropicalis*	Catheter	Added AmB	Yes (72)
0.7, F	Congenital cardiopathy	AmB	0.9 mg/kg	4	Yes	Yes (10)	*C. krusei*	Catheter, ascitis	Increased AmB dose	Yes (13)
49, F	Pelvic sarcoma	AmB	1.2 mg/kg	12	Yes	Yes (7)	*C. tropicalis*	Urine	Unchanged	No
52, M	Leukemia	AmB	0.9 mg/kg	6	Yes	Yes (2)	*C. tropicalis*	-	Increased AmB dose	Yes (3)
2, F	Germ cell cancer	Flu	4.9 mg/kg	6	Yes	Yes (4)	*C. tropicalis*	Catheter	Changed to AmB	No
0.1, F	Congenital malform.	AmB	0.2 mg/kg	4	Yes	Yes (1)	*C. tropicalis*	Catheter, urine	Increased AmB dose	Yes (4)
15, M	Leukemia, BMT	L-AmB	3.5 mg/kg	27	Yes	Yes (6)	*C. globosa*	-	Unchanged	No
3, F	Wilms tumor	AmB	0.1 mg/kg	5	Yes	Yes (11)	*C. albicans*	-	Added Flu	No
41, F	AIDS	Flu	2.1 mg/kg	11	Yes	Yes (11)	*C. Albicans*	-	Unchanged	No
0.4, F	Intestinal	AmB	1.0	3	No	-	*C.*	-	Increased	Yes

	obstruction		mg/kg				*parapsilosis*		AmB and added Flu	(11)
0.1, F	Neonatal sepsis	AmB	0.4 mg/kg	3	Yes	Yes (13)	*C. albicans*	Urine	Unchanged	Yes (66)
4, M	Leukemia	Flu	10.5 mg/kg	3	Yes	Yes (7)	*C. parapsilosis*	Catheter	Changed to AmB	No
6, F	Esophageal stenosis	AmB	1.0 mg/kg	18	Yes	Yes (1)	*C. parapsilosis*	Urine, trach asp	Unchanged	Yes (64)

M = Male; F = Female; AmB = Amphotericin B desoxycholate; L-Amb = Liposomal amphotericin B; Flu = Fluconazole; Keto = Ketoconazole; 5-FU = Flucytosine; TX = Transplantation; BMT = Bone marrow transplantation; AIDS = Acquired immunodeficiency syndrome; CVC = Central venous catheter; trach asp = tracheal aspirate.

Table 2. Major demographic factors, underlying diseases, predisposing conditions, antifungal treatment and outcome among patients with and without breakthrough (BT) candidemia.

Variables			BT (%)	Non-BT (%)	p value
Demographic factors	Age	1st quartile	0.3	0.9	
		2nd quartile (median)	5.3	41.1	0.075 [c]
		3rd quartile	49.3	64.9	
Major underlying diseases	Female sex		60.0	50.9	0.440 [a]
	Cancer		40.0	38.6	0.903 [a]
	Diabetes mellitus		15.0	12.9	0.730 [b]
	HIV infection		5.0	4.7	1.000 [b]
	Chronic renal failure		0.0	5.8	0.603 [b]
	Neutropenia < 1000 cells/mm^3		30.0	15.4	0.116 [b]
	Duration of neutropenia	1st quartile	3	4	
		2nd quartile (median)	6	6	0.944 [c]
		3rd quartile	21	14	
	Neutropenia < 100 cells/mm^3		20.0	10.7	0.262 [b]
	Mucositis		15.0	2.4	0.027 [b]
Predisposing conditions	Diarrhea		30.0	26.3	0.725 [a]
	Ileus		40.0	32.9	0.528 [a]
	Gastrointestinal bleeding		20.0	20.6	1.000 [b]
	Steroids		65.0	47.1	0.129 [a]
	H2 blockers		70.0	52.6	0.140 [a]
	Proton pump inhibitors		35.0	40.6	0.629 [a]
	Chemotherapy		20.0	16.4	0.751 [b]
	Previous intensive care unit stay		65.0	66.7	0.881 [a]
	Median duration of ICU stay (days)		23.5	11.5	0.015 [c]
	Previous blood transfusion		80.0	70.2	0.359 [a]
	Previous vasopressors requirement		50.0	42.7	0.533 [a]

	Central venous catheter (CVC)	95.0	76.6	0.081 [b]
	Median duration of CVC (days)	21.0	16.0	0.022 [c]
	Port-a-cath	20.0	9.4	0.236 [b]
	Urinary catheter	75.0	60.2	0.198 [a]
	Duration of urinary catheter (days)	16.0	7.5	0.039 [c]
	Hyperalimentation	50.0	35.1	0.190 [a]
Invasive	Duration of hyperalimentation (days)	20.0	12.5	0.046 [c]
medical	Mechanical ventilation	55.0	53.2	0.880 [a]
procedures	Duration of mechanical ventilation (days)	15.0	8.0	0.018 [c]
	Enteral feeding	35.0	59.1	0.040 [a]
	Hemodialysis	5.0	5.3	1.000 [b]
	Chest tube	15.0	18.7	1.000 [b]
	Arterial catheter	25.0	22.8	0.784 [b]
	Major surgery	40.0	49.1	0.440 [a]
	Median duration of antibiotics (days)	24	15	0.006 [c]
	Median number of antibiotics	5	4	0.108 [c]
Antibiotic	Glycopeptides	80.0	55.0	0.032 [a]
use	Carbapenems	60.0	24.0	0.001 [a]
	2^{nd} or 3^{rd} generation cephalosporins	15.0	43.3	0.015 [a]
	4^{th} generation cephalosporins	30.0	30.4	0.970 [a]
Previous bacteremia		35.0	33.3	0.881 [a]
Concomitant bacteremia		25.0	16.4	0.350 [b]
Days between	1^{st} quartile	15	13	
admission and	2^{nd} quartile (median)	28	20	0.065 [c]
candidemia	3^{rd} quartile	60	30	
	No antifungal treatment	5.0	21.1	0.132 [b]
Antifungal	Amphotericin B (desoxycholate)	73.7	78.7	0.568 [b]
treatment	Fluconazole	57.9	50.0	0.519 [a]
	Flucytosine	10.5	2.9	0.158 [b]
	Shock requiring vasopressors	25.0	30.4	0.617 [a]

Death during hospitalization	55.0	49.7	0.654 [a]
Total (n)	20	171	191

[a] Chi-square test; [b] Fisher's test; [c] Non-parametric Mann-Whitney test.

5 CONSIDERAÇÕES FINAIS

Este trabalho permitiu a construção de um grande banco de dados, que segue sendo prospectivamente alimentado, sobre pacientes com candidemia. Embora não tenhamos aqui avaliado a incidência de candidemia, a mortalidade atribuível à doença, os preditores de mortalidade, o impacto da remoção dos cateteres ou os fatores de risco para candidemia por diferentes espécies de *Candida*, estas são metas para próximas publicações. Em função do consumo crescente de antifúngicos na Instituição (dados não mostrados), é importante que sigamos monitorando as espécies de *Candida* associadas a candidemia, bem como o padrão de suscetibilidade das mesmas aos antifúngicos.

É importante, ainda, reconhecer algumas limitações deste estudo. Por ter sido realizado em única Instituição, onde a prevalência de pacientes com malignidades hematológicas é baixa e o uso profilático de antifúngicos não é prática comum, é possível que não possamos generalizar os dados para Instituições com características outras que as aqui descritas. O desenho retrospectivo deste estudo, podendo ter levado a perda de informações, e a ausência de testes de suscetibilidade aos antifúngicos são também limitações a serem reconhecidas. Finalmente, este estudo não foi desenhado para avaliar risco; devido à ausência de grupo controle sem candidemia, é possível que muitas das diferenças observadas entre os subgrupos de pacientes com candidemia sejam reflexo de diferenças naturais entre estas diversas populações, independente da presença de candidemia. Ainda, o pequeno número de pacientes em muitos destes subgrupos impediu o uso de técnicas estatísticas mais sofisticadas, como regressão logística.

6 CONCLUSÕES

Conclusões gerais do estudo

- Os pacientes com diagnóstico de candidemia na Santa Casa Complexo Hospitalar entre fevereiro de 1995 e dezembro de 2003 foram em sua maioria do sexo feminino e a idade mediana foi de 41,0 anos. O percentual de crianças foi de 39,0%;

- Câncer foi a doença de base mais prevalente entre os pacientes com candidemia. A baixa prevalência de pacientes com neoplasias hematológicas neste estudo se deve às características da Instituição, que não é centro de referência para estas malignidades;

- As três espécies mais prevalentes em pacientes com candidemia foram *Candida albicans*, *Candida parapsilosis* e *Candida tropicalis*. *Candida glabrata* ocorreu em 3,8%, e *Candida krusei* em 2,4%. Outras espécies pouco freqüentes foram *Candida guilliermondii*, *Candida sake*, *Candida humicola*, *Candida famata*, *Candida lusitaniae*, *Candida intermedia*, *Candida dubliniensis*, *Candida lypolitica*, *Candida globosa* e *Candida valida*. Três pacientes tiveram fungemia por mais de uma espécie (1,5%): um caso de fungemia por *Candida glabrata* concomitante com fungemia por *Cryptococcus neoformans* (0,5%), um caso de fungemia por *Candida albicans* e *Candida tropicalis* (0,5%) e outro de *Candida tropicalis* e *Candida dubliniensis* (0,5%). Esses dados estão de acordo com estudos prévios confirmando a emergência de espécies não-*Candida albicans* no Brasil e no mundo; assim como em outros estudos brasileiros, foi baixa a prevalência de espécies com possível sensibilidade reduzida ou resistência ao fluconazol, como *Candida glabrata* e *Candida krusei*;

- Fatores de risco descritos em outros estudos foram freqüentemente encontrados nos pacientes com candidemia neste estudo, como procedimentos cirúrgicos, número de antimicrobianos, uso de antimicrobianos de amplo espectro, internação prévia em unidade de terapia intensiva, transfusão de hemoderivados, uso de bloqueadores H2 e corticosteróides, uso prévio de cateter venoso central, cateter urinário, dieta enteral, ventilação mecânica e nutrição parenteral;

- Candidemia *breakthrough* (de escape) ocorreu em 9,5% de todos os pacientes com candidemia;

- O exame do fundo de olho foi realizado em apenas 7,6% dos pacientes com candidemia neste estudo, e em nenhum caso foi documentada alteração compatível com endoftalmite por *Candida*;

- A mortalidade global entre os pacientes com candidemia neste estudo foi de 50,5%, semelhante àquela descrita em outros estudos.

Candidemia comunitária

- Os episódios de candidemia foram classificados como comunitários em 9,0% das vezes. O tempo mediano para a ocorrência da candidemia nosocomial foi de 20,0 dias;

- As principais doenças de base na população de pacientes com candidemia comunitária foram câncer (47,4%) e insuficiência renal crônica (36,8%). Previamente à candidemia, foi freqüente nesse grupo o uso de cateter venoso central e tratamento com hemodiálise, bem como o uso de antimicrobianos e o uso de corticosteróides. Insuficiência renal crônica ($p<0,001$) e hemodiálise ($p=0,027$) foram mais freqüentes em pacientes com candidemia comunitária do que naqueles com candidemia nosocomial, ao contrário da realização prévia de procedimentos invasivos, mais comum no grupo de pacientes com candidemia nosocomial (incluindo procedimentos cirúrgicos, uso de cateter venoso central, nutrição parenteral, ventilação mecânica invasiva, cateter urinário, cateter arterial, dieta enteral e dreno de tórax). Antimicrobianos foram também mais freqüentemente utilizados no grupo de pacientes com candidemia nosocomial, que também tiveram com maior frequência, previamente à candidemia, bacteremia, íleo e sangramento gastrointestinal. Uso de inibidores de bomba de prótons, internação em unidade de terapia intensiva, transfusão de hemoderivados e necessidade de vasopressores foram também mais freqüentes no grupo com candidemia nosocomial. Devido à ausência de grupo controle sem candidemia, é possível que as diferenças observadas sejam apenas diferenças naturais entre pacientes tratados dentro do ambiente hospitalar ou fora dele;

- *Candida parapsilosis* foi a espécie mais prevalente nos pacientes com candidemia comunitária, uma espécie comumente associada a infecções

relacionadas a cateteres. Não se observou diferença entre a distribuição das espécies de *Candida* causando candidemia no grupo de pacientes com infecção comunitária ou nosocomial;

- A maioria dos pacientes com candidemia comunitária havia sido hospitalizada nos 60 dias que precederam a candidemia e, em 21,1% dos pacientes, *Candida* foi isolada de cateter venoso central. Embora *Candida* pertença à microbiota da pele, é sabido que a freqüência de colonização se eleva durante hospitalizações. É possível que estes pacientes tenham sido colonizados durante hospitalizações prévias, e que as doenças de base, associadas ao uso de antimicrobianos e procedimentos médicos invasivos, possam ter facilitado o desenvolvimento da candidemia;

- A gravidade do evento, medida pelo escore APACHE II (em adultos), e a mortalidade global foi a mesma em indivíduos com candidemia comunitária e nosocomial;

- Como consideração final, é importante salientar que, embora tenhamos aqui separado os episódios de candidemia em “comunitários” e “nosocomiais”, esta classificação é, de certa forma, arbitrária, visto não termos a pretensão, com o emprego da denominação “comunitária”, de assegurar que a origem da infecção tenha sido na comunidade, mas sim que a candidemia foi lá manifesta;

Candidemia em crianças

- A proporção de crianças entre os pacientes com candidemia nosocomial foi de 40,8%. Entre estes, 19 (24,4%) eram neonatos, 76,5% dos quais eram prematuros;

- As principais doenças de base nos pacientes pediátricos foram malformações congênitas e câncer. Fatores de risco para candidemia foram comumente encontrados nos pacientes pediátricos deste estudo, incluindo cateteres venosos centrais, ventilação mecânica, cateter urinário, nutrição parenteral, uso de antimicrobianos e procedimentos cirúrgicos;

- Comparado com adultos, crianças com candidemia nosocomial foram mais expostas a terapia antimicrobiana de amplo espectro, bloqueadores H2, vasopressores, transfusão de hemoderivados, cateter arterial, gastrostomia, dreno de tórax, cirurgia cardiotorácica, ventilação mecânica invasiva e nutrição parenteral;

- Espécies não-*Candida albicans* foram a causa de 78,2% dos episódios de candidemia nosocomial em crianças, em especial *Candida parapsilosis* (38,5%); a freqüência de candidemia nosocomial por *Candida parapsilosis* foi maior em crianças do que em adultos (p=0,002), bem como o isolamento de *Candida* spp. de cateteres (p=0,019);

- Crianças foram mais freqüentemente tratadas para candidemia nosocomial com anfotericina B desoxicolato do que adultos (p<0,001), que por sua vez foram mais freqüentemente tratados com fluconazol (p=0,013); estas diferenças podem refletir preferências dos pediatras em tratar agressivamente candidemia em crianças, uma população onde, muitas vezes, a toxicidade da anfotericina B é menor do que em adultos;

- A mortalidade 30 dias após a candidemia foi maior em adultos do que em crianças (p=0,005), realidade já refletida em outros estudos na literatura;

- A proporção de adultos que não recebeu terapia antifúngica foi maior do que a de crianças (p=0,001), o que pode ter sido devido à mortalidade precoce encontrada no grupo de adultos, ocorrida muitas vezes antes do diagnóstico de candidemia;

Candidemia em pacientes com câncer

- A prevalência de câncer foi elevada no grupo de pacientes com candidemia nosocomial (38,7%). Diferentemente de muitos estudos já publicados sobre o tema, onde pacientes com malignidades hematológicas predominam entre aqueles com câncer e candidemia nosocomial, o diagnóstico de tumores sólidos foi mais comum neste estudo (77,0%), o que pode refletir as características dos pacientes atendidos na nossa Instituição;

- A maioria dos pacientes com candidemia e tumores sólidos tinha diagnóstico de doença neoplásica não-avançada (63,8%), e o principal sítio primário nos pacientes com tumores sólidos foi o tubo digestivo (36,6%). O diagnóstico mais freqüente em pacientes com malignidades hematológicas foi leucemia aguda, o que está de acordo com dados encontrados na literatura. As neoplasias hematológicas foram classificados como iniciais ou crônicas (35,3%), progressivas ou resistentes (29,4%), linfoma estágio I ou II (17,6%) e linfoma em estágio III ou IV (17,6%);

- Espécies não-*Candida albicans* causaram 59,1% dos episódios de candidemia nosocomial em pacientes com câncer, principalmente *Candida parapsilosis* (29,7%) e *Candida tropicalis* (13,5%); *Candida glabrata* e *Candida krusei* foram infreqüentes (2,7% cada). Não se observou diferença entre a distribuição de espécies de *Candida* causando candidemia nosocomial entre pacientes com ou sem câncer e entre pacientes com tumores sólidos ou malignidades hematológicas;

- Na estratificação de pacientes com candidemia nosocomial entre aqueles com câncer ou outros diagnósticos, observou-se que pacientes com câncer foram mais velhos e tiveram mais freqüentemente neutropenia, mucosite, presença de cateter do tipo *porth-a-cath* e exposição a cefalosporinas de 4ª geração. Por outro

lado, pacientes sem câncer tiveram maior exposição a procedimentos invasivos, antibióticos de amplo espectro, como glicopeptídeos e carbapenêmicos, e cirurgia;

- Entre os pacientes com candidemia nosocomial, uso prévio de corticosteróides, quimioterapia e cefepima foi mais comum em pacientes com malignidades hematológicas, comparando-se aos pacientes com tumores sólidos. Por sua vez, cirurgias foram mais comuns em pacientes com tumores sólidos, principalmente procedimentos cirúrgicos envolvendo o trato gastrointestinal, o que corrobora os dados encontrados na literatura;

- A mortalidade global entre os pacientes com candidemia nosocomial foi de 50,3%, similar entre pacientes com ou sem câncer e entre pacientes com tumores sólidos ou malignidades hematológicas;

- Estes dados demonstram que pacientes com câncer e candidemia nosocomial diferiram em vários aspectos quando estratificados de acordo com a doença de base. Mais estudos são necessários para esclarecer os fatores de risco para candidemia em pacientes com tumores sólidos;

Candidemia “de escape” (*breakthrough*)

- A prevalência de candidemia “de escape” (*breakthrough*) entre os pacientes com candidemia nosocomial neste estudo foi de 10,5%. A baixa prevalência de candidemia *breakthrough* neste estudo pode estar relacionada às características da Instituição, onde a prevalência de pacientes com malignidades hematológicas é baixa e terapia antifúngica profilática não é uma prática comum;

- A maioria dos pacientes com candidemia *breakthrough* vinha em uso de anfotericina B desoxicolato, em doses terapêuticas, por período mediano de 6,5 dias;

- Espécies não-*Candida albicans* foram a etiologia de 75% dos episódios de candidemia nosocomial no grupo de pacientes com infecção “de escape”. *Candida parapsilosis* (30,0%) e *Candida tropicalis* (25,0%) foram os principais agentes etiológicos neste grupo;

- Quando os pacientes com candidemia nosocomial foram estratificados como tendo infecção *breakthrough* ou não-*breakthrough*, não se observou diferença com respeito a sexo, idade, doenças de base, espécies de *Candida* causando candidemia ou mortalidade global. Mucosite foi mais comum em pacientes com candidemia *breakthrough*, que haviam estado na unidade de terapia intensiva por maior período, tendo também recebido, por período mais prolongado, nutrição parenteral, ventilação mecânica, cateter urinário e antimicrobianos, em especial glicopeptídeos e carbapenêmicos. O isolamento de *Candida* spp. de sítios outros que sangue foi mais freqüente em pacientes com infecção *breakthrough* (p=0,028); houve uma tendência a maior isolamento de *Candida* spp. de cateteres no grupo de pacientes com candidemia *breakthrough* (p=0,057);

- Após o diagnóstico de candidemia, o tratamento antifúngico foi trocado na maioria dos pacientes com candidemia *breakthrough*, através de incremento da dose, adição de antifúngico ou troca para novo antifúngico;

- Os dados sugerem que a fonte de candidemia *breakthrough* pode ser não apenas endógena, a partir do trato gastrointestinal, mas também exógena. A contribuição de cateteres venosos na gênese de candidemia *breakthrough* merece avaliação em novos estudos.

7 ANEXOS

7.1 Instrumento de coleta dos dados

1. IDENTIFICAÇÃO

Nome: _____ Registro: _____

Data de internação: ___/___/___ Idade: _____ Sexo: □ M □ F

Hospital: _____ N° IPD: _____ N° mestrado: _____

2. DADOS PRÉ-CANDIDEMIA

Condições predisponentes

Diabete melito □ Sim □ Não □ NI

IRC □ Sim □ Não □ NI

HIV □ Sim □ Não □ NI □ UDI

CD_4: _____ (ou número de linfócitos: ____)

Neoplasia □ Sim Qual: _____ □ Não

Transplantado □ Sim De que: _____

Há ___ meses □ Não □ NI

Queimado □ Sim (____ %) □ Não □ NI

Doença inflamatória intestinal □ Sim □ Não □ NI

Outras doenças GI _____

Anormalidade estrutural GU □ Sim Qual _____

□ Não □ NI

Outras doenças (pré-existentes) _____

_____

Dados microbiológicos

Candida isolada PRÉ-CANDIDEMIA em outro foco (listar no quadro)

□ Urina □ Pele □ Vagina □ Fezes □ Oral
□ Esôfago □ Cateter □ Escarro
□ Outros: _____
Data dos isolados: _____
□ Suspeita clinica sem isolamento Sitio(s): _____

Dados sobre a candidemia

Espécie: _____ Data do primeiro isolado: __/__/__
Método: □ Isolator® □ BacT/Alert® □ NI
Tempo crescimento: _____ h
Dados sobre a sensibilidade:_____
Mais de uma espécie □ SimQuais: _____ □ Não □ NI
Outras informações: _____

Dados clínicos

Motivos da internação: _____
_____

Fundo de olho □ Sim □ Não □ NI

Achados: _____

Unidade de internação: □ Clínica □ Cirúrgica

Cirurgia □ Sim □ Não □ NI

Mucosite □ Sim □ Não □ NI

Diarréia □ Sim □ Não □ NI

Íleo □ Sim □ Não □ NI

Hemorragia gastrointestinal □ Sim □ Não □ NI

Azotemia □ Sim □ Não □ NI

Leucopenia □ Sim □ Não □ NI
Mín. albumina _____ Máx. glicemia _____

Neutropenia (< 1000) □ Sim □ Não □ NI

Resolução: □ Sim □ Não □ NI
Nº de dias < 1000: ____ < 500: _____ < 100: _____

Valor no momento da candidemia: _____

UTI □ Sim □ Não □ NI

Período:_____

Peso do paciente: _____kg □ NI

Drogas

Anfotericina □ Sim □ Não □ NI

Anti-fúngicos orais □ Sim □ Não □ NI
Corticoterapia □ Sim □ Não □ NI
Quimioterapia □ Sim □ Não □ NI
Anti-ácidos □ Sim □ Não □ NI
Bloqueadores H_2 □ Sim □ Não □ NI
Inib. bomba prótons □ Sim □ Não □ NI

Outros

Hemodiálise □ Sim □ Não □ NI
Diálise peritoneal □ Sim □ Não □ NI

Radioterapia □ Sim □ Não □ NI
Transfusões □ Sim □ Não □ NI
Datas: _____

Neonatos

DN: ___/___/___ Capurro/IG: _____ Apgar 5min: _____
Via de parto: □ N □ Ces. □ NI
Complic. neonatais: _____
Idade mãe: _____ Pré-natal: □ Sim □ Não □ NI Nº cons.: _____
Peso nasc.: _____ kg □ PIG □ AIG □ GIG

3. DADOS PÓS-CANDIDEMIA

Primeiras 24h

△ Temp _____ △ FC _____ △ FR _____ △ PAM _____
△ PAS _____ △ PAD _____
Outros exames disponíveis: _____
_____
Internado na UTI? □ Sim □ Não □ NI
□ VM □ NPT □ Vasopressor

Intervenções

□ Sem tratamento especifico Data de início do tratamento: __/__/__
Outros dados sobre o tratamento: _____
_____
Necessitou: □ UTI □ VM □ NPT □ Vasopressor

Desfecho

□ Alta hospitalar Data: __/__/__ Duração total internação ____ dias
□ Óbito Data: __/__/__ Tempo seguimento: ____ dias
□ Complicações
Quais?_____
_____

4. TODOS OS CULTURAIS POSITIVOS

Data	Sítio	Microorganismo (s)

5. PROCEDIMENTOS REALIZADOS

Procedimento	Data (início-fim)

Incluir os 30 dias que antecederam a candidemia até o final do seguimento (TOT, SVD, flebotomia, cirurgias, CVC, SNG/SNE, drenos, entre outros).

6. ANTIMICROBIANOS UTILIZADOS

Fármaco	Início	Término	Número de dias

Inclui dados dos 30 dias que antecederam a candidemia até o final do seguimento.
Para antifúngicos, incluir a dose e a via.

CÁLCULO DO ESCORE APACHE II

A = Escore fisiológico agudo

Pontos	+4	+3	+2	+1	0	+1	+2	+3	+4
Temperatura (°C)	≥41	39-40,9		38,5-38,9	36-38,4	34-35,9	32-33,9	30-31,9	≤29,9
Pressão arterial média	≥160	130-159	110-129		70-109		50-69		≤49
Freqüência cardíaca	≥180	140-179	110-139		70-109		55-69	40-54	≤39
Freqüência respiratória	≥50	35-49		25-34	12-24	10-11	6-9		≤5
A-aPO_2 [a]	≥500	350-499	200-349		< 200				
PaO_2 [b]					> 70	61-70		55-60	<55
pH arterial	≥7,7	7,6-7,69		7,5-7,59	7,33-7,49		7,25-7,32	7,15-7,24	<7,15
Bicarbonato sérico	≥52	41-51,9		32-40,9	23-31,9		18-21,9	15-17,9	<15
Sódio sérico	≥180		160-179	155-159	150-154	130-149	120-129	111-119	≤110
Potássio sérico	≥7	6-6,9		5,5-5,9	3,5-5,4	3-3,4	2,5-2,9		<2,5
Creatinina sérica	≥3,5	2-3,4	1,5-1,9		0,6-1,4		< 0,6		
Hematócrito	≥60		50-59,9	46-49,9	30-45,9		20-29,9		<20
Contagem de leucócitos	≥40		20-39,9	15-19,9	3-14,9		1-2,9		<1
15 – (escala Glasgow) =									

[a] Se FiO_2 > 0,5
[b] Se FiO_2 < 0,5

B = Ajuste para a idade

Idade (anos)	Pontos
< 45	0
45-54	2
55-64	3
65-74	5
> 74	6

C = Ajuste para condições crônicas

Para qualquer um dos seguintes (5 pontos cada):[a]

1. Cirrose hepática comprovada por biópsia
2. Insuficiência cardíaca (classe funcional IV da NYHA)
3. Doença pulmonar obstrutiva crônica (DPOC) grave (hipercapnia, uso de oxigênio domiciliar)
4. Diálise crônica
5. Imunodepressão

[a] Adicionar 2 pontos se cirurgia eletiva ou neurocirurgia, e 5 pontos se cirurgia de emergência

Escore APACHE II total = A + B + C = _____

8 REFERÊNCIAS

1. Eggimann P, Garbino J, Pittet D. Epidemiology of *Candida* species infections in critically ill non-immunosuppressed patients. Lancet Infect Dis 2003;3:685-702.
2. Coleman DC, Rinaldi MG, Haynes KA, Rex JH, Summerbell RC, Anaissie EJ, Li A, Sullivan DJ. Importance of *Candida* species other than *Candida albicans* as opportunistic pathogens. Med Mycol 1998;36(Suppl 1):156-65.
3. Wey SB. Efeito da candidemia hospitalar sobre a letalidade e o tempo de hospitalização [tese]. São Paulo: Universidade Federal de São Paulo; 1988.
4. Braude AI, Rock JA. The syndrome of acute disseminated moniliasis in adults. Arch Intern Med 1959;104:93-100.
5. Hurley R. Acute disseminated (septicaemic) moniliasis in adults and children. Postgrad Med J 1964;40:644-53.
6. Richards KE, Parson CL, Bucciarelli L, Fellar I. Monialial sepsis in the surgical patient. Surg Clin North Am 1972;52:1399-406.
7. Dennis DL, Peterson CG, Fletcher WS. *Candida* septicemia in the severely traumatizes patient. J Trauma 1968;8:177-85.
8. Bodey GP. Candidiasis in cancer patients. Am J Med 1984;77(Suppl 40):13-19.
9. McGowan JE Jr, Barnes MW, Finland M. Bacteremia at Boston City Hospital: Occurrence and mortality during 12 selected years (1935-1972), with special reference to hospital-acquired cases. J Infect Dis 1975;132:316-335.
10. Allen JR, Hightower AW, Martin SM, Dixon RE. Secular trends in nosocomial infections: 1970-1979. Am J Med 1981;70:389-92.
11. Morrison AJ, Freer CV, Searcy MA, Landry SM, Wenzel RP. Nosocomial bloodstream infections: secular trends in a statewide surveillance program in Virginia. Infect Control 1986;7:550-3.
12. Hughes JM, Culver DH, White JW, Jarvis WR, Morgan MW, Munn VP, Mosser JL, Emori TG. Nosocomial infection surveillance, 1980-1982. MMWR Surveill Summ 1983;32(Suppl 4):1-16.
13. Jarvis WR, White JW, Munn VP, Mosser JL, Emori TG, Culver DH, Thornsberry C, Hughes JM. Nosocomial infection surveillance, 1983. MMWR Surveill Summ 1984;33(Suppl 2):9-21.
14. Anaissie E, Bodey GP. Nosocomial fungal infections: old problems and new challenges. Infect Dis Clin North Am 1989;3:867-82.
15. Bodey GP. The emergence of fungi as major hospital pathogens. J Hosp Infect 1988; 11(Suppl A):411-26.
16. Harvey RL, Myers JP. Nosocomial fungemia in a large community teaching hospital. Arch Intern Med 1987;147:2117-20.
17. Horn R, Wong B, Kiehn TE, Armstrong D. Fungemia in a cancer hospital: changing frequency, earlier onset, and results of therapy. Rev Infect Dis 1985;7:646-55.
18. Beck-Sague CM, Jarvis WR. Secular trends in the epidemiology of nosocomial fungal infections in the United States, 1980-1990. J Infect Dis 1993;167:1247-51.
19. Pfaller M, Wenzel R. Impact of changing epidemiology of fungal infections in the 1990s. Eur J Clin Microbiol Infect Dis 1992;11:287-91.
20. Banerjee SN, Emori G, Culver DH, Gaynes RP, Jarvis WR, Horan T, Edwards JR, Tolson J, Henderson T, Martone WJ. Secular trends in nosocomial primary bloodstream infections in the United States, 1980-1989. Am J Med 1991;91(3B):86-9.

21. Pfaller MA, Jones RN, Messer SA, Edmond MB, Wenzel RP. National surveillance of nosocomial blood stream infection due to *Candida albicans*: frequency

of occurrence and antifungal susceptibility in the SCOPE Program. Diagn Microbiol Infect Dis 1998;31:327-32.
22. Pfaller MA, Jones RN, Messer SA, Edmond MB, Wenzel RP. National surveillance of nosocomial blood stream infection due to species of *Candida* other than *Candida albicans*: frequency of occurrence and antifungal susceptibility in the SCOPE Program. Diagn Microbiol Infect Dis 1998;30:121-9.
23. Jarvis WR. Epidemiology of nosocomial fungal infections, with emphasis on *Candida* species. Clin Infect Dis 1995;20:1526-30.
24. Edmond MB, Wallace SE, McClish DK, Pfaller MA, Jones RN, Wenzel RP. Nosocomial bloodstream infections in United States hospitals: a three-year analysis. Clin Infect Dis 1999;29:239-44.
25. Trick WE, Fridkin SK, Edwards JR, Hajjeh RA, Gaynes RP. Secular trend of hospital-acquired candidemia among intensive care unit patients in the United States during 1989–1999. Clin Infect Dis 2002;35:627-30.
26. Karlowsky JA, Zhanel GG, Klym KA, Hoban DJ, Kabani AM. Candidemia in a Canadian tertiary care hospital from 1976 to 1996. Diagn Microbiol Infect Dis 1997;2:5-9.
27. Viscoli C, Girmenia C, Marinus A, Collette L, Martino P, Vandercam B, Doyen C, Lebeau B, Spence D, Krcmery V, De Pauw B, Meunier F. Candidemia in cancer patients: a prospective, multicenter surveillance study by the Invasive Fungal Infection Group (IFIG) of the European Organization for Research and Treatment of Cancer (EORTC). Clin Infect Dis 1999;28:1071-9.
28. Tortorano AM, Peman J, Bernhardt H, Klingspor L, Kibbler CC, Faure O, Biraghi E, Canton E, Zimmermann K, Seaton S, Grillot R. Epidemiology of candidaemia in Europe: results of 28-month European Confederation of Medical Mycology (ECMM) hospital-based surveillance study. Eur J Clin Microbiol Infect Dis 2004;23:317-22.
29. Krčméry V Jr, Kovacicova G. Longitudinal 10-year prospective survey of fungaemia in Slovak Republic: trends in etiology in 310 episodes. Diagn Microbiol Infect Dis 2000;36:7-11.
30. Sandven P. Epidemiology of candidemia. Rev Iberoam Micol 2000;17:73-81.
31. Chakrabarti A, Chander J, Kasturi P, Panigrahi D. Candidaemia: a 10-year study in an Indian teaching hospital. Mycosis 1992;35:47-51.
32. Hung CC, Chen YC, Chang SC, Luth KT, Hsieh WC. Nosocomial candidemia in a university in Taiwan. J Formos Med Assoc 1996;95:19-28.
33. Nguyen MH, Peacock JE Jr, Tanner DC, Morris AJ, Nguyen ML, Snydman DR, Wagner MM, Yu V. Therapeutic approaches in patients with candidemia. Evaluation in a multicenter, prospective, observational study. Arch Intern Med 1995;155:2429-35.
34. Phillips P, Shafran S, Garber G, Rotstein C, Smaill F, Fong I, Salit I, Miller K, Conly JM, Singer J, Ioannu S. Multicenter randomized trial of fluconazole versus amphotericin B for treatment of candidemia in non-neutropenic patients. Eur J Clin Microbiol Infect Dis 1997;16:337-45.
35. Rex JH, Bennet JE, Sugar AM, Pappas PG, Van der Horst CM, Edwards JE, Washburn RG, Scheld WM, Krchmer AW, Dine AP, Levenstein MJ, Weeb D. A randomized trial comparing fluconazole with amphotericin B for the treatm candidemia in patients without neutropenia. N Engl J Med 1994;331:1325-30.

36. Nguyen MH, Peacock JE, Morris AJ, Tanner DC. The changing face of candidemia: Emergence of non-*Candida albicans* species and antifungal resistance. Am J Med 1996;100:617-23.
37. Wingard JR. Importance of *Candida* species other than *Candida albicans* as pathogens in oncology patients. Clin Infect Dis 1995;20:115-25.

38. Price MF, LaRocco MT, Gently LO. Fluconazole suscetibilities of *Candida* species and distribuition of species recovered from blood cultures over a 5-year period. Antimicrob Agents Chemother 1994;38:1422-7.
39. Pfaller MA. Nosocomial candidiasis: emerging species, reservoirs, and modes of transmission. Clin Infect Dis 1996; 22(Suppl 2):89-94.
40. Rex JH, Pfaller MA, Barry AL, Nelson PW, Webb CD. Antifungal susceptibility testing of isolates from a randomized, multicenter trial of fluconazole vs. amphotericin B as treatment of non-neutropenic patients with candidemia. Antimicrob Agents Chemother 1995;39:40-4.
41. Abi-Said D, Anaissie E, Uzun O, Pinzcowski H, Vartivarian S. The epidemiology of hematogenous candidiasis caused by different *Candida* species. Clin Infect Dis 1997;24:1122-8.
42. Wenzel RP. Nosocomial candidemia: risk factors and attributable mortality. Clin Infect Dis 1995;20:1531-4.
43. Wingard JR, Merz WG, Rinaldi MG, Miller CB, Karp JE, Saral S. Association of *Torulopsis glabrata* infections with fluconazole prophylaxis in neutropenic bone marrow transplant patients. Antimicrob Agents Chemother 1993;37:1847-9.
44. Goodman JL, Winston DJ, Greenfield RA, Chandrasekar PH, Fox B, Kaizer H, Shadduck RK, Shea TC, Stiff P, Friedman DJ. A controlled trial of fluconazole to prevent fungal infections in patients undergoing bone marrow transplantation. N Engl J Med 1992;326:845-51.
45. Winston DJ, Chandrasekar PH, Lazarus HM, Goodman JL, Silber JL, Horowitz H, Shadduck RK, Rosenfeld CS, Ho WG, Islam MZ, et al. Fluconazole prophylaxis of fungal infections in patients with acute leukemia. Results of a randomized placebo-controlled, double-blind, multicenter trial. Ann Intern Med 1993;118:495-503.
46. Antunes AGV, Pasqualotto AC, Diaz MC, d'Azevedo PA, Severo LC. Candidemia in a Brazilian tertiary care hospital: species distribution and antifungal susceptibility patterns. Rev Inst Med trop S Paulo 2004;46:239-41.
47. Colombo AL, Nucci M, Salomão R, Branchini ML, Richtmann R, Derossi A, Wey SB. High rate of non-albicans candidemia in Brazilian tertiary care hospitals. Diagn Microbiol Infect Dis 1999;34:281-6.
48. Weinstein MP, Towns ML, Quartey SM, Mirrett S, Reimer LG, Parmigiani G, Reller LB. The clinical significance of positive blood cultures in the 1990s: a prospective comprehensive evaluation of the microbiology, epidemiology, and outcome of bacteremia and fungemia in adults. Clin Infect Dis 1997;24:584-602.
49. Pfaller MA, Jones RN, Doern GV, Sader HS, Messer SA, Houston A, Coffman S, Hollis RJ. Bloodstream infections due to *Candida* species: SENTRY antimicrobial surveillance program in North America and Latin America, 1997-1998. Antimicrob Agents Chemother 2000;44:747-51.
50. Kao AS, Brandt ME, Pruitt WR, Conn LA, Perkins BA, Stephens DS, Baughman WS, Reingold AL, Rothrock GA, Pfaller MA, Pinner RW, Hajjeh RA. The epidemiology of candidemia in two United States cities: results of a population-active surveillance. Clin Infect Dis 1999;29:1164-70.

51. Debusk CH, Daoud R,Thirumoorthi MC,Wilson FM, Khatib R. Candidemia: current epidemiologic characteristics and long-term follow-up of the survivors. Scand J Infect Dis 1994;26:697-703.
52. Rangel-Frausto MS, Wiblin T, Blumberg HM, Saiman L, Patterson J, Rinaldi M, Pfaller M, Edwards JE Jr, Jarvis W, Dawson J, Wenzel RP. National Epidemiology of Mycoses Survey (NEMIS): variations in rates of bloodstream infections due to *Candida* species in seven surgical intensive care units and six neonatal intensive care units. Clin Infect Dis 1999;29:253-8.

53. [137] Fraser VJ, Jones M, Dunkel J, Storfer S, Medoff G, Dunagan WC. Candidemia in a tertiary care hospital: epidemiology, risk factors, and predictors of mortality. Clin Infect Dis 1992;15:414-21.
54. Klingspor L, Törnqvist E, Johansson A, Petrini B, Forsum U, Hedin G. A Prospective Epidemiological Survey of Candidaemia in Sweden. Scand J Infect Dis 2004;36:52-5.
55. Hope W, Morton A, Eisen DP. Increase in prevalence of nosocomial non-*Candida albicans* candidaemia and the association of *Candida krusei* with fluconazole use. J Hosp Infect 2002;50:56-65.
56. Slavin MA. The epidemiology of candidaemia and mould infections in Australia. J Antimicrob Chemother 2002;49(Suppl 1): 3-6.
57. Pfaller MA, Diekema DJ. Twelve years of fluconazole in clinical practice: global trends in species distribution and fluconazole susceptibility of bloodstream isolates of *Candida*. Clin Microbiol Infect 2004;10(Suppl 1):11-23.
58. Denning DW, Kibbler CC, Barnes RA. British Society for Medical Mycology proposed standards of care for patients with invasive fungal infections. Lancet Infect Dis 2003;3:230-40.
59. Colombo AL, Perfect J, DiNubile M, Bartizal K, Motyl M, Hicks P, Lupinacci R, Sable C, Kartsonis N. Global distribution and outcomes for *Candida* species causing invasive candidiasis: results from an international randomized double-blind study of caspofungin versus amphotericin B for the treatment of invasive candidiasis. Eur J Clin Microbiol Infect Dis 2003;22:470-4.
60. Mora-Duarte J, Betts R, Rotstein C, Colombo AL, Thompson-Moya L, Smietana J, Lupinacci R, Sable C, Kartsonis N, Perfect J. Comparison of caspofungin and amphotericin B for invasive candidiasis. N Engl J Med 2002;347:2020-9.
61. Pfaller MA, Diekema DJ, Jones RN, Sader HS, Fluit AC, Hollis RJ, Messer SA. International surveillance of bloodstream infections due to *Candida* species: frequency of occurrence and in vitro susceptibilities to fluconazole, ravuconazole, and voriconazole of isolates collected from 1997 through 1999 in the SENTRY antimicrobial surveillance program. J Clin Microbiol 2001;39:3254-9.
62. Pfaller MA, Jones RN, Doern GV, Fluit AC, Verhoef J, Sader HS, Messer SA, Houston A, Coffman S, Hollis RJ. International surveillance of blood stream infections due to *Candida* species in the European SENTRY Program: species distribution and antifungal susceptibility including the investigational triazole and echinocandin agents. Diagn Microbiol Infect Dis 1999;35:19-25.
63. Godoy P, Tiraboschi IN, Serero LC, Bustamante B, Calvo B, Almeida LP, da Matta DA, Colombo AL. Species distribution and antifungal susceptibility profile of *Candida* spp. bloodstream isolates from Latin American hospitals. Mem Inst Oswaldo Cruz 2003;98:401-5.
64. Colombo AL, Guimarães T. Epidemiology of hematogenous infections ([137]
Candida spp. Rev Soc Bras Med Trop 2003;36:599-607.
65. Nucci M, Silveira MI, Spector N, Silveira F, Velasco E, Martins CA, Derossi A, Colombo AL, Pulcheri W. Fungemia in cancer patients in Brazil: predominance of non-*albicans* species. Mycopathologia 1998;141:65-8.
66. Colombo AL, Nakagawa Z, Valdetaro F, Branchini MLM, Kussano EJU, Nucci M. Susceptibility profile of 200 bloodstream isolates of *Candida* spp. collected from Brazilian tertiary care hospitals. Med Mycol 2003;41:235-9.
67. Costa SF, Marinho I, Araújo EA, Manrique AE, Medeiros EA, Levin AS. Nosocomial fungaemia: a 2-year prospective study. J Hosp Infect 2000;45:69-72.

68. Pais LPF. Avaliação do comportamento epidemiológico e de práticas terapêuticas nos episódios de candidemia registrados em dois hospitais universitários no período de 1994 a 1998 [Tese]. São Paulo: Universidade Federal de São Paulo; 1999.
69. Rosas RC, Salomão R, da Matta DA, Lopes HV, Pignatari AC, Colombo AL. Bloodstream infections in late-stage acquired immunodeficiency syndrome patients evaluated by a lysis centrifugation system. Mem Inst Oswaldo Cruz 2003;98:529-32.
70. Matsumoto FE, Gandra RF, Ruiz LS, Auler ME, Marques SAV, Pires MFC, Gambale W, Paula CR. Yeasts isolated from blood and catheter in children from a Public Hospital of São Paulo, Brazil. Mycopathologia 2001;154:63-9.
71. Marques SR. Candidemias: aspectos preditivos da infecção em crianças hospitalizadas [tese]. São Paulo: Coordenação dos Institutos de Pequisa da Secretaria da Saúde do Estado de São Paulo; 2002.
72. Feferbaum R, Picchi M, Diniz EMA, Cecon MEJR, Krebs VLI, Ramos JCA, Vaz FAC. Fatores associados à candidíase em recém-nascidos em unidade de terapia intensiva neonatal. Rev Paul Pediatr 2000;18:121-4.
73. Goldani LZ, Mário PSS. *Candida tropicalis* fungemia in a tertiary care hospital. J Infection 2003;46:155-60.
74. Edwards JE, Bodey GP, Bowden RA, Büchner T, de Pauw BE, Filler SG, Ghannoum MA, Glauser M, Herbrecht R, Kauffman CA, Kohno S, Martino P, Meunier F, Mori T, Pfaller MA, Rex JH, Rogers TR, Rubin RH, Solomkin J, Viscoli C, Walsh TJ, White M. International conference for the development of a consensus on the management and prevention of severe candidal infections. Clin Infect Dis 1997;25:43-59.
75. Ascioglu S, Rex JH, de Pauw B, Bennett JE, Bille J, Crokaert F, Denning DW, Donnelly JP, Edwards JE, Erjavec Z, Fiere D, Lortholary O, Maertens O, Meis JF, Patterson TF, Ritter J, Selleslag D, Shah PM, Stevens DA, Walsh TJ. Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus. Clin Infect Dis 2002;34:7-14.
76. Berenguer J, Buck M, Witebsky F, Stock F, Pizzo PA, Walsh TJ. Lysis-centrifugation blood cultures in the detection of tissue-proven invasive candidiasis. Disseminated versus single-organ infection. Diagn Microbiol Infect Dis 1993;17:103-9.
77. Stevens DA. Diagnosis of fungal infections: current status. J Antimicrob Chemother 2002;49(Suppl 1):11-9.
78. Murray PR. Comparison of the lysis-centrifugation and agitated biphasic blood culture systems for detection of fungemia. J Clin Microbiol 1991;29:96-8.
79. Lyon R, Woods G. Comparison of the BacT/Alert and Isolator blood cu systems for recovery of fungi. Am J Clin Pathol 1995;103:660-2.
80. Hellinger WC, Cawley JJ, Alvarez S, Hogan SF, Harmsen WS, Ilstrup DM, Cockerill FR 3rd. Clinical comparison of the isolator and BacT/Alert aerobic blood culture systems. J Clin Microbiol 1995;33:1787-90.
81. Khan A, Okhravi Narciss, Lightman S. The eye in systemic sepsis. Clinical Medicine 2002;2:444-8.
82. Yeo SF, Wong B. Current status of nonculture methods for diagnosis of invasive fungal infections. Clin Microbiol Rev 2002;15:465-84.
83. Bjornson HS, Colley R, Bower RH, Duty VP, Schwartz-Fulton JT, Fischer JE. Association between microorganism growth at the catheter insertion site and colonization of the catheter in patients receiving total parenteral nutrition. Surgery 1982;92:720-7.
84. Spebar MJ, Pruitt BA. Candidiasis in the burned patient. J Trauma 1981;21:237-9.

85. Benoit D, Decruyenaere J, Vandewoude K, et al. Management of candidal thrombophlebitis of the central veins: Case report and review. Clin Infect Dis 1998;26:393-397.
86. Cole GT, Halawa AA, Anaissie EJ. The role of the gastrointestinal tract in hematogenous candidiasis: from the laboratory to the bedside. Clin Infect Dis 1996;22(Suppl 2):73-88.
87. Levy I, Rubin LG, Vasishtha S, Tucci V, Sood SK. Emergence of *Candida parapsilosis* as the predominant species causing candidemia in children. Clin Infect Dis 1998;26:1086-8.
88. Weems JJ. *Candida parapsilosis:* epidemiology, pathogenicity, clinical manifestations, and antimicrobial susceptibility. Clin Infect Dis 1992;14:756-66.
89. Nucci M, Anaissie E. Revisiting the source of candidemia: skin or gut? Clin Infect Dis 2001;33:1959-67.
90. Lundstrom T, Sobel J. Nosocomial candiduria: a review. Clin Infect Dis 2001;32:1602-7.
91. Ang BS, Telenti A, King B, Steckelberg JM, Wilson WR. Candidemia from a urinary tract source: microbiological aspects and clinical significance. Clin Infect Dis 1993;17:662-6.
92. Myerowitz RL, Pazin GJ, Allen CM. Disseminated candidiasis. Changes in incidence, underlying diseases, and pathology. Am J Clin Pathol 1977;68:29-38.
93. Meunier-Carpentier F, Kiehn TE, Armstrong D. Fungemia in the immunocompromised host. Changing patterns, antigenemia, high mortality. Am J Med 1981;71:363-70.
94. DeGregorio MW, Lee WM, Linker CA, Jacobs RA, Ries CA. Fungal infections in patients with acute leukemia. Am J Med 1982;73:543-8.
95. Wey SB, Mori M, Pfaller MA, Woolson RF, Wenzel RP. Risk factors for hospital-acquired candidemia. A matched case-control study. Arch Intern Med 1989;149:2349-53.
96. Safdar N, Maki DG. The commonality of risk factors for nosocomial colonization and infection with antimicrobial-resistant *Staphylococcus aureus*, enterococcus, gram-negative bacilli, *Clostridium difficile*, and *Candida*. Ann Intern Med 2002;136:834-44.
97. Bross J, Talbot GH, Maislin G, Hurwitz S, Strom BL. Risk factors for nosocomial candidemia: a case-control study in adults without leukemia. Am J Med 1989;87 20.

98. Schwartz RS, Mackintosh FR, Schrier SL, Greenberg PL. Multivariate analysis of factors associated with invasive fungal disease during remission induction therapy for acute myelogenous leukemia. Cancer 1984;53:411-9.
99. Karabinis A, Hill C, Leclercq B, Tancrède C, Baume D, Andremont A. Risk factors for candidemia in cancer patients: a case-control study. J Clin Microbiol 1988;26:429-32.
100. Wiley JM, Smith N, Leventhal BG, Silberman R, Oberle AD, Midgley G, Crow S, Jarvis WR. Invasive fungal disease in pediatric acute leukemia patients with fever and neutropenia during induction chemotherapy: a multivariate analysis of risk factors. J Clin Oncol 1990;8:280-6.
101. Richet HM, Andremont A, Tancrede C, Pico JL, Jarvis WR. Risk factors for candidemia in patients with acute lymphocytic leukemia. Rev Infect Dis 1991;13:211-5.
102. Saiman L, Ludington E, Pfaller M, Rangel-Frausto S, Wiblin RT, Dawson J, Blumberg HM, Patterson JE, Rinaldi M, Edwards JE, Wenzel RP, Jarvis W. Risk

factors for candidemia in neonatal intensive care unit patients. Pediatr Infect Dis J 2000;19:319-24.
103. Nucci M, Colombo AL. Risk Factors for Breakthrough Candidemia. Eur J Clin Microbiol Infect Dis 2002;21:209-11.
104. Pittet D, Monod M, Suter PM, Frenk E, Auckenthaler R. *Candida* colonization and subsequent infections in critically ill surgical patients. Ann Surg 1994;220:751-8.
105. Solomkin JS, Flohr AB, Quie PG, Simmons RL. The role of *Candida* in intraperitoneal infections. Surgery 1980;88:524-30.
106. Calandra T, Bille J, Schneider R, Mosimann F, Francioli P. Clinical significance of *Candida* isolated from peritoneum in surgical patients. Lancet 1989;2:1437-40.
107. Saiman L, Ludington E, Dawson JD, Patterson JE, Rangel-Frausto S, Wiblin RT, Blumberg HM, Pfaller M, Rinaldi M, Edwards JE, Wenzel RP, Jarvis W. Risk factors for *Candida* species colonization of neonatal intensive care unit patients. Pediatr Infect Dis J 2001;20:1119-24.
108. Sandven P, Qvist H, Skovlund E, Gierckscky KE. Significance of *Candida* recovered from intraoperative specimens in patients with intra-abdominal perforations. Crit Care Med 2002;30:541-7.
109. Nunes EP. Estudo sobre a colonização por espécies patogênicas de *Candida* spp. em pacientes internados em uma unidade de terapia intensiva [tese]. Rio de Janeiro: Universidade Federal do Rio de Janeiro; 2000.
110. Marino CGJ. Epidemiologia da colonização ou infecção por *Candida* spp. em pacientes internados em unidade de terapia intensiva [tese]. São Paulo: Universidade Federal de São Paulo; 1998.
111. Petri MG, König J, Moecke HP, Gramm HJ, Barkow H, Kujath P, Dennhart R, Schäfer H, Meyer N, Kalmar P, Thülig P, Müler J, Lode H. Epidemiology of invasive mycosis in ICU patients: a prospective multicenter study in 435 non-neutropenic patients. Intensive Care Med 1997;23:317-25.
112. Vazquez JA, Sanchez V, Dmuchowski C, Dembry LM, Sobel JD, Zervos MJ. Nosocomial acquisition of *Candida albicans*: an epidemiologic study. J Infect Dis 1993;168:195-201.
113. Patel R, Portela D, Badley AD, Harmsen WS, Larson-Keller JJ, Ilstrup DM, Keating MR, Wiesner RH, Krom RA, Paya CV. Risk factors of invasive *Candida* and non-*Candida* fungal infections after liver transplantation. Transplan 1996;62:926-34.
114. Tumbarello M, Tacconelli E, de Gaetano Donati K, Morace G, Fadda G, Cauda R. Candidemia in HIV-infected subjects. Eur J Clin Microbiol Infect Dis. 1999;18:478-83.
115. Blumberg HM, Jarvis WR, Soucie JM, Edwards JE, Patterson JE, Pfaller MA, Rangel-Frausto MS, Rinaldi MG, Saiman L, Wiblin RT, Wenzel RP. Risk factors for candidal bloodstream infections in surgical intensive care units: the NEMIS Prospective Multicenter Study. Clin Infect Dis 2001;33:177-86.
116. MacDonald L, Baker C, Chenoweth C. Risk factors for candidemia in a children's hospital. Clin Infect Dis 1998;26:642-5.
117. Anaissie EJ, Rex JH, Uzun O, Vartivarian S. Predictors of adverse outcome in cancer patients with candidemia. Am J Med 1998;104:238-45
118. Botas CM, Kurlat I, Young SM, Sola A. Disseminated candidal infections and intravenous hydrocortisone in preterm infants. Pediatrics 1995;95:883-7.
119. Collins LA, Samore MH, Roberts MS, Luzzati R, Jenkins RL, Lewis WD, Karchmer AW. Risk factors for invasive fungal infections complicating orthotopic liver transplantation. J Infect Dis 1994;170:644-52.

120. Slavin MA. The epidemiology of candidaemia and mould infections in Australia. J Antimicrob Chemother 2002;49(Suppl 1):3-6.
121. Lipsett PA. Fungal infections in surgical patients. Problems in General Surgery 2002;19:92-102.
122. Rossetti F, Brawner DL, Bowden R, Meyer WG, Schoch HG, Fisher L, Myerson D, Hackman RC, Shulman HM, Sale GE. Fungal liver infection in marrow transplant recipients: prevalence at autopsy, predisposing factors, and clinical features. Clin Infect Dis 1995;20:801-11.
123. Goodrich JM, Reed EC, Mori M, Fisher LD, Skerrett S, Dandliker PS, Klis B, Counts GW, Meyers JD. Clinical features and analysis of risk factors for invasive candidal infection after marrow transplantation. J Infect Dis 1991;164:731-40.
124. Solomon SL, Alexander H, Eley JW, Anderson RL, Goodpasture HC, Smart S, Furman RM, Martone WJ. Nosocomial fungemia in neonates associated with intravascular pressure-monitoring devices. Pediatr Infect Dis 1986;680-5.
125. Ekenna O, Sherertz RJ, Bingham H. Natural history of bloodstream infections in a burn patient population: the importance of candidemia. Am J Infect Control 1993;21:189-95.
126. Michalopoulos AS, Geroulanos S, Mentzelopoulos SD. Determinants of candidemia and candidemia-related death in cardiothoracic ICU patients. Chest 2003;124:2244-55.
127. Pappas PG, Rex JH, Sobel JD, Filler SG, Dismukes WE, Walsh TJ, Edwards JE. Guidelines for treatment of candidiasis. Clin Infect Dis 2004;38:161-89.
128. Marsh PK, Tally FP, Kellum J, Callow A, Gorbach SL. *Candida* infections in surgical patients. Ann Surg 1983;198:42-7.
129. Pittet D, Tarara D, Wenzel RP. Nococomial bloodstream infection in critically ill patients. Excess length of stay, extra costs, and attributable mortality. JAMA 1994;271:1598-601.
130. Gudlaugsson O, Gillespie S, Lee K, Berg JV, Hu J, Messer S, Herwaldt L, Pfaller M, Diekema D. Attributable Mortality of Nosocomial Candidemia, Revisited. Clin Infect Dis 2003;37:1172-7.
131. Blot SI, Hoste EA, Vandewoude KH, Colardyn FA. Estimates of attribu mortality of systemic candida infection in the ICU. J Crit Care 2003;18:130-1.
132. Lark RL, Chenoweth C, Saint S, Zemencuk JK, Lipsky BA, Plorde JJ. Four year prospective evaluation of nosocomial bacteremia: epidemiology, microbiology, and patient outcome. Diagn Microbiol Infect Dis 2000;38:131-40.
133. Luzzati R, Amalfitano G, Lazzarini L, Soldani F, Bellino S, Solbiati M, Danzi MC, Vento S, Todeschini G, Vivenza C, Concia E. Nosocomial candidemia in non-neutropenic patients at an Italian tertiary care hospital. Eur J Clin Microbiol Infect Dis 2000;19:602-7.
134. Voss A, le Noble JL, Verduyn Lunel FM, Foudraine NA, Meis JF. Candidemia in intensive care unit patients: risk factors for mortality. Infection 1997;25:8-11.
135. Hadley S, Lee WW, Ruthazer R, Nasraway Jr SA. Candidemia as a cause of septic shock and multiple organ failure in nonimmunocompromised patients. Crit Care Med 2002;30:1808-14.
136. Viudes A, Pemán J, Cantón E, Úbeda P, López-Ribot JL, Gobernado M. Candidemia at a Tertiary-Care Hospital: Epidemiology, Treatment, Clinical Outcome and Risk Factors for Death. Eur J Clin Microbiol Infect Dis 2002;21:767-74.
137. Nolla-Salas J, Sitges-Serra A, León-Gil C, Martínez-González J, León-Regidor MA, Ibáñez-Lucía P, Torres-Rodríguez JM. Candidemia in non-neutropenic critically ill patients: analysis of prognostic factors and assessment of systemic antifungal therapy. Intensive Care Med 1997;23:23-30.

138. Uzun O, Ascioglu S, Anaissie EJ, Rex JH. Risk factors and predictors of outcome in patients with cancer and breakthrough candidemia. Clin Infect Dis 2001;32:1713-7.
139. Nucci M, Silveira MI, Spector N, Silveira F, Velasco E, Akiti T, Barreiros G, Derossi A, Colombo AL, Pulcheri W. Risk factors for death among cancer patients with fungemia. Clin Infect Dis 1998;27:107-11.
140. Nucci M, Colombo AL, Silveira F, Richtmann R, Salomao R, Branchini ML, Spector N. Risk factors for death in patients with candidemia. Infect Control Hosp Epidemiol 1998;19:846-50.
141. Kovacicova G, Spanik S, Kunova A, Trupl J, Sabo A, Koren P, Sulcova M, Mateicka F, Novotny J, Pichnova E, Jurga L, Chmelik B, Obertik T, West D, Krcery V Jr. Prospective study of fungaemia in a single cancer institution over a 10-y period: aetiology, risk factors, consumption of antifungals and outcome in 140 patients. Scand J Infect Dis 2001;33:367-74.
142. Pappas PG, Rex JH, Lee J, Hamill RJ, Larsen RA, Powderly W, Kauffman CA, Hyslop N, Mangino JE, Chapman S, Horowitz HW, Edwards JE, Dismukes WE. A prospective observational study of candidemia: epidemiology, therapy, and influences on mortality in hospitalized adult and pediatric patients. Clin Infect Dis 2003;37:634-43.
143. Wey SB, Mori M, Pfaller MA, Woolson RF, Wenzel RP. Hospital acquired candidemia. The attributable mortality and excess length of stay. Arch Intern Med 1988;148:2642-5.
144. The ACCP/SCCM Consensus Conference Committee. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Chest 1992;101:1644-55.
145. Pollack MM, Ruttimann UE, Getson PR. Pediatric risk of mortality (PRISM) score. Crit Care Med 1998;16:1110-6.
146. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: A severity of disease classification system. Crit Care Med 1985;13:818-28.

Abstract

Objectives: To define demographic data, underlying diseases and risk factors associated with candidemia in Santa Casa Complexo Hospitalar, in the period comprising 02/17/1995 to 12/31/2003; to identify *Candida* species involved in these episodes; and to determine overall mortality among these patients.

Methods: retrospective cohort study with the inclusion of all consecutive cases of candidemia that were diagnosed in Santa Casa Complexo Hospitalar in the period of 1995-2003. For inclusion in this study, patients had to have signs and symptoms temporarily related to the isolation of *Candida* in blood culture obtained from a peripheral vein.

Results: 210 patients with candidemia were included in this study (91.0% of these infections were classified as nosocomial). Female sex was more prevalent (51.4%) and median age was 41.0 years-old. Cancer was the main underlying disease (solid tumors 30.5%, hematological diseases 9.0%). *Candida albicans* was the main *Candida* species (38.1%), followed by *Candida parapsilosis* (27.6%), and *Candida tropicalis* (15.7%); *Candida glabrata* occurred in 3.8%, and *Candida krusei* in 2.4%. Surgical procedures occurred in 43.8%, central venous catheters 74.8%, urinary catheter 57.1%, invasive mechanical ventilation 48.6%, and parenteral nutrition 33.8%; the median number of antibiotics prescribed was 4.0 (glycopeptides 54.3%, carbapenems 25.7%). Most of the patients with outpatient candidemia (52.6%) had been in the hospital in the 60 days preceding candidemia, and *Candida* was isolated from catheters in 21.1%; chronic renal failure ($p<0.001$) and hemodialysis ($p=0.027$) were more common in the outpatient group than in the nosocomial group; *Candida* species distribution was similar among groups. In the comparison to adults, pediatrics with nosocomial candidemia were more frequently exposed to large-spectrum

antibiotics (p<0.001), invasive mechanical ventilation (p=0,002), and parenteral nutrition (p<0.001). Nosocomial candidemia caused by *Candida parapsilosis* was more common in pediatrics (p=0.002), as well as *Candida* isolation from catheters (p=0.019); pediatrics were more frequently treated with amphotericin B than adults (p<0,001), who received mostly fluconazole (p=0.013). In patients with nosocomial candidemia, previous treatment with steroids (p=0.004), chemotherapy (p<0.001), and cefepime (p=0.004) were more common in hematological patients, compared with patients with solid tumors; otherwise, surgeries were more frequent in the latter (p<0.001), mainly in the gastrointestinal tract (p=0.016); *Candida* species distribution was similar among groups. Breakthrough candidemia occurred in 10.5% of patients with nosocomial candidemia; most of these patients were in use of amphotericin B, with doses in the therapeutic range, for a mean period of 9.6 days; *Candida* isolation from sites other than blood was more frequent in breakthrough patients (p=0.028). The overall mortality among patients with candidemia was 50.5%, with no difference regarding nosocomial or outpatient infection, cancer or other underlying diseases, and breakthrough or non-breakthrough infection. Mortality was higher in adults than in pediatrics (p=0.005).

Conclusion: Species other than *Candida albicans* were the main agents of candidemia in this study; similar to other Brazilian studies, the prevalence of species such as *Candida glabrata* and *Candida krusei* was low. Risk factors for candidemia described in other studies were frequently found in our patients, and the distribution of these risk factors differed according to the underlying characteristics of the patients. The mortality rate among patients with candidemia was similar to that found in the medical literature, higher in adults than in pediatrics.

Bibliografia consultada

Rother ET, Braga MER. Como elaborar sua tese: estruturas e referências. São Paulo: Projeto Gráfico e Editoração Eletrônica; 2001.