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Review

Characterisation of breakthrough invasive mycoses in echinocandin recipients: an evidence-based review

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ABSTRACT

The echinocandins have emerged as important antifungal agents in the current era. Despite their potent antifungal activity, breakthrough invasive mycoses occur in echinocandin recipients, however their precise incidence and causative pathogens are not well delineated. This review shows that breakthrough mycoses occur in 2.4% of patients receiving echinocandins as prophylaxis and are predominantly due to non-*albicans Candida* spp. and less frequently to invasive aspergillosis. *Candida* isolates demonstrating reduced susceptibility occurred following prolonged exposure to the echinocandins, primarily in severely immunocompromised patients, and manifested as recurrent episodes of candidaemia or invasive candidiasis.

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1. Introduction

The advent of the echinocandins has contributed substantially towards expansion of our armamentarium against invasive mycoses. Echinocandins inhibit the 1,3-β-D-glucan synthase complex, which synthesises β-D-glucan, an essential cell wall component of *Candida* and *Aspergillus* spp. [1]. Because of its unique mechanism of action, the echinocandins remain active against azole-resistant *Candida* spp. [2]. Furthermore, given their excellent safety profiles and minimal drug–drug interactions, they have emerged as an attractive option for the treatment of invasive candidiasis. However, zygomycetes, *Cryptococcus neoformans*, *Fusarium* spp. and *Trichosporon* spp. are innately resistant to the echinocandins [1]. Three echinocandins are currently available, caspofungin, micafungin and anidulafungin, and all are approved for the treatment of invasive and oroesophageal candidiasis. Additionally, caspofungin is also approved for empirical therapy of febrile neutropenia and for salvage therapy of aspergillosis, and micafungin for prophylaxis against invasive fungal infections (IFIs) in haematopoietic stem cell transplant (HSCT) recipients.

Although a prospective global surveillance study (2001–2006) did not observe echinocandin resistance in invasive candidiasis isolates [3], cases of breakthrough mycoses during echinocandin use or of echinocandin-resistant isolates are being increasingly reported, the majority of which are HSCT recipients or patients with haematological diseases. Nevertheless, the types of pathogens causing mycoses and how frequently these mycoses occur in echinocandin recipients are not well delineated. Thus, this review aimed to assess the incidence and characteristics of breakthrough mycoses in patients receiving echinocandins as prophylaxis or therapy.

2. Methods

2.1. Search strategy and selection criteria

English language articles regarding breakthrough mycoses or clinical isolates with reduced susceptibility or resistance to echinocandins during their prophylactic or therapeutic use were identified with a PubMed search from the 1950s to May 2009 by cross-referencing the keywords ‘echinocandins’, or ‘caspofungin’, or ‘micafungin’, or ‘anidulafungin’ and ‘prophylaxis’ or ‘treatment’, ‘candidiasis’, ‘aspergillosis’, or ‘invasive fungal infection’ or ‘mycoses’ or ‘breakthrough’ or ‘resistance’. Reference lists of original articles were reviewed for additional cases.

2.2. Definitions

Invasive mycoses were defined according to the criteria proposed by the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) [4]. Breakthrough mycoses were considered as proven or probable IFIs occurring during echinocandin receipt

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Table 1
Incidence of breakthrough invasive mycoses in echinocandin recipients.

	Case reports/series	Prophylactic use	Therapeutic use
No. of cases/studies	35 cases	9 studies	21 studies
Study populations (no. of cases/studies)	HSCT recipients (21), haematological disease/malignancy[a] (9), other[b] (5)	HSCT recipients (5), liver transplant recipients (2), AML or MDS[c] (1), abdominal disease[d] (1)	Patients with neutropenia (19; 2–100%), transplant recipients (17; SOT, 3.2–100% in 7; HSCT, 1.2–56.3% in 12), haematological disease/malignancy (14; 14.7–100%), diabetic patients (10; 2.1–35%), HIV patients (4; 1–5.7%)[e]
Echinocandins employed (no. of cases/studies)			
Caspofungin, micafungin, anidulafungin	Case numbers: 26, 8, 1	Study numbers: 5, 4, 0 Case numbers: 428, 527, 0	Study numbers: 12, 7, 3 Case numbers: 1422, 943, 282
Indications for echinocandin use (no. of cases/studies)	Prophylaxis (9) Treatment[f] (26)	Primary prophylaxis (8) Secondary prophylaxis (1)	Invasive candidiasis (16) Invasive aspergillosis (7) Suspicion of mycoses[g] (7)
Duration of echinocandin exposure before breakthrough mycoses (days) [median, range (no. of cases with data)]	26, 4–197 (35)	38, 5–88 (6)/63.5, 37–75 (6)[h]	N/A
No. of patients evaluable per study (median, range)	N/A	61, 6–425	48, 10–578
Incidence of breakthrough mycoses during study period (%, median, range)			
All mycoses	N/A	2.4, 0–7.3[i]	0, 0–13.6
Candidiasis		1.2, 0–5.3	0, 0–7.7
Aspergillosis		0, 0–2.8	0, 0–4.5
Trichosporonosis		0, 0–2	0, 0–0.2
Zygomycosis		0, 0–1.4	0, 0–0.4
Fusariosis		0, 0–0.9	0, 0–0.5
Cryptococcosis		0, 0–0.8	0, 0–4.5
Incidence of breakthrough mycoses during echinocandin use (%, median, range)			
All mycoses	N/A	1.4, 0–6.6	0, 0–13.6
Candidiasis		0.4, 0–5.3	0, 0–7.7
Aspergillosis		0, 0–2.8	0, 0–4.5
Trichosporonosis		0, 0–1.9	0, UC[j]
Zygomycosis		0, 0–0.2	0, UC[j]
Fusariosis		0, 0–0.9	0, 0–0.5
Cryptococcosis		0, 0–0.8	0, 0–4.5

HSCT, haematopoietic stem cell transplant; SOT, solid organ transplant; HIV, human immunodeficiency virus; N/A, not available.

[a] Patients with haematological malignancy included six patients with acute myeloid leukaemia, two patients with Hodgkin's lymphoma and one patient with acute lymphocytic leukaemia.

[b] Other included liver transplant recipient in one patient, systemic lupus erythematosus and lupus nephritis in one patient, myelodysplastic syndromes in one patient, bowel perforation in one patient and following elective pancreaticoduodenectomy in one patient.

[c] Patients with a new diagnosis of acute myeloid leukaemia or high-risk myelodysplastic syndromes undergoing induction chemotherapy.

[d] Patients with recurrent gastrointestinal perforation/anastomotic leakage or acute necrotising pancreatitis.

[e] Numbers in parenthesis denote the number of studies with such hosts and the range of reported percentages of such hosts in the studies.

[f] Echinocandins were used as therapeutic agents for febrile neutropenia (eight cases), invasive candidiasis (four cases), probable aspergillosis (two cases), pneumonia with unknown aetiology (two cases), fever of unknown origin (two cases), fever and otitis media (one case) and non-described diseases (seven cases).

[g] Including treatment for febrile neutropenia.

[h] Duration from echinocandin initiation to breakthrough infections during study periods/duration from echinocandin initiation to breakthrough infections during echinocandin use.

[i] Incidence was derived from eight studies of primary prophylaxis.

[j] UC, unable to calculate (range of incidence could not be calculated as all incidence was 0%).

or during the study period (the duration of echinocandin use and follow-up). Studies with breakthrough mycoses are discussed under three categories, which include case reports/series, and studies or clinical trials with echinocandin use as antifungal prophylaxis or as therapy. Primary prophylaxis was defined as prescription of echinocandins for the prevention of original infections in patients at risk for mycoses, and secondary prophylaxis as employment of echinocandins in patients with prior IFIs. Use of echinocandins for patients with invasive candidiasis, invasive aspergillosis or suspicion of invasive mycoses (including patients with febrile neutropenia) was defined as therapeutic use. The causative organisms of breakthrough mycoses were newly emerging fungi or fungal species different from the one isolated before echinocandin initiation. For studies with echinocandin use as treatment, only those providing explicit data to distinguish breakthrough from recurrent mycoses were included. For assessment of resistance to echinocandins, only studies where clinical information regarding echinocandin recipients was provided and (i) where paired fungal