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Impact of initial empirical antifungal agents on the outcome of critically ill patients with invasive candidiasis: analysis of the China-SCAN study

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ABSTRACT

The effect of different empirical antifungal agents on the clinical outcome of critically ill patients with invasive candidiasis (IC) has not been fully elucidated. In this study, 136 patients with proven IC who received empirical therapy in the China-SCAN multicentre study were retrospectively analysed. Initial empirical antifungal monotherapy consisted of a triazole [fluconazole ($n = 61$), voriconazole ($n = 20$) or itraconazole ($n = 12$)] or an echinocandin ($n = 43$). Hospital mortality as the primary outcome and global responses (clinical and microbiological) were assessed. The results indicated that rates of hospital mortality ($P = 0.006$) and intensive care unit (ICU) mortality ($P = 0.011$) were significantly lower in patients treated with an echinocandin compared with those receiving fluconazole, voriconazole or itraconazole. Multivariate regression analysis indicated that the type of antifungal agent used in empirical therapy was an independent predictor of hospital mortality ($P = 0.033$). Initial empirical echinocandin treatment was associated with decreased hospital mortality compared with fluconazole [odds ratio (OR) = 0.22, 95% confidence interval (CI) 0.06–0.85; $P = 0.028$], voriconazole (OR = 0.11, 95% CI 0.02–0.56; $P = 0.008$) or itraconazole (OR = 0.12, 95% CI 0.02–0.72; $P = 0.020$). Similar findings were observed for the clinical success endpoint. This study demonstrated that the initial empirical antifungal agent was an independent predictor of hospital mortality in critically ill patients with IC. Empirical therapy with an echinocandin was associated with decreased hospital mortality and greater clinical success than empirical therapy with fluconazole, voriconazole or itraconazole.

1. Introduction

Invasive candidiasis (IC) is a frequently occurring life-threatening infection in medical or surgical intensive care units (ICUs). It is associated with an increased duration of ICU and hospital stay, although controversies exist [1–3]. The concept that early initiation of adequate antifungal therapy improves the prognosis has been well established. In the treatment of *Candida* bloodstream infection, delayed antifungal therapy until a positive blood culture increased hospital mortality [4–6]. Early initiation of antifungal therapy is therefore recommended before candidaemia is ascertained, the causative *Candida* spp. is identified and its susceptibility to antifungal agents is known [5,7,8].

The preliminary selection of antifungal agents is also an important factor affecting the outcome of antifungal therapy. However, in critically ill patients with IC, none of the clinical trials conducted thus far have been adequately powered to assess the initial efficacy of antifungal agents in empirical therapy. Recent critiques of the guideline development process have advocated that further research is needed in actual clinical circumstances [9].

In the present study, we therefore carried out a retrospective cohort analysis of patients with proven IC who received empirical antifungal therapy in the China-SCAN study. The aim of the study was to evaluate whether the choice of the initial empirical antifungal agent would influence the clinical outcome.

2. Materials and methods

2.1. Study design and patients

The China-SCAN study is the largest prospective observational study on the prevalence of IC in China and was conducted between November 2009 and April 2011 in 67 participating ICUs across China.

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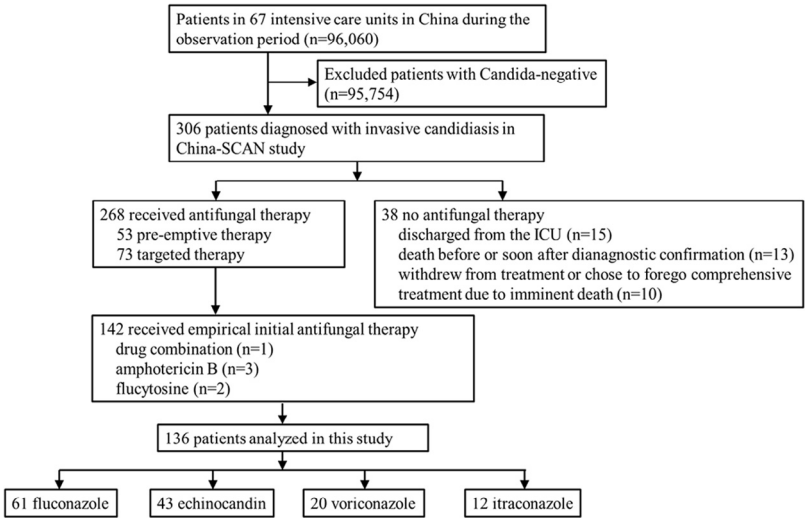

Fig. 1. China-SCAN study patient distribution and flowchart for this study.

Details of this study, including the study population as well as inclusion and exclusion criteria, have been published previously [10]. All participating hospitals accepted the Central Ethics Committee (Ethics Committee of Zhongda Hospital of Southeast University, Nanjing, China) review or conducted a further, independent, ethics review according to their own institutional policy. This clinical trial was registered at https://clinicaltrials.gov/ with ClinicalTrials.gov ID NCT01253954.

Fig. 1 presents a flowchart of patient screening and selection for this study. In the China-SCAN trial, 306 of 96,060 ICU patients were diagnosed with IC, of whom 268 (87.6%) received antifungal therapy. Furthermore, 142 of the 268 received empirical antifungal therapy, including 1 patient who simultaneously received two types of antifungal agents, 3 patients with amphotericin and 2 patients with flucytosine for empirical treatment. The medical records of 136 patients with empirical therapy were analysed. Based on the different types of antifungal therapy, all included patients were divided into four groups as follows: fluconazole ($n = 61$); echinocandin ($n = 43$); voriconazole ($n = 20$); and itraconazole ($n = 12$).

2.2. Evidence and definition of antifungal treatment

The evidence used to treat antifungal infection in the China-SCAN trial was divided into four categories based on guidelines for the diagnosis and management of candidiasis [11,12], as follows.

(a) Clinical signs of infection as diagnosed by the attending physician met at least two of the following clinical criteria: (i) body temperature ≥38 °C or <36 °C; (ii) respiratory rate ≥30 breaths/min; (iii) pulse rate ≥120 beats/min; and (iv) abnormal total peripheral white blood cell count ≥10,000/mm^3 or <4000/mm^3, or immature neutrophils >15%.
(b) Risk factors for fungal infection were as follows: aetiology-related factors such as neutropenia, haematological diseases, transplantation, surgery and tumours; treatment-related factors such as parenteral nutrition, broad-spectrum antibiotics and venous indwelling catheters; and other factors causing an increased rate of fungal infection such as the existence of underlying diseases, catheterisation and gastrointestinal dysfunction.
(c) Indirect evidence of fungal infections included the presence of the serological biomarkers galactomannan and β-D-glucan. The fungal colonisation index was calculated. The *Candida* colonisation index (CCI) was calculated as the ratio of the number of culture-positive surveillance sites to the total number of sites (mouth, lower respiratory tract, urine, wound and drainage tube) cultured. A CCI ≥0.5 was considered as indirect evidence of IC in this study.
(d) Fungal infections were directly determined from the culture of blood/tissue specimens obtained from normally sterile sites.

Based on the above classification, prophylactic, empirical, pre-emptive and targeted therapies were defined as follows: (i) prophylactic treatment was applied when the patient was at risk of developing candidiasis, but without clinical manifestations or evidence of infection; (ii) empirical therapy was defined as a situation of at-risk for IC and presenting with clinical features but without direct or indirect evidence of infection; (iii) pre-emptive therapy was defined as a therapy triggered by indirect evidence of candidiasis with clinical manifestations and risk factors present; and (iv) targeted treatment was initiated when direct evidence of candidiasis was proven. Patients receiving empirical antifungal therapy were included in this study.

The efficacy assessment was prospectively performed as part of the China-SCAN study. Complete clinical efficacy was defined as elimination of all signs and symptoms of IC; and partial efficacy was defined as improvement rather than complete elimination [10]. Microbiological elimination was defined as a negative culture from the original infection site [10]. The clinical success endpoint refers to complete remission and clinical improvement.

2.3. Statistical analysis

Quantitative data with normal distributions are denoted as the mean ± standard deviation. Student's *t*-test or one-way analysis of variance (ANOVA) was performed to compare means between groups. The rank-sum test was used to analyse abnormally distributed quantitative data, which were denoted using the median (interquartile range). The χ^2 test was applied to analyse categorical data. Variables significantly associated with mortality with a *P*-value of <0.01 by univariate analysis were introduced into a logistic stepwise regression model. All significant variables with collinearity were excluded from the regression model. The clinical relevance of each covariate was considered when deciding which ones should be retained as a candidate predictor for the multivariate model. The adjusted odds ratio (OR) and 95% confidence interval