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Attributable costs of patients with candidemia and potential implications of polymerase chain reaction–based pathogen detection on antifungal therapy in patients with sepsis☆,☆☆

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Abstract

Purpose: The purposes of this study were to calculate attributable costs of candidemia in patients with severe sepsis and to obtain preliminary data regarding the potential effects of polymerase chain reaction–based pathogen detection on antifungal therapy for these patients.

Methods: Patients treated between 2004 and 2010 because of severe sepsis were included into this retrospective analysis. The hospital management provided annual fixed costs per patient-day; data for variable intensive care unit costs were taken from the literature. Multiplex polymerase chain reaction (PCR) was used (VYOO®, SIRS-Lab, Jena, Germany) for pathogen detection in the blood.

Results: Thirty-two patients with candidemia were identified. Of 874 patients with sepsis, propensity score matching found 32 corresponding patients with sepsis but without candida infection but similar risk factors for developing candidemia. Attributable costs of candidemia were 7713.79 Euro (cost increase, 19.4%). Initiation of antifungal therapy was reduced from 67.5 (52.4, 90) hours in the group, where candida infection was determined by blood culture, to 31.0 (28.0, 37.5; $P < .01$) hours after detection by multiplex PCR.

Conclusions: Candidemia increases costs of care in patients with septic shock. Polymerase chain reaction–based pathogen detection significantly reduces the time to initiation of antifungal therapy. This might impact on the clinical course of the disease but need to be confirmed in further trials.

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☆☆ Conflicts of interest: K.R. and E.S. are shareholders of SIRS-Lab GmbH. E.S. and S.S. are inventors of a technique related to VYOO®.

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1. Introduction

Invasive candida infections are a significant burden for the health care system. The incidence of invasive candidosis was described with 19 to 29 infections per 100 000 inhabitants in a large US study between 1996 and 2003 [1]. On the intensive care unit (ICU), infection rates were reported to be 15.8 per 10 000 patient-days or 6.7 per 1000 admissions [2,3]. Invasive candida infection is associated with an increased ICU length of stay; crude mortality for invasive candidosis was estimated to be 61.8% [2].

Diagnosis of invasive candida infections is difficult. Microbiological cultures in upper airway secretions often reveal *Candida* spp, but these findings are rarely associated with invasive fungal infection [4]. Invasive fungal infection is commonly accompanied by candidemia [5]. Thus, a positive blood culture result or a positive culture result from a normally sterile body fluid should usually be required to initiate the administration of systemic antimycotics [6]. However, positive blood culture results for *Candida* species are a rare event and occur with an incidence of 1.42 per 1000 ICU-days [7]. This is in contrast to the frequent isolation of *Candida* spp from other sources in patients with sepsis [8,9].

Time to initiation of antifungal therapy is an important factor to avoid an unfavorable outcome [10-12]. The dilemma between the diagnostic uncertainty and the need for fast initiation of therapy remains an unresolved issue in the daily care of ICU patients. A preemptive antifungal treatment [13-15] in the presence of risk factors has been addressed as measures against the consequences of the diagnostic gap. However, the implementation is still a matter of debate.

Polymerase chain reaction (PCR)–based pathogen detection may offer a solution for this problem because PCR results are available within 1 working day and deliver more positive results compared with blood cultures in patients with presumed sepsis [16]. A recent meta-analysis concluded that PCR had a sensitivity of 0.95 and a specificity of 0.92 to diagnose candidemia [17]. Indeed, PCR-based detection of fungi has proven to be effective in the guidance of patients after stem cell transplantation [18]. Because the PCR is currently not able to replace culture methods, the application of PCR in clinical practice would significantly add to the costs of patient care. However, availability of data to assess cost-effectiveness is limited. Olaechea et al [19] estimated the additional costs for candida infections to 16 000 Euro in medical ICU patients. In the United States, costs of care associated with the therapy of candidemia were between $34 123 and $44 536, depending on the insurance status [20]. However, attributable costs of invasive candida infections in surgical ICU patients are not available.

The goal of this analysis was to estimate the attributable costs for candidemia in patients with severe sepsis. A second goal was to obtain preliminary results regarding the potential effects of PCR-based pathogen detection on the initiation of antifungal therapy for these patients.

2. Methods

2.1. Patients

This study was a retrospective propensity score–matched analysis comparing the costs of ICU therapy in patients with candidemia and those in patients with sepsis but without evidence of fungal infection. Patients eligible for inclusion into interventional and observational studies for severe sepsis and septic shock between 2004 and 2010 were identified from the study screening logs. All patients with at least 1 blood culture positive for *Candida* spp were considered having an invasive candida infection (candida group). Patients already having an antifungal therapy at that time were excluded from this group. Patients with sepsis without evidence of fungal infection were considered for matching (non–candida group).

In critically ill patients between May 2009 and June 2010, blood for PCR was obtained in parallel if a blood culture was taken for suspected sepsis. In a second analysis, time to antimicrobial therapy for patients from the candida group was compared with that for patients testing positive for fungi in the PCR (PCR group). Patients already having an antifungal therapy at that time were excluded from this group. The local ethics committee approved the study. The need for informed consent was waived due to the noninterventional and retrospective nature of the study. The study sponsors had no involvement in any part of the study as well as in the writing and decision for submission of the manuscript.

2.2. Procedures

Twenty milliliters of blood were taken by sterile venous puncture and distributed equally for conventional blood cultures into aerobic and anaerobic media by the treating physician. In the PCR group, 10 mL of EDTA blood were taken for PCR analysis, in addition to each pair of cultures. Polymerase chain reaction–based pathogen detection was done with a multiplex PCR-based assay (VYOO®; SIRS-Lab GmbH, Jena, Germany). This version of the assay detected DNA from a panel of 34 bacteria known to cause sepsis, as well as 5 genes coding for important antibiotic resistances [21]. In addition, VYOO® can specifically detect *Apergillus fumigatus* and *Candida krusei*. Other fungi are spotted by a panfungal detection addressing a DNA region conserved in all fungi. All measurements were accompanied by an empty buffer control to confirm that chemicals were not contaminated during the workflow. Polymerase chain

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