Infection

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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Candidemia;
Costs and cost analysis;
Antifungal agents;
Propensity score

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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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 ICU-days [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 antifungics [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
reaction results were disclosed to the treating physician as soon as they were available.

### 2.3. Estimation of ICU costs

Direct costs for ICU therapy for individual patients were estimated by using data derived by Moerer et al [22]. Briefly, the cost model consists of fixed and variable costs. Fixed costs were obtained from the hospital management by dividing the annual total staff and hotel costs by total patient-days of that year. Individual fixed costs were calculated by multiplying the fixed costs per day of the year corresponding to the patient’s ICU admission with the ICU length of stay. Variable costs used the estimated daily ICU therapy costs, depending on the survival status and the therapy applied (basic ICU therapy, sepsis therapy, respiratory failure therapy, renal replacement therapy, blood disorder therapy), as it has been calculated by Moerer et al [22] (Table 1 of the Supplementary Material). Individual variable costs were calculated by multiplying the daily therapy costs with the number of days where these therapies had been applied. Individual total ICU costs were calculated by the sum of fixed and variable costs.

### 2.4. Data analysis

Data were collected by data export from an electronic patient record (Copra System GmbH, Sasbachwalden, Germany), which provides complete daily documentation of the patient’s ICU stay such as vital status, medication, microbiological, and biochemistry results. This also includes all data necessary for matching and cost analysis.

A propensity score–matched pair analysis was performed to calculate attributable costs, as it has been described before [23]. Briefly, a logistic regression model obtaining variables known to impact risk of fungal infection (duration of antimicrobial therapy, dialysis, total parenteral nutrition, mechanical ventilation, and immunosuppressive therapy in days from ICU admission until onset of sepsis; presence of diabetes mellitus) with invasive fungal infection as the outcome was created. Year of ICU admission was also included into the matching algorithm. The propensity score to develop invasive fungal infection was used to match a patient to the non–candida group by the nearest-neighbor method in a 1:1 ratio. The median difference in costs between the candida group and the non–candida group was calculated as the attributable costs.

Discrete variables are expressed as percentages and continuous variables as median (25th and 75th percentiles), unless stated otherwise. Frequencies were compared using the $\chi^2$ test, and differences of medians were compared using the Mann-Whitney test. Analysis was performed with R, version 2.13.0 [24]. The R-package “nonrandom” was used for propensity score matching. A 2-sided $P$ less than .05 was considered statistically significant.

### 3. Results

Between January 2004 and April 2010, 1032 patients with sepsis were available in the sepsis database. One hundred fifty-eight patients were excluded because of antifungal therapy for any reason other than candidemia, resulting in 874 patients eligible for propensity score matching; 32 patients with positive blood culture for Candida spp were included into the candida group.

#### 3.1. Propensity score matching

The algorithm assigned 32 of the eligible 874 patients to the non–candida group. The quality of matching after propensity score matching according to the risk factors of invasive candida infections is shown in Table 1. Presence of risk factors was not different between the candida group and the non–candida group. Year of ICU admission was equally distributed between the 2 groups. Table 2 shows the demographic data of the patients, which entered the analysis. There was no difference in age, sex distribution, or severity of disease as measured by APACHE (Acute Physiology AND Chronic Health Evaluation) II-score and SAPS (Simplified Acute Physiology Score) II. Patients with candidemia had a higher ICU mortality than patients with

<table>
<thead>
<tr>
<th>Risk factors for invasive candida infection and year of admission</th>
<th>Candida group (n = 32)</th>
<th>Non–candida group (n = 32)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days on antibiotics</td>
<td>8 (1, 14.5)</td>
<td>7.5 (1, 15)</td>
<td>.699</td>
</tr>
<tr>
<td>Days on immunosuppressives</td>
<td>0 (0, 0)</td>
<td>0 (0, 0)</td>
<td>.586</td>
</tr>
<tr>
<td>Days on mechanical ventilation</td>
<td>6 (1, 12.5)</td>
<td>5 (1, 12.5)</td>
<td>.57</td>
</tr>
<tr>
<td>Days on dialysis</td>
<td>0 (0, 4.25)</td>
<td>0 (0, 4)</td>
<td>.982</td>
</tr>
<tr>
<td>Days on total parenteral nutrition</td>
<td>1 (0, 7.5)</td>
<td>1.5 (0.75, 5.5)</td>
<td>.74</td>
</tr>
<tr>
<td>Diabetes</td>
<td>9 (28.1%)</td>
<td>8 (25%)</td>
<td>.777</td>
</tr>
</tbody>
</table>

Distribution of parameters for propensity score matching between ICU admission and onset of sepsis. Candida group: patients with proof of Candida spp in the blood culture; non–candida group: patients without evidence of any fungal infection. Data are given as frequencies or medians (25th, 75th percentiles); $P$ values describe the statistical differences between the fungal group and the non–fungal group.
sepsis but without detectable candidemia. However, this difference did not reach statistical significance.

### 3.2. Cost analysis

The treatments, which govern the calculation of the variable costs, are shown in Table 3. Compared with the non–candida group, sepsis therapy defined as antimicrobial therapy and catecholamine administration was applied longer in the candida group. There was also a trend to more days of renal replacement therapy and blood disorder therapy in the candida group.

Patients of the candida group had higher total costs than did patients in the non–candida group, resulting in attributable costs for invasive candida infection of 7713.79 Euro (Table 4). This represents an increase in costs by 19.4%. However, difference in total costs did not reach statistical significance. This difference was mainly governed by the higher costs of sepsis therapy and blood disorder therapy in the candida group.

### 3.3. PCR-analysis

Eleven patients were identified having a positive PCR result for fungi. The demographic data of the PCR group compared with the candida group, where candidemia was diagnosed by blood culture, are shown in Table 5. In the PCR group, patients had a lower ICU mortality and a lower ICU length of stay. However, none of these differences reached statistical significance. Fig. 1 shows the detected fungi. In the candida group, blood cultures were positive mostly for *Candida albicans*. In the PCR group, all PCR detected a “pan-fungus.” VYOO detects a conserved gene contained by all fungi, reported as “pan-fungi” without further classification of the species. None of the PCR findings were confirmed by the concomitant blood culture.

Because the treating physicians were not blinded to the PCR results, a detection of panfungi resulted in the prescription of an antifungal therapy. Initiation of antifungal therapy was significantly reduced from 67.5 (52.4, 90) hours in the candida group, where candida infection was determined by blood culture, to 31.0 (28.0, 37.5; *P* < .01) hours in the PCR group (Fig. 2).

### 4. Discussion

The main finding of this study is that attributable costs of candidemia in patients with severe sepsis were 7713.79 Euro, representing an increase in costs by 19.4% in comparison with septic patients without candidemia. Median total costs of the ICU stay were extremely high in the candida group and non–candida group. Moerer et al [22] had calculated the median total costs of about €20 000 for surgical ICU patients with sepsis by using the same algorithm as in this study. This difference is mainly caused by the difference in ICU length of stay. In the study by Moerer et al, ICU length of stay was 16.4 days. In this study, patients with blood culture positive for *Candida* spp were patients with a prolonged ICU length of stay of about 28 days with several days of mechanical ventilation and antimicrobial pretreatment before onset of candidemia. This is in agreement with previous studies where invasive candida infection markedly

### Table 2  Demographic data for septic patients with and without candidemia

<table>
<thead>
<tr>
<th></th>
<th>Candida group (n = 32)</th>
<th>Non–candida group (n = 32)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>21 (65.6%)</td>
<td>19 (59.4%)</td>
<td>.606</td>
</tr>
<tr>
<td>Age (y)</td>
<td>65.8 (53.6, 70)</td>
<td>67.85 (54.38, 76.17)</td>
<td>.227</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.23 (23.29, 28.44)</td>
<td>27.55 (25.95, 29.41)</td>
<td>.225</td>
</tr>
<tr>
<td>SAPS II</td>
<td>49.5 (39.75, 63.5)</td>
<td>47 (36.75, 61.5)</td>
<td>.837</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>23 (18, 29)</td>
<td>20 (16, 30)</td>
<td>.676</td>
</tr>
<tr>
<td>ICU length of stay (d)</td>
<td>27.5 (17, 41.25)</td>
<td>26.5 (16.75, 35)</td>
<td>.595</td>
</tr>
<tr>
<td>ICU mortality</td>
<td>17 (53.1%)</td>
<td>10 (31.2%)</td>
<td>.076</td>
</tr>
</tbody>
</table>

Candida group: patients with proof of *Candida* spp in the blood culture; non–candida group: patients without evidence of any fungal infection.

### Table 3  Treatments during ICU stay that affect the variable cost calculation

<table>
<thead>
<tr>
<th></th>
<th>Candida group (n = 32)</th>
<th>Non–candida group (n = 32)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days with sepsis therapy</td>
<td>18 (12.75, 28.5)</td>
<td>12.5 (6.75, 19)</td>
<td>.004</td>
</tr>
<tr>
<td>Days on antibiotics</td>
<td>27.5 (17.25, 38.5)</td>
<td>21.5 (11.75, 28.25)</td>
<td>.103</td>
</tr>
<tr>
<td>Days on catecholamines</td>
<td>18 (12.75, 31.75)</td>
<td>13 (6.75, 21.5)</td>
<td>.015</td>
</tr>
<tr>
<td>Days with respiratory failure therapy</td>
<td>23 (14, 35.5)</td>
<td>22 (8.75, 31.25)</td>
<td>.207</td>
</tr>
<tr>
<td>Days with renal replacement therapy</td>
<td>4 (0, 14)</td>
<td>0 (0, 7.25)</td>
<td>.059</td>
</tr>
<tr>
<td>Days with blood disorder therapy</td>
<td>10 (8, 15)</td>
<td>7.5 (4, 12)</td>
<td>.055</td>
</tr>
</tbody>
</table>

Candida group: patients with proof of *Candida* spp in the blood culture; non–candida group: patients without evidence of any fungal infection. Data are given as medians (25th, 75th percentiles); P values describe the statistical differences between the fungal group and the non–fungal group.
increased ICU length of stay and, thereby, costs of patients' care [19]. Indeed, Olaechea et al [19] calculated a higher rate of additional costs of 16,000 Euro for candida infection. In the latter study, differences were calculated between patients who developed candida infection and patients who did not. Unfortunately, the groups were not matched. Thus, severity of disease was very different between the comparators. We have chosen a different approach. Because the non–candida group and candida group were matched for risk factors of invasive candida infections, both groups were similar in severity of disease and ICU length of stay. However, there were still higher costs in the group with candidemia. These costs were mainly caused by longer application of sepsis therapy consisting of antimicrobial, antifungal, and catecholamine therapy. Thus, even in critically ill patients, candidemia generates attributable costs.

Calculation of attributable costs by using propensity score matching has been successfully used before [23], but the results depend on the quality of matching. The pool of patients without evidence of fungal infections was large enough to ensure a 1:1 matching with the candida group. Main risk factors for candida in this patient population were mechanical ventilation and preceding antimicrobial therapy. The matching algorithm successfully found corresponding patients with similar risk factors but without proven evidence of fungal infection.

A second finding of this study is that time to antifungal therapy can be significantly reduced when the results of PCR are available for the treating physicians immediately. Although a turnaround time for PCR of 8 hours was not achievable in the routine care setting, the time to antifungal therapy was halved compared with the blood culture. This was associated with a trend to lower ICU mortality and ICU length of stay. Intensive care unit length of stay is the main cost driver in candida infections; Olaechea et al [19] reported an extended ICU stay of 12.7 days for patients with candida infection. We reported a similar difference of 10 days in ICU stay in patients where PCR initiated an earlier antifungal therapy than in the blood culture group. However, outcome parameters between PCR-positive and blood culture–positive patients were not statistically different in our patients with similar risk factors but without proven evidence of fungal infection.

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### Table 4 Median costs per patient in Euro

<table>
<thead>
<tr>
<th></th>
<th>Candida group (n = 32)</th>
<th>Non–candida group (n = 32)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total costs</td>
<td>47 464.5 (29 144.75, 67 387.5)</td>
<td>39 976 (22 053.5, 56 094.75)</td>
<td>.214</td>
</tr>
<tr>
<td>Fixed costs</td>
<td>20 612.5 (12 187.5, 29 715)</td>
<td>18 816 (11 317.5, 23 645)</td>
<td>.524</td>
</tr>
<tr>
<td>Variable costs</td>
<td>25 325.5 (17 300.75, 38 595.5)</td>
<td>19 270 (11 133.75, 31 203.5)</td>
<td>.06</td>
</tr>
<tr>
<td>Basic ICU therapy</td>
<td>15 313 (8670.75, 23 059.5)</td>
<td>12 213 (7112.25, 20 286)</td>
<td>.268</td>
</tr>
<tr>
<td>Sepsis therapy</td>
<td>3465 (2318.25, 5591.5)</td>
<td>2145 (1113.75, 3248)</td>
<td>.002</td>
</tr>
<tr>
<td>Respiratory failure therapy</td>
<td>207 (126, 319.5)</td>
<td>198 (78.75, 281.25)</td>
<td>.207</td>
</tr>
<tr>
<td>Renal replacement therapy</td>
<td>196 (0, 700)</td>
<td>0 (0, 350)</td>
<td>.071</td>
</tr>
<tr>
<td>Blood disorder therapy</td>
<td>5960 (4,005, 10 616.25)</td>
<td>4460 (1780, 6118.75)</td>
<td>.021</td>
</tr>
</tbody>
</table>

Candida group: patients with proof of Candida spp in the blood culture; non–candida group: patients without evidence of any fungal infection. Fixed costs represent staff and hotel costs; variable costs represent the treatment applied on a daily basis. Data are given as medians (25th, 75th percentiles); P values describe the statistical differences between the fungal group and the non–fungal group.

### Table 5 Demographic data of patients in the PCR group compared with the fungal group where candidemia was diagnosed by blood culture

<table>
<thead>
<tr>
<th></th>
<th>Candida group (blood culture) (n = 32)</th>
<th>PCR group (n = 11)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>21 (65.6%)</td>
<td>9 (81.8%)</td>
<td>.313</td>
</tr>
<tr>
<td>Age (y)</td>
<td>65.8 (53.6, 70)</td>
<td>69 (66, 71.5)</td>
<td>.282</td>
</tr>
<tr>
<td>SAPS 2 score</td>
<td>49.5 (39.75, 63.5)</td>
<td>38 (33, 48.5)</td>
<td>.092</td>
</tr>
<tr>
<td>ICU length of stay</td>
<td>27.5 (17, 41.25)</td>
<td>19 (16.5, 31)</td>
<td>.386</td>
</tr>
<tr>
<td>ICU mortality</td>
<td>17 (53.1%)</td>
<td>3 (27.3%)</td>
<td>.138</td>
</tr>
</tbody>
</table>

Candida group: patients with proof of Candida spp in the blood culture; PCR group: patients with detection of fungi in the PCR. Data are given as frequencies or medians (25th, 75th percentiles); P values describe the statistical differences between the fungal group and the PCR group.

**Fig. 1** Frequency of detected fungi in either blood culture or PCR. VYOO detects a conserved gene contained by all fungi, reported as panfungi without further classification of the species.
This study has several limitations. Proof of candidemia by blood cultures is an infrequent event. Therefore, the sample size was low. This is also true for the PCR group where only 11 patients tested positive for fungi. Therefore, several differences did not reach statistical significance. These data are therefore of preliminary nature only, but they warrant the need for a large multicenter study addressing this issue. The calculations of the variable costs were based on estimations from 2002. It must be expected that the variable costs have increased over the observation period. This is not accounted for in the current analysis. To avoid that this systematic error contributes to differences in costs between the groups, the year of ICU admission was added as matching variable. The distribution of the admission years is not unequal between the groups. Therefore, an increase in the true variable costs within the observation period should not have affected the attributable cost analysis. However, the impact of the PCR-dependent fungi detection on the costs of these patients could not be calculated because PCR was only available for a limited time where no sufficient number of matching candidates was available. Clinical data assessing the diagnostic accuracy of VYOO® are currently rare; several clinical studies are underway but have not yet been published. A recent study suggested that VYOO® performs similar to SeptiFast® (Roche Diagnostics) [28], which has a sensitivity of 0.8 and a specificity of 0.77 when compared with blood culture [16].

In conclusion, this preliminary study suggests that candidemia in patients with severe sepsis increases costs in patients with severe sepsis even when compared with a group of patients with similar disease severity. Polymerase chain reaction–based pathogen detection significantly reduces the time to antifungal therapy. This might contribute to a shorter ICU length of stay and might help not only to improve patient care but also to reduce costs in this group of patients. Further studies are warranted to prove whether PCR-guided antifungal can alter the clinical course of ICU patients with invasive fungal infections.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jcrc.2012.07.011.

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