VALUE IN HEALTH ▮ (2017) ▮▮▮–▮▮▮

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Cost-Effectiveness of *Candida* Polymerase Chain Reaction Detection and Empirical Antifungal Treatment among Patients with Suspected Fungal Peritonitis in the Intensive Care Unit

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ABSTRACT

Background: Mortality from intra-abdominal candidiasis in intensive care units (ICUs) is high. It takes many days for peritoneal-fluid fungal culture to become positive, and the recommended empirical antifungal therapy involves excessive costs. Polymerase chain reaction (PCR) should produce results more rapidly than fungal culture. **Objectives:** To perform a cost-effectiveness analysis of the combination of several diagnostic and therapeutic strategies to manage *Candida* peritonitis in non-neutropenic adult patients in ICUs. **Methods:** We constructed a decision tree model to evaluate the cost-effectiveness. Cost and effectiveness were taken into account in a 1-year time horizon and from the French National Health Insurance perspective. Six strategies were compared: fluconazole or echinocandin as an empirical therapy, plus diagnosis by fungal culture or detection by PCR of all *Candida* species, or use of PCR to detect most fluconazole-resistant *Candida* species (i.e., *Candida krusei* and *Candida glabrata*). **Results:** The use of fluconazole empirical treatment and PCR to detect all *Candida* species is more cost-effective than using fluconazole empirical treatment without PCR (incremental cost-effectiveness ratio of €40,055/quality-adjusted life-year). Empirical treatment with echinocandin plus PCR to detect *C. krusei* and *C. glabrata* is the most effective strategy, but has an incremental cost-effectiveness ratio of €93,776/quality-adjusted life-year. If the cost of echinocandin decreases, then strategies involving PCR plus empirical echinocandin become more cost-effective. **Conclusions:** Detection by PCR of all *Candida* species and of most fluconazole-resistant *Candida* species could improve the cost-effectiveness of fluconazole and echinocandin given to non-neutropenic patients with suspected peritoneal candidiasis in ICUs.

Keywords: antifungal drug, *Candida*, cost-effectiveness, diagnostic test, PCR, peritonitis.

Introduction

Over several decades, invasive candidiasis in intensive care units (ICUs) has become a significant cause of morbidity and mortality [1–3], including for non-neutropenic patients [4–6]. This observation particularly concerns *Candida* peritonitis [7–11]. When invasive candidiasis is suspected, a delay in initiating antifungal therapy and inappropriate treatments are associated with increased mortality [12–15], increased hospital stay, and extra supportive costs [16].

Culture remains the criterion standard diagnostic test, and the choice of appropriate antifungal therapy relies on identifying the fungal species and testing for antifungal susceptibility when the culture is positive. Because culture and susceptibility testing require several days to complete, international guidelines recommend immediate empirical treatment with echinocandin or fluconazole [17,18]. Fluconazole is the first-line agent. Nevertheless, some *Candida* species are often fluconazole-resistant, particularly *Candida krusei* and *Candida glabrata* [19]. They represent between 20% and 30% of cases of *Candida* peritonitis [9,10]. In these cases, echinocandins (caspofungin, micafungin, and anidulafungin) are preferred because less resistance is found with these drugs. Consequently, for critically ill patients, some guidelines recommend initial empirical therapy with echinocandin instead of fluconazole [20], whereas other guidelines prioritize both [17,18]. When antifungal susceptibility testing is available, echinocandins should be replaced by fluconazole if the pathogen is sensitive to this antifungal; otherwise echinocandin therapy

Conflicts of interest: The authors declare that they have no conflicts of interest.

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1098-3015$36.00 – see front matter

http://dx.doi.org/10.1016/j.jval.2017.06.009

should be maintained. Recent studies suggest that a step-down from echinocandin to fluconazole is not harmful, including for patients in ICUs who have a systemic infection, if the *Candida* identified is fluconazole-sensitive [21,22].

For many reasons, the challenge now is to minimize the duration of empirical treatment. First, the widespread and sometimes inadequate use of echinocandin has promoted the emergence of echinocandin-resistant strains [23]. Furthermore, empirical treatment with echinocandin is off-label for non-neutropenic patients in Europe and may expose some patients to unnecessary treatment and its attendant potential side effects. Finally, because the daily cost of echinocandin is much higher than that of fluconazole, the cost-effectiveness of a systematic echinocandin empirical therapy has been questioned [24,25].

In this context, any diagnostic test that allows rapid and sensitive detection of *Candida* species is likely to have important clinical and economic impacts. New in vitro diagnostic assays, based on polymerase chain reaction (PCR), are now available and should allow faster adjustment of antifungal treatments [26–29].

This study aimed to perform a cost-effectiveness analysis of the combination of several diagnostic and therapeutic strategies to manage *Candida* peritonitis in non-neutropenic adult patients in an ICU. Some of these strategies include the use of PCR to detect the most common fluconazole-resistant species (i.e., *C. krusei* and *C. glabrata*) or to detect all *Candida* strains, regardless of species. Although another study has focused on the economics of *Candida* infections within the bloodstream [30], our analysis has focused on non-neutropenic patients with severe peritonitis, for the following reasons: *Candida* peritonitis is a major cause of invasive candidiasis in patients in ICUs [31], the use of echinocandin for this indication is off-label, and there is particular benefit for clinicians to rationalize echinocandin prescriptions in this context.

Methods

Decision Model

A decision tree model was designed to compare the cost-effectiveness of six strategies combining three diagnostic methods applied to peritoneal fluid (use of PCR to detect *C. krusei* and *C. glabrata* only; use of PCR to detect all *Candida* species; and current practices based only on fungal-culture isolation) and the initial empirical treatment (echinocandin or fluconazole) (Fig. 1). We chose a decision tree model because the interventions (PCR and antifungal treatments) were implemented over a short period and peritoneal candidiasis is an acute pathology [32]. The parameters used in the model came from the published literature (data until December 1, 2016) and from expert opinions (reached by consensus among two medical mycologists, an infectiologist, and an intensive care physician) when no published data were available (Table 1). The perspective was of the French National Health Insurance and the time horizon was 1 year. Outcomes and costs linked to the treatments were assessed. The costs were expressed in 2015 euros. The checklist items from the Consolidated Health Economic Evaluation Reporting Standards [33] were used to assess cost-effectiveness.

Population

Selection

The target population was defined as all adult patients with peritonitis receiving empirical antifungal therapy in the ICU according to severity criteria [34].

Candida peritonitis: Prevalence and mortality

The prevalence of peritoneal candidiasis in the target population (patients with empirical antifungal treatment) was taken from a published study based on this pathology [11]. The proportions of different *Candida* and fluconazole-resistant species were obtained from a subgroup of patients with peritonitis from the AmarCand study [9].

Mortality related to candidiasis in the literature varies from 5% to 71%, depending on the population and study design [35]. The data for mortalities of patients with and without peritoneal candidiasis used in our model were taken from a study on *Candida* peritonitis (subgroup from the AmarCand2 study) [11].

Choice of antifungal therapy

An empirical therapy was started with echinocandin or injectable fluconazole until the culture or PCR results became available, respectively, 4 days and 1 day. If the *Candida* identified was not *C. glabrata* or *C. krusei*, echinocandin was replaced with fluconazole, or fluconazole was continued. For other cases, echinocandin was continued or introduced. The treatment was then modified according to results from the antifungal-susceptibility test. Average treatment duration was based on the European Society of Clinical Microbiology and Infection guidelines (14 days after the first negative sample) [17]. This interval could be reduced to take into account early mortality in the ICU.

Culture and PCR Characteristics

In this study, therapeutic decisions (choice of antifungal drug) were guided by results from tests. This situation is similar to a stratified medicine approach; thus, we decided to integrate test performances into the model [36]. PCR specificity and sensitivity were derived from a meta-analysis related to PCR detection of *Candida* in the blood [28] and culture specificity and sensitivity from an exploratory study related to detection of *Candida* in cultured peritoneal fluid [29]. A difference in limits of detection was observed between the use of PCR to detect *C. krusei* and *C. glabrata* and the use of PCR to detect all *Candida* species [26]. Thus, this suggests that the use of PCR to detect *C. krusei* and *C. glabrata* was more sensitive than the use of PCR to detect all *Candida* species, even though this difference has not been previously quantified. As a result, we hypothesized a 10% difference in sensitivity between these two types of PCR (expert opinion).

Outcomes

Efficacy and duration of antifungal treatment

We considered the effectiveness of antifungal therapy on a sensitive *Candida* strain to be similar between caspofungin and micafungin [37] and between the echinocandins and fluconazole [38]. In our model, the effectiveness of early antifungal therapy was defined by a reduction in mortality, which was estimated for patients with peritoneal candidiasis using data from the AmarCand2 study [11]. The probability of mortality of early treated patients was the probability of mortality of patients who were treated for peritoneal candidiasis multiplied by the decrease in mortality in case of early treatment. The probability of mortality for untreated patients was considered to be equal to that of patients in case of treatment failure [11]. The effectiveness was measured using life-years and quality-adjusted life-years (QALYs) gained. For the QALY calculation, we used the average number of days in the ICU for both survivors and deceased patients with peritonitis (data were from the French National Hospital Database: PMSI hospital database) and the utility for immunocompromised patients with an acute fungal infection to weight the ICU stays [39].