Economic Comparison of an Empirical Versus Diagnostic-Driven Strategy for Treating Invasive Fungal Disease in Immunocompromised Patients

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ABSTRACT

Purpose: Patients with persistent or recurrent neutropenic fevers at risk of invasive fungal disease (IFD) are treated empirically with antifungal therapy (AFT). Early treatment using a diagnostic-driven (DD) strategy may reduce clinical and economic burdens. We compared costs and outcomes of both strategies from a UK perspective.

Methods: An empirical strategy with conventional amphotericin B deoxycholate (C-AmB), liposomal amphotericin B (L-AmB), or caspofungin was compared with a DD strategy (initiated based on positive ELISA results for galactomannan antigen) and/or positive results for *Aspergillus* species on polymerase chain reaction assay) using C-AmB, voriconazole, or L-AmB in a decision-analytic model. Rates of IFD incidence, overall mortality, and IFD-related mortality in adults expected to be neutropenic for $\geq$10 days were obtained. The empirical strategy was assumed to identify 30% of IFD and targeted AFT to improve survival by a hazard ratio of 0.589. AFT-specific adverse events were obtained from a summary of product characteristics. Resource use was obtained, and costs were estimated by using standard UK costing sources. All costs are presented in 2012 British pounds sterling.

Findings: Total costs were 32% lower for the DD strategy (£1561.29) versus the empirical strategy (£2301.93) due to a reduced incidence of adverse events and decreased use of AFT. Administration of AFT was reduced by 41% (DD strategy, 74 of 1000; empirical strategy, 125 of 1000), with similar survival rates.

Implications: This study suggests that a DD strategy is likely to be cost-saving versus empirical treatment for immunocompromised patients with persistent or recurrent neutropenic fevers. (*Clin Ther*. 2015;37:1317–1328)

Key words: antifungal therapy, aspergillosis, cost benefit, fungal infection.

INTRODUCTION

Invasive fungal disease (IFD) is associated with high mortality rates in severely immunocompromised patients, such as those undergoing intensive chemotherapy or stem cell transplantation.[1] IFD results in increased hospital and intensive care unit costs, with

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pharmacy expenditures (including antifungal treatment) the main cost driver.[2]

Because IFD is life-threatening, empirical therapy is commonly used in at-risk patients.[3] With this strategy, patients are treated for suspected IFD when they present with persistent or recurrent neutropenic fevers that are unresponsive to broad-spectrum antibacterial therapy for 72 to 96 hours. Conventional amphotericin B deoxycholate (C-AmB), liposomal amphotericin B (L-AmB), and caspofungin are currently the only antifungal agents licensed for empirical treatment in the setting of persistent or recurrent neutropenic fevers. Empirical treatment can be costly, however,[4–6] with the potential for overtreatment of nonfungal fever, resulting in increased toxicity and treatment-related costs.[7]

Early use of diagnostic assays in a diagnostic-driven (DD) therapy strategy is 1 way to potentially identify patients with invasive aspergillosis (IA) more accurately and, consequently, to better select treatments for these patients. In addition, earlier diagnosis and targeted therapy may reduce costs and improve outcomes by eliminating unnecessary toxic treatment. Several studies have helped us to better understand the clinical impact of a DD strategy compared with a standard empirical strategy.[7–12] However, these studies do not highlight the economic impact of a DD therapy strategy.

In the present study, we examined the impact on costs and outcomes that may occur in neutropenic patients with a suspected IFD caused by *Aspergillus* species when treated by using either a typical empirical strategy with antifungal therapy administered to all patients or an early-treatment DD strategy with more targeted antifungal therapy.

PATIENTS AND METHODS

A decision-analytic model was developed to examine the costs and outcomes associated with the standard empirical strategy, in which all patients with persistent or recurrent neutropenic fevers were treated with C-AmB, L-AmB, or caspofungin, compared with a DD strategy, in which selected patients were treated with C-AmB, L-AmB, or voriconazole. Antifungal agents were chosen based on the indications listed in the summaries of product characteristics as well as expert feedback.

The model was developed from a UK perspective and included a time horizon of 5 months.[13] All costs are presented in 2012 British pounds sterling. Costs and outcomes were not discounted because the time horizon was <1 year.

Population

Patients were assumed to be aged ≥ 18 years with hematologic malignancies, undergoing chemotherapy or autologous/allogeneic hematopoietic stem cell transplantation, and expected to be severely neutropenic (neutrophil count $<0.5 \times 10^9$ cells/L) for ≥ 10 days.[7–12] Patients could not have had a diagnosis of proven or probable IFD or have received treatment with an investigational antifungal agent in the previous 6 months.

Comparators

DD Strategy

Patients began antifungal therapy when they were suspected of having an IFD based on characteristic lesions on computed tomography scan, *Aspergillus* species colonization, and/or positive ELISA results for galactomannan antigen (GM) and/or positive results for *Aspergillus* species on polymerase chain reaction (PCR) assay. Patients were treated with C-AmB, L-AmB, or voriconazole.

Empirical Strategy

Patients began antifungal therapy when they had persistent or recurrent neutropenic fevers that failed to defervesce despite broad-spectrum antibacterial therapy for 72 to 96 hours, with no IFD identified. Patients were treated with C-AmB, L-AmB, or caspofungin.

Model Structure

The decision model (Figures 1A–1C) was designed as a standard decision tree, with chance nodes representing the probability of occurrence of each event and decision nodes representing decision points. Patients at risk for IFD, such as those with IA, were entered into the model and were assigned to each strategy as soon as they became neutropenic. At baseline for treatment of initial neutropenic fevers, patients underwent a standard diagnostic evaluation, which included blood cultures, urine cultures, body site–specific microbiologic cultures, serum biochemistry, and hematology studies. After the standard diagnostic evaluation, initial empirical broad-spectrum antibacterial therapy was initiated. Thereafter, other monitoring and microbiologic tests were performed, as