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Integrating rapid diagnostics and antimicrobial stewardship improves outcomes in patients with antibiotic-resistant Gram-negative bacteremia

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Summary *Background:* An intervention for Gram-negative bloodstream infections that integrated mass spectrometry technology for rapid diagnosis with antimicrobial stewardship oversight significantly improved patient outcomes and reduced hospital costs. As antibiotic resistance rates continue to grow at an alarming speed, the current study was undertaken to assess the impact of this intervention in a challenging patient population with bloodstream infections caused by antibiotic-resistant Gram-negative bacteria.
Methods: A total of 153 patients with antibiotic-resistant Gram-negative bacteremia hospitalized prior to the study intervention were compared to 112 patients treated post-implementation. Outcomes assessed included time to optimal antibiotic therapy, time to active treatment when inactive, hospital and intensive care unit length of stay, all-cause 30-day mortality, and total hospital expenditures.
Results: Integrating rapid diagnostics with antimicrobial stewardship improved time to optimal antibiotic therapy (80.9 h in the pre-intervention period versus 23.2 h in the intervention period, $P < 0.001$) and effective antibiotic therapy (89.7 h versus 32 h, $P < 0.001$). Patients in the pre-intervention period had increased duration of hospitalization compared to those in the intervention period (23.3 days versus 15.3 days, $P = 0.0001$) and longer intensive care unit length of stay (16 days versus 10.7 days, $P = 0.008$). Mortality among patients during the intervention period was lower (21% versus 8.9%, $P = 0.01$) and our study intervention remained

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a significant predictor of survival (OR, 0.3; 95% confidence interval [CI], 0.12—0.79) after multivariate logistic regression. Mean hospital costs for each inpatient survivor were reduced $26,298 in the intervention cohort resulting in an estimated annual cost savings of $2.4 million ($P = 0.002$).

Conclusions: Integration of rapid identification and susceptibility techniques with antimicrobial stewardship resulted in significant improvements in clinical and financial outcomes for patients with bloodstream infections caused by antibiotic-resistant Gram-negatives. The intervention decreased hospital and intensive care unit length of stay, total hospital costs, and reduced all-cause 30-day mortality.

Introduction

Antibiotic-resistant Gram-negative bacteria are a major global health risk and therapeutic challenge.[1—6] A declining pipeline of clinically-useful antibiotics has made the need for more effective strategies to combat escalating drug resistance and improve patient care more urgent than ever.[1,2,6,7] Patients who develop bloodstream infections (BSIs) caused by antibiotic-resistant bacteria, including extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae and multidrug-resistant (MDR) *Pseudomonas aeruginosa* and *Acinetobacter* spp., have limited therapeutic alternatives, and are at greater risk for mortality, complications, and prolonged hospitalization.[8—15]

In addition to supporting the development of new agents and diagnostic tests for resistant bacteria, efforts to prevent and mitigate antimicrobial resistance must focus on optimizing the use of currently available antibacterial drugs through infection control, surveillance, and antimicrobial stewardship.[1,2,6,7,13,16,17] Integrating results from rapid laboratory methods for organism identification and susceptibility testing with an antimicrobial stewardship program allows clinicians to streamline therapy and enables the timely addition of life-saving treatment for patients with serious infections.[7,18—22] The prudent administration of antimicrobials reduces unnecessary exposure to broad-spectrum antibiotics and helps prevent the development of antimicrobial resistance in the long term.[18—20]

We recently showed that the use of matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) to provide timely, accurate identification of the infecting organism coupled with rapid susceptibility testing and antimicrobial stewardship reduced hospital length of stay (LOS) and decreased healthcare expenditures in patients with Gram-negative BSIs.[22] However, the impact of this intervention on a growing number of patients with few treatment options has not been assessed. In the current study, we examined the clinical and economic effects of rapid identification and susceptibility testing coupled with active antimicrobial stewardship on patients with BSIs caused by MDR and/or ESBL-producing Gram-negative bacteria.

Methods

Study location and patient population

We implemented our study intervention on February 1, 2012 at Houston Methodist Hospital in Houston, Texas, a 1000-bed quaternary-care academic hospital. Consecutive patients aged ≥18 years with ≥1 blood culture with an antibiotic-resistant Gram-negative organism between January 2009 and November 2011 (pre-intervention period) and February 2012 through June 2013 (intervention period) were screened for eligibility. Only the first BSI episode was evaluated for each patient. Patients were excluded if: i) the pathogen ultimately identified was not an aerobic MDR or ESBL-producing Gram-negative bacillus; ii) the index blood culture grew >1 microorganism species (polymicrobial cultures pending validation on MALDI-TOF MS); iii) the patient died prior to the index blood culture becoming positive; and/or iv) discharge disposition was determined by medical circumstances unrelated to BSI, i.e., Medicare Severity Diagnosis-Related Group (MS DRG) that included: heart transplant or implant of heart assist system, extracorporeal membrane oxygenation (ECMO) or tracheostomy with mechanical ventilation ≥96 h or principal diagnosis except face, mouth, and neck with major operating room procedure, or bone marrow transplant. BSI onset was defined as the collection time of the first blood sample yielding the study isolate (index blood culture). This study was approved by the Institutional Review Board of Houston Methodist Research Institute (IRB1011-0200). No private sector funds were used in support of this study. The authors vouch for the accuracy and completeness of the reported data and the fidelity of this report to the study protocol.

Data collection

We collected data on demographic characteristics, clinical signs and symptoms of infection, microbiology results, antibiotic therapy, severity of illness, and course of hospital stay.[23,24] Infection-related characteristics collected included source, causative pathogen and susceptibility data, and time, dose, and route of therapy with individual antimicrobial agents relative to time of index culture collection, including antibiotic agents administered in the emergency department. The source of bacteremia was determined according to the definitions published by the Centers for Disease Control and Prevention.[25,26] Immunosuppressive therapy was defined as receipt of cytotoxic agents within 6 weeks, corticosteroids at a dosage ≥15 mg of prednisolone daily for longer than 1 week within 4 weeks, or other immunosuppressive agents within 2 weeks before bacteremia onset.

Antibiotic-resistant Gram-negative bacteria included ESBL-producing *Escherichia coli* and *Klebsiella* spp. isolates