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Impact of the introduction of real-time therapeutic drug monitoring on empirical doses of carbapenems in critically ill burn patients

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ABSTRACT

Purpose: Adequate empirical antibiotic dose selection for critically ill burn patients is difficult due to extreme variability in drug pharmacokinetics. Therapeutic drug monitoring (TDM) may aid antibiotic prescription and implementation of initial empirical antimicrobial dosage recommendations. This study evaluated how gradual TDM introduction altered empirical dosages of meropenem and imipenem/cilastatin in our burn ICU.

Methods: Imipenem/cilastatin and meropenem use and daily empirical dosage at a five-bed burn ICU were analyzed retrospectively. Data for all burn admissions between 2001 and 2011 were extracted from the hospital's computerized information system. For each patient receiving a carbapenem, episodes of infection were reviewed and scored according to predefined criteria. Carbapenem trough serum levels were characterized. Prior to May 2007, TDM was available only by special request. Real-time carbapenem TDM was introduced in June 2007; it was initially available weekly and has been available 4 days a week since 2010.

Results: Of 365 patients, 229 (63%) received antibiotics (109 received carbapenems). Of 23 TDM determinations for imipenem/cilastatin, none exceeded the predefined upper limit and 11 (47.8%) were insufficient; the number of TDM requests was correlated with daily dose ($r = 0.7$). Similar numbers of inappropriate meropenem trough levels (30.4%) were below and above the upper limit. Real-time TDM introduction increased the empirical dose of imipenem/cilastatin, but not meropenem.

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Abbreviations: ABA, American Burn Association; ICU, intensive care unit; MDR, multidrug-resistant; MIC, minimum inhibitory concentration; TBSA, total body surface area; TDM, therapeutic drug monitoring.

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Conclusions: Real-time carbapenem TDM availability significantly altered the empirical daily dosage of imipenem/cilastatin at our burn ICU. Further studies are needed to evaluate the individual impact of TDM-based antibiotic adjustment on infection outcomes in these patients.

1. Introduction

Sepsis is the major cause of morbidity and mortality in burn patients. Burn shock and respiratory failure, previously regarded as the major causes of mortality, have progressively been replaced by consideration of sepsis and multiple organ failure as primary causes [1,2]. Treatment failure commonly occurs several weeks, or even months, after injury as a consequence of sepsis, frequently caused by multidrug-resistant (MDR) microorganisms [2–4]. The introduction of early surgery combined with topical and systemic antibiotherapy has dramatically improved survival of sepsis after burn trauma, but further improvement has been limited by the rapid emergence of difficult-to-treat MDR bacteria [5–7].

The correct prescription of anti-infective agents is a potential means of hindering the steady increase in MDR microorganism infections. Major hemodynamic and metabolic changes induced by burn trauma considerably alter important pharmacokinetic parameters [8]. In addition, burn trauma patients usually experience large fluid shifts among intravascular, intercellular, and intracellular compartments, and are often hypoalbuminemic and proteinemic. Moreover, they present with a profoundly modified metabolism, especially with regard to liver and kidney functions [9]. All of these aspects render burn victims highly susceptible to the under- and overprescription of anti-infective agents [10–13].

Several studies demonstrated that therapeutic drug monitoring (TDM) has improved antibiotic prescription in different populations of hospitalized patients, including critically ill patients [13–19]. Studies focusing specifically on burn patients are scarce, and no recommendation has been established regarding empirical initial doses of anti-infective agents in burn victims [10,20–23].

Over the last decade, TDM has gradually evolved in our institution to an automated multiplex assay performed by ultra-performance liquid chromatography coupled with tandem mass spectrometry [24,25]. This approach has dramatically improved its availability. In this context, we retrospectively evaluated whether these changes impacted imipenem/cilastatin and meropenem prescription in our burn intensive care unit (ICU). Therefore, the objective of this study was to determine the impact of TDM upon the appropriateness of carbapenem dosage in a burn ICU.

2. Material and methods

2.1. Study design and setting

We retrospectively analyzed imipenem/cilastatin and meropenem use between 2001 and 2011 at a five-bed Swiss tertiary reference burn ICU nested in a 32-bed medicosurgical ICU. This study was approved by the Institutional Review Board of the Centre Hospitalier Universitaire Vaudois and the Ethics Committee of the State of Vaud, Switzerland.

2.2. Data collection

All patients admitted to the burn ICU were included in the study. Age, gender, burn characteristics [total body surface area (TBSA) burned], and Ryan score [26] were collected from medical records for each burn patient hospitalized between January 2001 and December 2011. Data regarding antibiotic administration, including date and time of administration, molecule type, and dose administered, were extracted from our computerized information system (Metavision; IMDsoft, Tel Aviv, Israel). Medical records were screened in order to assess major adverse events such as seizures.

2.3. Characterization of infection episodes

For each patient receiving a carbapenem, two experts from the burn ICU reviewed episodes of infection and scored them according to the predefined criteria (see Supplemental Information for details). *Infection severity* (sepsis, severe sepsis, septic shock) was diagnosed according to criteria proposed by the 2001 Society of Critical Care Medicine/European Society of Intensive Care Medicine/American College of Chest Physicians/American Thoracic Society/Surgical Infection Society International Sepsis Definitions Conference [27] and adapted for burn patients according to the 2007 American Burn Association (ABA) criteria [28]. *Infection sites* were defined according to criteria published by Garner et al. [29] and Calandra and Cohen [30]. Burn wound infections were defined according to the ABA consensus criteria [28]. *Community-acquired infection* was defined as infection manifesting before or within 48 h after hospital admission, and *nosocomial infection* was defined as infection manifesting at least 48 h after hospital admission. An infection was deemed *microbiologically documented* when a sample collected within a time window ranging from 24 h before to 48 h after the onset of antibiotic therapy yielded a positive culture with pathogenic or potentially pathogenic bacteria.

2.4. Antimicrobial treatment

During the study period, our burn ICU had no antibiotic stewardship program; all prescriptions and TDM requests were at the physicians' discretion. Carbapenem manufacturers' recommendations (imipenem/cilastatin, 500 mg infused over 30 min every 6 h; meropenem, 1 g infused over 30 min every 8 h) were adapted to calculated glomerular filtration rates (derived from age, gender, total body weight,