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Impact of inappropriate antimicrobial therapy on patients with bacteremia in intensive care units and resistance patterns in Latin America

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ABSTRACT

Patient care in an intensive care unit (ICU) is associated with an increased risk of developing nosocomial infections. Bacteremia is responsible for a great number of cases, 23% of which have attributable mortality in developed countries and can affect up to 52% of ICU patients. The main cause of mortality is inadequate and inappropriate antimicrobial empirical therapy. The incorrect use of antimicrobials is a major risk for identifying multidrug-resistant microorganisms, thereby involving increased morbidity, mortality and costs. Implementing several surveillance systems and becoming acquainted with resistance patterns represent a valuable tool for identifying, preventing and treating this infectious complication. There is paucity of data regarding antimicrobial resistance in bacteremic patients in Latin America, and the available data reveals a worrying scenario.

Key words: bacteremia, nosocomial infection, Latin America, intensive care units, antimicrobial drug resistance

INTRODUCTION

A growing number of patients in Latin American countries require management in an intensive care unit (ICU), which is associated with a greater risk of contracting cross infections (32). Among these, bacteremia frequently occurs and has been reported in about 52% of patients requiring management in the ICU, accounting for 23% attributable mortality in developed countries (6).

Additionally, the excessive, inadequate and inappropriate use of antimicrobial agents represents one of the main risk factors for bacterial resistance, which in turn produces a vicious circle due to the increasing use of (frequently inappropriate) broad-spectrum treatments and greater identification of multi-resistant microorganisms. This also implies an increase in derived costs due to management (newer and more expensive drugs having a broader spectrum), longer stays in ICUs and mortality (19).

The following text reviews the definitions for the incorrect use of antimicrobial drugs, the outcomes associated with this treatment in ICU patients, and the resistance rates reported for bacteremia in ICUs from Latin America.

DEFINITIONS

The American Thoracic Society and the Infectious Disease Society of America define appropriate therapy as the choice of an antimicrobial agent having in vitro activity against the pathogen involved (1); an adequate anti-
microbial treatment does not just define the administration of the active antibiotic (appropriate) but also the different factors determining a correct response to treatment (dose, interval dose, administration route, penetration at the infection site and combination of antibiotics when indicated).

**CLINICAL IMPACT OF INAPPROPRIATE THERAPY**

One of the fundamental roles of antibiotics is a reduction in mortality. This is taken for granted today; however, historical studies dating back to the beginning of antimicrobial therapy reported that in 1938, the use of an antibiotic reduced mortality from 27% to 8% amongst patients suffering from pneumonia (11).

A meta-analysis conducted by Kuti et al. identified 22 studies in which differences in mortality were evaluated in patients with bacteremia (18). The general result showed that mortality was greater in patients receiving inappropriate antibiotic therapy at the start of treatment, with an odds ratio (OR) of 2.33 (1.96-2.76, 95% confidence interval). These studies were carried out on hospital-acquired infections caused by different microorganisms (gram-positive and gram-negative ones, see Table 1).

In a cohort of patients having nosocomial bacteremia, Garrouste-Orgeas et al., demonstrated the favourable impact of an early and adequate establishment of antimicrobial treatment on patients with ICU-acquired bacteremia. Mortality in the control group (paired by previous stay in ICU and comorbidities) that was not in the ICU at the moment of bacteremia was between 34.9% and 39.9%, while the mortality rate for patients in the ICU was 57.3% and 69.7% for those receiving appropriate and inappropriate antibiotic treatment, respectively (9).

A retrospective study of bacteremia at Rush Hospital in Chicago (20) revealed differences in mortality amongst patients with bacteremia and neutropenia in an ICU, compared to those who had not been admitted to ICU. Even though inappropriate therapy was correlated with mortality in both groups, OR was 17 in the group in the ICU and 5 in the group which had been in ICU.

**ECONOMIC IMPACT OF INAPPROPRIATE THERAPY**

Increasing bacterial resistance has become a public health problem involving patients, healthcare institutions and health-service administrators. In addition to the increase in morbidity and mortality, the costs inherent to the disease or to different interventions have increased (prolonged hospitalisation, increased stay in ICU, antibiotic treatment, administrative process and equipment for isolating patients, and microbiological studies) (22, 27).

Many studies have sought to quantify the cost attributable to diagnosing and treating ICU-acquired bacteremia, in order to demonstrate the impact on the economy, by evaluating the available data, and proposing preventive strategies for reducing nosocomial infections and increased costs (10).

The sum of the evidence available to date has supported the concept of increased costs and prolonged hospital stay associated with the use of inappropriate antibiotic therapy. However, evaluating costs associated with hospital-acquired infection is complex and depends on a number of variables including pre-established objectives in the studies, yielding variability in the results according to the chosen population, the number of patients and their individual condition (4), the standardization of local or international currency, hospitalisation costs according to the complexity level of different institutions, the treatment time in the different countries where the studies were carried out and quantification of direct and indirect costs (19, 27).

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Additional mortality* (%)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>11.0</td>
<td>Kim <em>et al.</em>, 2006 (17)</td>
</tr>
<tr>
<td></td>
<td>14.1</td>
<td>Khatib <em>et al.</em>, 2005 (16)</td>
</tr>
<tr>
<td></td>
<td>18.4</td>
<td>Lodise <em>et al.</em>, 2003 (21)</td>
</tr>
<tr>
<td></td>
<td>22.0</td>
<td>Wang <em>et al.</em>, 2008 (31)</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>12.9</td>
<td>Micek <em>et al.</em>, 2005 (23)</td>
</tr>
<tr>
<td></td>
<td>15.7</td>
<td>Kang <em>et al.</em>, 2003 (12)</td>
</tr>
<tr>
<td></td>
<td>15.0</td>
<td>Cheong <em>et al.</em>, 2008 (3)</td>
</tr>
<tr>
<td><em>Acinetobacter baumannii</em></td>
<td>25.8</td>
<td>Falagas <em>et al.</em>, 2006 (8)</td>
</tr>
<tr>
<td><em>Enterobacteriaceae</em></td>
<td>11.0</td>
<td>Kang <em>et al.</em>, 2005 (13)</td>
</tr>
<tr>
<td><em>(E. coli, Klebsiella spp.)</em></td>
<td>3.4</td>
<td>Kang <em>et al.</em>, 2004 (14)</td>
</tr>
<tr>
<td></td>
<td>12.0</td>
<td>Thom KA <em>et al.</em>, 2008 (29)</td>
</tr>
</tbody>
</table>

* Additional mortality is the difference between mortality among control and case groups.
Dimick et al. published a prospective study in 2001 comparing costs for patients with or without bacteremia (7). Average cost in dollars for the latter were less than half the costs for patients with bacteremia (US$ 40,313 vs. US$ 102,965, a statistically significant difference). Multivariate analysis revealed that bacteremia was associated with a 120% increase in the total hospitalisation cost (mean $ 56,167; $ 11,523 to $ 165,735 95% confidence interval; p = 0.001).

Vandijck et al. have recently made a direct evaluation of the costs arising from antimicrobial therapy aimed at quantifying the daily cost of antibiotic treatment in patients with bacteremia in ICU, without considering associated costs (attention by specialised personnel, days being managed in an ICU, laboratory tests) (30). This study included 310 patients presenting 446 episodes of bacteremia (1.4 episodes/patient), and found that the daily antimicrobial therapy cost was € 114.3, which was higher in patients with bacteremia without a documented infectious focus (€ 137.7), followed by catheter-related bacteremia (€ 122.7), pulmonary focus (€ 112.8), abdominal focus (€ 98.0), surgical wound infection (€ 89.2), and urinary tract infection (€ 87.9) (30).

Coagulase-negative staphylococci were the microorganisms isolated with greatest frequency in this work (€ 129.04), followed by Escherichia coli. Daily antibiotic treatment cost for a patient having multi-resistant organisms was 50% higher than that for susceptible ones (€ 165.09 vs. € 82.67; p < 0.001). Gram-positive bacteremia was more costly compared to that caused by gram-negative bacteria (€ 117.1 vs. € 86.8; p = 0.152) (30).

**IMPACT ON HOSPITAL STAY**

The previously mentioned article by Dimick et al. analyzed the impact on the length of stay. In patients with bacteremia an extra length of stay of 22 days was observed (range between 7 and 70). Patients with bloodstream infection had an increased ICU stay of 20 days (range, 0.1 - 58) (7).

**RESISTANCE RATES IN PATIENTS WITH BACTEREMIA IN LATIN AMERICA**

The importance of growing resistance to antibiotics in both nosocomial and community-acquired infections is widely known and has thus generated worldwide alarm. An important factor contributing to resistance in Latin America is the high frequency of self-medication and the use of leftover antibiotics (15, 25). Several publications have advised against this widespread practice, which might be responsible for the high level of antimicrobial resistance found in primary care and the impact on those patients requiring in-hospital assistance (33). This has led to the design of different surveillance systems, which provide important information about variability in antimicrobial resistance in different countries and hospitals; and also serve as therapeutic guidelines providing valuable information for prevention, control and detection of resistance (24).

The SENTRY surveillance program, a longitudinal, multicenter study (more than 80 medical institutions around the world, 10 of which are in Latin America) was begun in 1997, and represents the most complete surveillance program in the world. It is characterised by rapidity in communication and socialisation of data regarding the emergence of antimicrobial resistance (28). Table 2 presents the results of this program and other studies in Latin America for different microorganisms. The information about resistance in bloodstream infections for the region is scarce and our group has provided some data on the problem in Colombia.

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Year</th>
<th>Scenario</th>
<th>Resistance rate (%)</th>
<th>Country or region</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oxacillin-resistant</strong> S. aureus</td>
<td>1997-2002</td>
<td>Hospital</td>
<td>32.4</td>
<td>Latin America</td>
</tr>
<tr>
<td></td>
<td>2001-2007</td>
<td>ICU</td>
<td>57.3</td>
<td>Colombia</td>
</tr>
<tr>
<td><strong>E. coli</strong> (ESBL)</td>
<td>2000-2004</td>
<td>Hospital</td>
<td>2.0</td>
<td>Argentina</td>
</tr>
<tr>
<td></td>
<td>2001-2007</td>
<td>ICU</td>
<td>7.7-8.7</td>
<td>Colombia</td>
</tr>
<tr>
<td><strong>Klebsiella spp.</strong> (ESBL)</td>
<td>1997-2002</td>
<td>ICU</td>
<td>31.1</td>
<td>Latin America</td>
</tr>
<tr>
<td></td>
<td>2001-2007</td>
<td>ICU</td>
<td>31.3-35.3</td>
<td>Colombia</td>
</tr>
<tr>
<td><strong>Pseudomonas aeruginosa</strong> (imipenem-resistant)</td>
<td>1997-2002</td>
<td>ICU</td>
<td>10.4</td>
<td>Latin America</td>
</tr>
<tr>
<td></td>
<td>2001-2007</td>
<td>ICU</td>
<td>21.0</td>
<td>Colombia</td>
</tr>
<tr>
<td><strong>Acinetobacter baumannii</strong> (imipenem-resistant)</td>
<td>1997-2001</td>
<td>ICU</td>
<td>13.5</td>
<td>Latin America</td>
</tr>
<tr>
<td></td>
<td>2001-2007</td>
<td>ICU</td>
<td>41.4</td>
<td>Colombia</td>
</tr>
</tbody>
</table>
CONCLUSION

Bacteremia represents a frequent complication arising from hospital stay, especially in critically ill patients. Its occurrence is associated with increased mortality and longer hospital stays with increased costs in those who survive. Inappropriate therapy means the antimicrobial therapy to which a particular microorganism is resistant in vitro. Inadequate therapy also includes other aspects such as dosage and administration intervals. Antimicrobial resistance in Latin America is far-reaching amongst the microorganisms identified so far in bacteremia. It constitutes a worrying issue, bearing in mind that it is associated with a greater probability of inappropriate empirical therapy and is greatly responsible for bacteremia-related mortality and complications.

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Transparency declarations

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