International Journal of Antimicrobial Agents 34S (2009) S21–S25

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: http://www.elsevier.com/locate/ijantimicag

Gram-negative bloodstream infections

Martin E. Stryjewski [a,b]*, Helen W. Boucher [c]

[a] Division of Infectious Diseases, Department of Medicine, Centro de Educación Médica e Investigaciones Clínicas "Norberto Quirno" (CEMIC), Buenos Aires, Argentina
[b] Duke Clinical Research Institute, Durham, NC, USA
[c] Division of Infectious Diseases, Tufts Medical Center and Tufts University School of Medicine, Boston, MA, USA

ARTICLE INFO

Keywords:
Bloodstream infections
Gram-negative bacteria
Epidemiology
Antimicrobial drug resistance

ABSTRACT

Gram-negative bloodstream infection (BSI) is both dangerous and challenging. The incidence of Gram-negative BSI rises with age in both men and women, but there are still some gender differences in terms of aetiology and acquisition. Clinical elements such as organ dysfunction are helpful in determining prognosis. During the last few years we have observed dramatic increases in resistance among Gram-negative organisms, including those causing bloodstream infections. Gram-negative pathogens producing extended-spectrum β-lactamases are now common, and are associated with high rates of inadequate empirical treatment and mortality. In addition, carbapenem resistance is increasing, leaving clinicians with limited therapeutic options. Better knowledge of local epidemiology can help to optimize therapies. The use of cefepime has been questioned based on a recent meta-analysis showing increased mortality in patients treated with the drug. However, an analysis performed by the US Food and Drug Administration has not confirmed these results. Unfortunately, antimicrobial development has not kept pace with resistance, particularly for Gram-negative pathogens. We need therefore to better utilize current antibiotics and undertake rigorous infection control measures to prevent these life-threatening infections.

© 2009 Elsevier B.V. and the International Society of Chemotherapy. All rights reserved.

1. Epidemiology

In recent decades, Gram-positive (GP) pathogens surpassed Gram-negative (GN) pathogens as the most prevalent organisms causing bloodstream infections (BSI) [1]. However, BSI caused by GN pathogens are re-emerging; in the last few years, studies conducted in hospital settings have begun to report an increasing incidence of BSI caused by GN pathogens [2,3]. In a Spanish study that included more than 27 000 episodes of bloodstream infection over 22 years, the rate of GN bacteraemia increased from 64 episodes per 100 000 inhabitants in 1985 to 142 episodes per 100 000 inhabitants in 2006, and the rate of BSI at the end of the study period was higher for GN pathogens than for GP pathogens (142 vs. 138 per 100 000 inhabitants) [3]. In certain centres, increasing rates of healthcare-related BSI caused by GN were not particularly driven by infections in patients on oncology units, but in patients on general wards [2]. In addition, higher rates of BSI caused by GN pathogens were also described in very specific populations, such as in patients undergoing hematopoietic stem-cell transplantation (HSCT). A study conducted in a single centre in 132 HSCT patients observed a GP/GN bacteraemia ratio of 2.4 in 2004, which decreased to 1 in 2007 [4]. Taken together, these findings suggest that the rate of bloodstream infection caused by GN pathogens is increasing in different settings.

Gram-negative bacteraemia is frequently found in clinical practice among all age groups. However, the prevalence of the infection increases with age in both men and women. In addition, some studies suggest that it is more prevalent in men aged >80 years. A population-based study conducted in Minnesota, USA showed a mean prevalence of 85 cases per 100 000 subjects per year. However, the prevalence of BSI at 80 years was several-fold higher (ca. 600 per 100 000 subjects per year) [5]. The rate of BSI caused by GN pathogens was similar in women and men up to the age of 80 years. However, the rate after 80 years of age increased more sharply in men; at the age of 90 years, men had double the rate of women.

Both the type of pathogen and the acquisition of BSI depend on the population studied. In a Spanish study, *Escherichia coli* was the most common single pathogen producing BSI [3]. The incidence of BSI produced by *E. coli* per 100 000 inhabitants increased from 23 episodes in 1985 to 79 in 2006. Other common GN pathogens included *Klebsiella* spp., *Pseudomonas aeruginosa*, *Enterobacter* spp., *Salmonella* spp. and *Proteus* spp. Regarding the acquisition of BSI, the population-based study conducted in Minnesota showed that the proportion of healthcare-related BSI was similar in men and women (ca. 36%) [5]. However, nosocomial BSI was more common in men (24% vs. 14%) and community-acquired BSI more common in women (50% vs. 40%). Reflecting the different patterns of acquisition, *E. coli* was the most common agent producing BSI in women, whereas *Staphylococcus aureus* was the most common pathogen producing BSI in men.

* Corresponding author. Present address: Av. Las Heras 2939, 2nd floor, Dept. of Medicine, Capital Federal (C1425ASG), Buenos Aires, Argentina. Tel.: +54 114 809 8200 extn 1891; fax: +54 114 809 1992.
E-mail address: stryj001@mc.duke.edu (M.E. Stryjewski).

0924-8579/$ – see front matter © 2009 Elsevier B.V. and the International Society of Chemotherapy. All rights reserved.

2. Presentation and prognosis

Although the clinical presentation in patients with BSI is heterogeneous, some features are important. Among critically ill adults with systemic inflammatory response syndrome (SIRS), the presence of BSI is more commonly associated with hypotension (58% vs. 34%; $P < 0.001$), acidosis (54% vs. 41%; $P = 0.02$), renal impairment (48% vs. 24%; $P < 0.001$) and death in both the intensive care unit (ICU) (33% vs. 16%; $P < 0.001$) and the general hospital (40% vs. 26%; $P < 0.01$) [6]. Interestingly, the ICU mortality among these patients increases incrementally with the increasing number of components of SIRS, being around 10% with two components, >30% with the addition of hypotension and sepsis, and >40% with septic shock. In addition, organ failure is crucial in determining the prognosis in patients with BSI; for example in one study, patients with SIRS with no organ dysfunction had a mortality of 7.5%. Mortality rates were twofold higher (ca. 16%) in patients who had dysfunction of one organ, and fivefold higher (37%) in those who had dysfunction of two or more organs [7].

The type of organism producing BSI also influences outcomes. Certain Gram-negative pathogens in specific hosts are associated with a very high mortality. For example, 7 day mortality in stem-cell transplant patients with *P. aeruginosa* bacteraemia was 39% in a recent study [4]. Similarly, a 10 year series in patients with BSI caused by *P. aeruginosa* reported a mortality of 42% in patients who had transplants (mostly solid) and 32% in patients who did not undergo transplantation [8].

By contrast with BSI caused by Gram-positive pathogens, BSI caused by Gram-negative organisms (other than HACEK) is infrequently associated with infective endocarditis (IE). A prospective study by the International Collaboration on Endocarditis (ICE) recently found than <2% of cases of IE were caused by Gram-negative (non-HACEK) pathogens [9]. When IE caused by Gram-negative pathogens occurred, almost half of the cases were caused by *E. coli* and *Pseudomonas* spp. Although infrequent, IE caused by Gram-negative pathogens was commonly healthcare associated (59%), occurred in patients with endovascular devices (29%), required surgical treatment (51%) and was associated with a high mortality (24%).

3. Extended-spectrum β-lactamases

Bacterial resistance is increasing in both Gram-positive and Gram-negative pathogens causing BSI [3,10,11]. Extended-spectrum β-lactamases (ESBLs) have spread around the world, with varying success among Gram-negative pathogens [12–17]. ESBL-producing strains have become a difficult challenge for clinicians [18]. A wide variety of ESBLs, such as TEM, SHV, OXA, and CTX, has been described in detail [19]. Overall, patients with BSI caused by ESBL-producing pathogens have a higher risk of death than those with BSI caused by non ESBL-producing pathogens. One meta-analysis in patients with BSI caused by GN pathogens showed a relative risk of death of 1.85 in those patients with ESBL-producing strains compared with those with non-ESBL-producing strains [20].

The presence of BSI caused by ESBL-producing strains seems to correlate with healthcare exposure and prior antibiotic use (Table 1). A prospective study conducted in 6 countries analyzed 455 episodes of *Klebsiella pneumonia* bacteraemia, and showed that 19% of the organisms were phenotypically positive for ESBLs [12]. However, the rate of infection caused by ESBL-producing organisms was higher in patients who acquired their infection in hospital (31%), particularly those who were ICU patients (44%). The rate of infection caused by ESBL-producing organisms varied from 59% in Argentina, to 25% in the USA and 12% in Belgium. In this study, prior administration of oxyimino-cephalosporins (e.g. ceftriaxone or ceftazidime) was associated with an almost fourfold increase in the risk of developing infection caused by ESBL-producing organisms. Although the mortality in this cohort was high (24%), treatment with carbapenems was associated with a significant decrease in the risk of death [21]. Data from the SENTRY database in 2002 confirmed the presence of regional variation in the rate of ESBL production among bacterial strains causing BSI [22]. Among >1200 isolates of *K. pneumoniae* from patients with BSI, the rate of ESBL production was 36% in Latin America, 17% in Europe and 5% in the USA. Similarly, the rates of multidrug resistant (MDR) *Pseudomonas* spp. causing BSI were also more frequent in Latin America and Europe than the USA (19%, 12% and 3%, respectively).

Table 1
Common characteristics of patients with bloodstream infections caused by extended-spectrum β-lactamase-producing organisms

Significant exposure to the healthcare system (e.g. prior hospitalization)
Prior antibiotic use (particularly oxyimino-cephalosporins)
Frequent inadequate initial antibacterial therapy
Inadequate initial antibacterial therapy is associated with higher mortality
Unknown source of infection may be associated with a worse prognosis
Treatment with carbapenems is associated with lower mortality

Inadequate empirical antibacterial therapy in patients with serious infections has been associated with increased mortality [23–25]. This finding has also been observed in patients with BSI caused by ESBL-producing pathogens [26,27]. One study conducted in Italy investigated 186 patients with BSI caused by ESBL-producing strains [27]. Most of these were nosocomial (90%), and most patients had received prior antimicrobial therapy (61%). Pathogens isolated included *E. coli*, *K. pneumoniae* and *Proteus mirabilis*. Initial therapy was considered to be inadequate in almost half of these patients, and the most common inadequate antibiotics were oxyimino cephalosporins and quinolones. Mortality at 3 weeks was 60% in patients who received inadequate initial antimicrobial therapy vs. 19% in patients who received adequate initial antimicrobial therapy ($P < 0.001$). In addition, multivariable analysis showed two factors associated with death: unidentifiable source of infection (OR 2.69; 95% CI 1.28, 5.27) and inadequate initial antibacterial therapy (OR 6.28; 95% CI 3.18, 12.42). The association between an unknown source of infection and death may be related to a lower frequency of urinary tract infection (UTI; which is believed to have a better outcome) among these patients and/or the administration of less standardized antibiotic protocols in these patients. Here again, the lowest mortality was observed in those patients treated with carbapenems.

Another study from the same group investigated 129 patients with BSI caused by ESBL-producing *E. coli* [26]. Most BSIs were nosocomial, with UTI being the most frequent source. More than 40% of these patients received inadequate antimicrobial therapy, and approximately half of these antimicrobials were oxyimino cephalosporins. Factors associated with inadequate antibacterial therapy were: unknown source of infection, resistance to three or more types of antibacterial, prior hospitalization and prior antibiotic therapy. These factors reflect a degree of exposure to the healthcare system. Mortality at 3 weeks among patients with BSI caused by ESBL-producing *E. coli* was high (29%). Importantly, mortality was markedly lower in patients who received adequate therapy vs. those who had received inadequate therapy (12% vs. 52%; $P < 0.001$). Finally, patients with non-urinary tract infections caused by ESBL-producing organisms had a longer hospital stay and incurred higher medical costs [28,29].

Understanding the prevalence of ESBL-producing strains among patients in whom BSI is suspected is crucial. Knowledge of the risk will inform the decision to provide empirical therapy active against the most likely pathogens until culture/susceptibility test results are obtained [30].

Download English Version:

https://daneshyari.com/en/article/3359829

Download Persian Version:

https://daneshyari.com/article/3359829

Daneshyari.com