Journal of Global Antimicrobial Resistance 15 (2018) 41–47

Contents lists available at ScienceDirect

Journal of Global Antimicrobial Resistance

journal homepage: www.elsevier.com/locate/jgar

Prevalence and predictors of spontaneous bacterial peritonitis due to ceftriaxone-resistant organisms at a large tertiary centre in the USA

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ARTICLE INFO

Article history:
Received 2 March 2018
Received in revised form 3 May 2018
Accepted 21 May 2018
Available online 26 May 2018

Keywords:
Antimicrobial resistance
Epidemiology
Chronic liver disease

ABSTRACT

Objectives: The epidemiology of spontaneous bacterial peritonitis (SBP) due to ceftriaxone-resistant organisms has not been well studied in the USA. The primary objective of this study was to assess the prevalence and predictors of ceftriaxone-resistant SBP at a large US tertiary-care centre.
Methods: This 1:1:4 case–case–control study included 141 adults with liver cirrhosis admitted from November 2011 to March 2016. Case group 1 were patients with SBP with a ceftriaxone-resistant organism ($n = 21$). Case group 2 were patients with SBP with a ceftriaxone-susceptible organism ($n = 26$). The control group were patients without SBP ($n = 94$). Multiple logistic regression analysis was used to identify predictors of ceftriaxone-resistant SBP.
Results: Fifty isolates were identified from 47 patients with culture-positive SBP (case groups 1 and 2). Of these 50 isolates, 32 (64%) were Gram-negatives [mostly Enterobacteriaceae (91%)], 15 (30%) were Gram-positives and 3 (6%) were *Candida* spp. The prevalence of ceftriaxone resistance in patients with culture-positive SBP was 45% (21/47). The most common ceftriaxone-resistant organisms were ESBL-producing Enterobacteriaceae (45%). Independent predictors of ceftriaxone-resistant SBP included duration of β-lactam therapy in the past 90 days (aOR = 1.07, 95% CI 1.01–1.13) and recent invasive gastrointestinal procedure (aOR = 12.47, 95% CI 2.74–56.67).
Conclusions: The prevalence of ceftriaxone-resistant SBP was significant at a US tertiary centre. Local epidemiological data and identification of risk factors associated with ceftriaxone-resistant SBP, e.g. increased usage of previous β-lactam therapy and invasive gastrointestinal procedure, may help clinicians identify patients requiring alternative empirical antibiotics.

1. Introduction

Spontaneous bacterial peritonitis (SBP) is diagnosed in one of four cirrhotic patients hospitalised with bacterial infections, with an all-cause 30-day mortality rate ranging from 26% to 49% [1–4]. *Escherichia coli*, *Klebsiella pneumoniae* and *Streptococcus pneumoniae* are the most common causative pathogens in SBP, making third-generation cephalosporins such as ceftriaxone the empirical drugs of choice [5]. However, recent studies from Europe, Canada and Asia have demonstrated increased rates of ceftriaxone-resistant SBP. A significant proportion (16–67%) of SBP cases warranted an agent other than ceftriaxone owing to isolation of resistant organisms, including extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae, *Pseudomonas aeruginosa*, methicillin-resistant *Staphylococcus aureus* (MRSA) and *Enterococcus* spp. [1–4,6–10].

However, resistance rates vary between geographic regions. To our knowledge, only three studies have evaluated the epidemiology of SBP in the USA. In a study conducted at the Pittsburgh Veterans Affairs Medical Center (Pittsburgh, PA), the prevalence of multidrug-resistant organisms in 42 episodes of SBP or bacterascites increased from 8% in 1991–1995 to 39% in 1996–2001 [11]. In another study at the Yale–New Haven Hospital (New Haven, CT) in 2009–2010, the prevalence of ceftriaxone resistance among 18 episodes of SBP or spontaneous bacterial empyema was 39% [12]. More recently, in a study at Mount Sinai Hospital (New York, NY) in

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https://doi.org/10.1016/j.jgar.2018.05.015

2010–2014, 23% of 61 culture-positive SBP cases were ceftriaxone-resistant [13]. The generalisability of these studies is limited due to similar geographical regions of the study centres and/or study time periods. The primary objective of the current study was to assess the prevalence and predictors of ceftriaxone-resistant SBP at a large tertiary centre in Houston, TX. A secondary objective was to describe the outcomes of patients with ceftriaxone-resistant SBP.

2. Materials and methods

2.1. Study design, setting and patient population

This was a 1:1:4 case–case–control study conducted at an 850-bed tertiary-care centre in the Texas Medical Center (Houston, TX). Historically, 50–70 SBP cases are diagnosed annually at the study hospital, of which 25–30% of cases are culture-positive. The study was approved by the Institutional Review Board at the study hospital.

Hospitalised patients who had an ascitic fluid cell count and culture performed between November 2011 and March 2016 were identified from the clinical microbiology department and were screened. Inclusion criteria were age ≥18 years and diagnosis of liver cirrhosis. Exclusion criteria included ascitic fluid culture positive for common skin contaminants (i.e. coagulase-negative staphylococci, *Corynebacterium*, *Propionibacterium*, diphtheroids or *Bacillus* spp.), bacterascites, culture-negative SBP or secondary peritonitis. Bacterascites was defined as ascitic fluid polymorphonuclear (PMN) count <250 cells/mm^3 and positive ascitic fluid culture [14]. Culture-negative SBP was defined as a PMN count ≥250 cells/mm^3 and negative ascitic fluid culture. Secondary peritonitis was defined as growth of more than one organism from an ascitic fluid culture and clinical and/or radiological findings consistent with secondary peritonitis.

Patients who did not meet the exclusion criteria were included and were categorised into one of three groups. Case group 1 were patients with culture-positive SBP with a ceftriaxone-resistant organism. Case group 2 were patients with culture-positive SBP with a ceftriaxone-susceptible organism. If a patient had multiple culture-positive SBP episodes, only the most recent episode was included. The control group were patients without SBP. Controls were randomly selected (using computer-generated random numbers) from cirrhotic patients admitted to the study hospital for acute decompensated cirrhosis or for other acute illnesses that required inpatient admission. Controls had to be hospitalised during the study time period and in whom SBP was ruled out (i.e. ascitic fluids were sent for cell count and culture but did not meet the criteria for SBP) [14]. Each patient was included in the study once.

2.2. Definitions

The diagnosis of liver cirrhosis was based on clinical, laboratory, histopathological and radiological data. SBP was defined as ascitic fluid PMN count ≥250 cells/mm^3 [14]. Culture-positive SBP was defined as SBP and growth of at least one organism from an ascitic fluid culture. Community-acquired SBP was defined as SBP diagnosed within ≤48 h of hospitalisation, whereas nosocomial SBP was defined as SBP diagnosed after >48 h of hospitalisation. Recent contact with the healthcare system was defined as ≥48 h of hospitalisation within the past 90 days, admission from a nursing home or long-term care facility, or chronic haemodialysis within the past 30 days. The time from date of hospital admission to the date of ascitic fluid culture collection determined the length of hospital stay prior to SBP onset. Chronic kidney disease was defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 clinical practice guidelines [15]. Septic shock was defined as sepsis-induced hypotension despite adequate fluid challenge [16].

An organism susceptible to ceftriaxone based on 2012 Clinical and Laboratory Standards Institute (CLSI) breakpoints was deemed ceftriaxone-susceptible. An organism intrinsically resistant to ceftriaxone (e.g. *Enterococcus* spp.) or classified as intermediate or resistant to ceftriaxone based on CLSI breakpoints was deemed ceftriaxone-resistant. Gram-negative organisms were termed multidrug-resistant (MDR) or extensively drug-resistant (XDR) based on consensus definitions [17]. In brief, MDR was defined as non-susceptibility to at least one agent in three or more antimicrobial categories, and XDR was defined as susceptibility to only two antimicrobial categories.

Empirical therapy was defined as anti-infective therapy administered within 24 h of ascitic fluid culture collection. Appropriate empirical therapy was defined as empirical therapy that included at least one anti-infective agent(s) to which the organism was found to be susceptible in vitro and the doses used were appropriate for the end organ function(s) of the patient.

Attributable length of hospital stay was defined as the difference between discharge date and the date of SBP diagnosis (date of ascitic fluid culture collection). All-cause 30-day mortality was defined as death due to any cause within 30 days of SBP diagnosis. Patients discharged prior to Day 30 were deemed alive unless proven otherwise.

2.3. Laboratory testing

Ascitic fluid was obtained aseptically by paracentesis as part of standard clinical care. Samples were sent to the haematology laboratory for cell count and differential as well as to the microbiology laboratory for Gram staining and culture. A VITEK®2 automated system (bioMérieux, Durham, NC) provided species identification of organisms and antimicrobial susceptibility of most Enterobacteriaceae. Susceptibility testing of non-lactose fermenting Gram-negative organisms and yeasts was done using Sensititre GN4F and YeastOne™ panels, respectively (TREK Diagnostic Systems, Independence, OH). ESBL production was detected using the double-disk diffusion phenotypic confirmatory test as recommended by the CLSI [18].

2.4. Data collection

Data collected included patient demographics, aetiology of cirrhosis, Child–Pugh score, Model for End-Stage Liver Disease (MELD)-Na score, co-morbidities, potential risk factors for ceftriaxone resistance (e.g. recent antimicrobial use, recent contact with the healthcare system, presence of ceftriaxone-resistant organisms on previous cultures such as urine, ascitic fluid and blood cultures), length of hospital stay prior to SBP onset, invasive gastrointestinal procedures (including major surgeries and invasive procedures such as endoscopic interventions or placement of a transjugular intrahepatic portosystemic shunt) within the past 14 days, and location of care [intensive care unit (ICU) vs. general ward]. Details of SBP infection, including isolated organisms and in vitro anti-infective susceptibility profile, empirical anti-infective therapy, severity of illness and patient outcomes, were also collected.

2.5. Statistical analysis

Univariate and multivariate logistic regression analyses were used to identify predictors of ceftriaxone-resistant SBP. Each case group was compared separately with the control group. A single control group was utilised in both case–control analyses because the source populations for both case groups were similar, and this allowed for direct comparison between both models [19]. Univariate analysis evaluated differences between cases and controls using the Fisher's exact test or χ^2 test for categorical