International Journal of Antimicrobial Agents 48 (2016) 498–503

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

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

Effectiveness of oral antibiotics for definitive therapy of Gram-negative bloodstream infections *

Leila F. Kutob [a], Julie Ann Justo [b,c], P. Brandon Bookstaver [b], Joseph Kohn [c], Helmut Albrecht [d], Majdi N. Al-Hasan [d,*]

[a] University of South Carolina School of Medicine, Columbia, SC, USA
[b] Department of Clinical Pharmacy and Outcomes Science, South Carolina College of Pharmacy, University of South Carolina, Columbia, SC, USA
[c] Department of Pharmacy, Palmetto Health Richland, Columbia, SC, USA
[d] Department of Medicine, Division of Infectious Diseases, University of South Carolina School of Medicine, Columbia, SC, USA

ARTICLE INFO

Article history:
Received 15 March 2016
Accepted 15 July 2016

Keywords:
Bacteraemia
Sepsis
Antibacterial agents
Fluoroquinolone
Recurrence
Escherichia coli

ABSTRACT

There is paucity of data evaluating intravenous-to-oral antibiotic switch options for Gram-negative bloodstream infections (BSIs). This retrospective cohort study examined the effectiveness of oral antibiotics for definitive treatment of Gram-negative BSI. Patients with Gram-negative BSI hospitalised for <14 days at Palmetto Health Hospitals in Columbia, SC, from 1 January 2010 through 31 December 2013 and discharged on oral antibiotics were included in this study. The cohort was stratified into three groups based on bioavailability of oral antibiotics prescribed (high, ≥95%; moderate, 75–94%; and low, <75%). Kaplan–Meier analysis and multivariate Cox proportional hazards regression were used to examine treatment failure. Among the 362 patients, high, moderate and low bioavailability oral antibiotics were prescribed to 106, 179 and 77 patients, respectively, for definitive therapy of Gram-negative BSI. Mean patient age was 63 years, 217 (59.9%) were women and 254 (70.2%) had a urinary source of infection. Treatment failure rates were 2%, 12% and 14% in patients receiving oral antibiotics with high, moderate and low bioavailability, respectively ($P = 0.02$). Risk of treatment failure in the multivariate Cox model was higher in patients receiving antibiotics with moderate [adjusted hazard ratio (aHR) = 5.9, 95% CI 1.6–38.5; $P = 0.005$] and low bioavailability (aHR = 7.7, 95% CI 1.9–51.5; $P = 0.003$) compared with those receiving oral antimicrobial agents with high bioavailability. These data demonstrate the effectiveness of oral antibiotics with high bioavailability for definitive therapy of Gram-negative BSI. Risk of treatment failure increases as bioavailability of the oral regimen declines.

1. Introduction

Gram-negative bloodstream infection (BSI) is a leading cause of hospitalisation in the USA, as nearly 250,000 individuals develop Gram-negative BSI annually [1,2]. There is a wealth of knowledge on the importance of appropriate empirical antimicrobial therapy and the utility of different empirical treatment strategies in hospitalised patients with Gram-negative BSI [3–11]. However, there is a paucity of evidence-based data on the effectiveness of definitive antimicrobial regimens, particularly oral options, for Gram-negative BSI after discharge from the hospital. Expert reviews recommend switching patients from intravenous (i.v.) to oral antimicrobial agents with high bioavailability for the completion of treatment of Gram-negative BSI merely based on opinion [12].

This retrospective cohort study examined treatment failure rates based on the bioavailability of oral antimicrobial agents prescribed for definitive therapy of Gram-negative BSI.

2. Patients and methods

2.1. Settings

This study was conducted at Palmetto Health Hospital system, including Richland and Baptist campuses in Columbia, SC, USA. Palmetto Health Hospital system has >1000 licensed beds, serves residents of Richland County and receives regional referrals from the surrounding areas in South Carolina. The institutional review board at Palmetto Health approved the study and waived informed consent.

2.2. Definitions

Gram-negative BSI was defined as growth of any aerobic Gram-negative bacillus in a blood culture. Primary source of BSI was defined

* Preliminary results of this study were presented in part at IDWeek 2015, 7–11 October 2015, San Diego, CA [abstract # 50334].

* Corresponding author. University of South Carolina School of Medicine, 2 Medical Park, Suite 502, Columbia, SC 29203, USA. Fax: +1 803 540 1079.
E-mail address: majdi.alhasan@uscmed.sc.edu (M.N. Al-Hasan).

http://dx.doi.org/10.1016/j.ijantimicag.2016.07.013
0924-8579/

based on US Centers for Disease Control and Prevention (CDC) criteria [13]. The site of infection acquisition was classified as community-acquired, healthcare-associated or hospital-acquired as previously defined [14]. Oral antimicrobial agents were classified based on pre-determined bioavailability into high (≥95%), moderate (75–94%) and low groups (<75%) according to pharmacokinetic and pharmacodynamic properties [15,16]. The high bioavailability group included respiratory fluoroquinolones such as levofloxacin and moxifloxacin, the moderate group included ciprofloxacin and trimethoprim/sulfamethoxazole (SXT), whereas the low bioavailability group included oral penicillins and cephalosporins. The definition of bioavailability groups and categorisation of oral antibiotics by bioavailability were determined prior to data collection. Immunocompromised hosts were defined as those with neutropenia (absolute neutrophil count <500 cells/mL), recent chemotherapy within 30 days of BSI, human immunodeficiency virus (HIV) infection with CD4 count <200 cells/μL, transplant recipients, and treatment with corticosteroids (equivalent of prednisone 20 mg daily or higher for ≥7 days) or other immunosuppressive medications. Patients were considered to have urological complications if they had bladder outlet obstruction, neurogenic bladder or required placement of an indwelling urinary catheter or ureteral stent prior to BSI. Inadequate source control was defined as delay >72 h in drainage of an abscess or removal of the source of BSI such as a central venous catheter or retained biliary stone. Antimicrobial therapy was considered appropriate if patients received an adequately dosed antimicrobial agent for a given creatinine clearance with in vitro activity against the Gram-negative bloodstream isolate based on Clinical and Laboratory Standards Institute (CLSI) criteria [5,6]. Treatment failure was defined as all-cause mortality or recurrent infection within 90 days of the initial episode of BSI. Recurrence was defined as either subsequent BSI or primary site infection (urinary, intra-abdominal, respiratory, etc.) due to the same genus and species of micro-organism as in the initial episode. Patients were considered to have recurrent primary site infection only if they had local symptoms of infection at the same initial primary site in addition to growth of the same Gram-negative bacillus as in the initial episode. A positive culture at the primary site of infection without local symptoms, as in asymptomatic bacteriuria, was not considered recurrence.

2.3. Case ascertainment

In this retrospective cohort study, all hospitalised patients with Gram-negative BSI from 1 January 2010 through 31 December 2013 were identified through microbiology laboratory databases at Palmetto Health. Adult patients with first episodes of Gram-negative BSI during the study period who survived hospitalisation, were hospitalised for <14 days and were discharged from the hospital on oral antimicrobial agents were included in the study ($n = 362$). Children <18 years old ($n = 125$) and patients who did not survive hospitalisation ($n = 113$) were excluded. Patients who were hospitalised for ≥14 days ($n = 173$) were also excluded as they likely finished antimicrobial therapy for BSI during their hospitalisation. In addition, patients who were discharged from the hospital with no documented antimicrobial regimens ($n = 184$) were not included in the study. Oral antimicrobial regimens were collected from hospital discharge summary or clinical progress notes on the last day of hospitalisation and were confirmed in either patient hospital discharge instructions or electronic prescriptions in medical records.

2.4. Statistical analysis

The cohort was divided into three groups based on the bioavailability of oral antimicrobial agents used for definitive therapy of Gram-negative BSI (high, moderate and low). Baseline demographics and clinical variables were compared across the three bioavailability groups. In addition, since oral antibiotics with low bioavailability had no coverage for *Pseudomonas aeruginosa* and limited utility for chromosomally-mediated AmpC-producing Enterobacteriaceae (CAE), including *Enterobacter*, *Serratia*, *Citrobacter* and *Morganella* spp., the proportion of BSI due to either *P. aeruginosa* or CAE was compared across the three groups. Student's *t*-test was used to examine continuous variables, and χ^2 test or Freeman–Halton extension of Fisher's exact test was used to examine categorical variables as appropriate.

Patients were followed for 90 days from the onset of BSI or until treatment failure. Kaplan–Meier survival analysis was used to allow for censoring of patients who were lost to follow-up within 90 days of BSI. Patients who were lost to follow-up were censored at the date of their last documented healthcare encounter. Kaplan–Meier survival curves were used to demonstrate treatment failure rates in the three bioavailability groups. Log-rank *P*-value was used to examine the difference in treatment failure between the three groups.

Cox proportional hazards regression was used to examine risk factors for treatment failure in patients with Gram-negative BSI. Variables with a *P*-value of <0.10 in the univariate Cox model and those that differed across the three oral antimicrobial agent groups in the initial comparison were included in the multivariate Cox proportional hazards regression analysis. Oral antimicrobial agents used for definitive therapy of Gram-negative BSI were included in the Cox model as a categorical variable (high, moderate and low bioavailability). Hazard ratios, adjusted hazard ratios and 95% confidence intervals were used to characterise the associations of each variable with treatment failure. JMP v.11.0 (SAS Institute Inc., Cary, NC) was used for statistical analysis. The level of statistical significance was defined as a two-sided *P*-value of <0.05 unless otherwise specified.

3. Results

During the 4-year study period, 362 eligible patients with Gram-negative BSI were discharged on oral antimicrobial agents. The mean patient age was 63 years, 217 (59.9%) were women, 254 (70.2%) had a urinary source of infection and 243 (67.1%) had BSI due to *Escherichia coli*. Among these patients, 106 (29.3%), 179 (49.4%) and 77 (21.3%) received oral antimicrobial agents with high, moderate and low bioavailability, respectively, for definitive therapy of Gram-negative BSI (Table 1). All Gram-negative bloodstream isolates were susceptible in vitro to the prescribed oral antibiotics for definitive therapy.

The baseline demographics and clinical characteristics of patients who received oral antimicrobial agents with high, moderate and low bioavailability for definitive therapy of Gram-negative BSI are shown in Table 2. Patients who received oral antimicrobial agents with high bioavailability were more likely to have end-stage renal disease than those in the other two groups. Patients in the moderate bioavailability group were more likely to have urological complications than those in the comparator groups. Patients who were prescribed oral antimicrobial agents with low bioavailability were less likely to have central venous catheters at the time of BSI than the remaining two groups. In addition, there were only 2 patients (2.6%) in the low bioavailability group who had BSI due to either *P. aeruginosa* or CAE (both had BSI due to CAE) compared with 14 (13.2%) and 25 (14.0%) in the high and moderate bioavailability groups, respectively ($P = 0.008$) (Table 3). Overall, patients with Gram-negative BSI in all three groups received a mean of 4.7 days of appropriate i.v. antimicrobial therapy during hospitalisation followed by 9.1 days of oral antimicrobial agents.

Overall, within 90 days of BSI, 27 patients had treatment failures, 233 survived without recurrences and the remaining 102 were