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Impact of fluoroquinolone resistance in Gram-negative bloodstream infections on healthcare utilization

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Abstract

There has been a concerning increase in fluoroquinolone resistance among Gram-negative bloodstream isolates. This retrospective cohort study examines the implications of fluoroquinolone resistance on use of healthcare resources in patients with Gram-negative bloodstream infections (BSI). Hospitalized adults with first episodes of community-onset Gram-negative BSI from 2010 to 2012 at Palmetto Health Hospitals in Columbia, SC, USA were identified. Multivariate linear regression was used to examine risk factors for prolonged hospital length of stay (HLOS) in survivors of Gram-negative BSI. Among 474 unique patients, 384 (81%) and 90 (19%) had BSI due to fluoroquinolone-susceptible (FQ-S) and fluoroquinolone non-susceptible (FQ-NS) Gram-negative bacilli, respectively. The FQ-NS bloodstream isolates, particularly *Escherichia coli*, were more likely than FQ-S isolates to be multi-drug resistant (56% versus 6%, $p < 0.001$). Compared with patients with BSI due to FQ-S bloodstream isolates, those with FQ-NS isolates were more likely to receive inappropriate empirical antimicrobial therapy (26% versus 3%, $p < 0.001$), have longer mean HLOS (11.6 versus 9.3 days, p 0.03) and treatment duration with intravenous antibiotics during hospitalization (9.1 versus 7.1 days, p 0.001), and use outpatient intravenous antibiotics at hospital discharge (15% versus 8%, p 0.05). After adjustments in the multivariate model, inappropriate empirical antimicrobial therapy was an independent risk factor for prolonged HLOS in survivors of Gram-negative BSI (parameter estimate 3.65 days, 95% CI 0.43–6.86). Multi-drug resistance among FQ-NS bloodstream isolates limits both empirical and definitive antimicrobial treatment options and poses excessive burdens on the healthcare system.

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Introduction

Bloodstream infections (BSI) make a major contribution to the morbidity and mortality of the general population in North America and Europe [1–4]. The survival benefit from appropriate antimicrobial therapy for BSI has emphasized the importance of optimizing both empirical and definitive treatment regimens [5–7]. Due to relatively high bioavailability of fluoroquinolones, this class of antimicrobial agents has been popular for intravenous to oral switch therapy in hospitalized patients with serious Gram-negative infections, including BSI. However, recent increase in antimicrobial resistance rates of fluoroquinolones among *Escherichia coli* and other Gram-negative bloodstream isolates has limited antimicrobial treatment options [8–10]. In addition, the association between resistance to fluoroquinolones and other antimicrobial agents such as trimethoprim-sulfamethoxazole and amoxicillin-clavulanate has left many patients without reliable oral antimicrobial options for definitive outpatient therapy [8,10]. This

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may constitute an excessive burden on the healthcare system as more patients may stay longer in the hospital to receive inpatient intravenous antimicrobial therapy or to allow arrangements for outpatient intravenous antibiotics.

In this retrospective cohort study, we examined the impact of fluoroquinolone non-susceptibility (FQ-NS) in patients with community-onset Gram-negative BSI on hospital length of stay (HLOS) and need for outpatient intravenous antibiotics upon hospital discharge.

Materials and methods

Setting

The Palmetto Health System in Columbia, SC, USA, includes Palmetto Health Richland Hospital and Palmetto Health Baptist Hospital with a combined bed capacity of >1100 licensed beds. Both hospitals provide care for local residents of Richland County as well as for regional referrals from within the State of South Carolina, in a wide variety of medical and surgical subspecialties.

Definitions

Gram-negative BSI was defined as the growth of any aerobic Gram-negative bacillus in a blood culture. The primary source of infection was identified according to the Centers for Disease Control and Prevention criteria [11]. The site of infection acquisition was divided into community-onset and hospital-acquired. Community-onset BSI was further divided into community-acquired or healthcare-associated as defined by Friedman [12]. FQ-NS isolates were defined as Gram-negative bacilli that were not susceptible *in vitro* to ciprofloxacin according to the CLSI with MIC $\geq$2. Gram-negative bacilli were considered multi-drug resistant if they were non-susceptible to three or more classes of antibiotics [13]. Empirical antimicrobial therapy was defined as antimicrobial agents received within the first 48 h following collection of the first set of positive blood cultures. Appropriate empirical antimicrobial therapy was defined as receipt of an empirical antimicrobial agent with appropriate route and dosage and *in vitro* activity against Gram-negative bloodstream isolates using CLSI guidelines as previously defined [5,6].

Case ascertainment

All patients with BSI due to aerobic Gram-negative bacilli from 1 January 2010 to 31 December 2012 were identified through the Palmetto Health microbiology laboratory database. Hospitalized adults with first episodes of community-onset Gram-negative BSI were included in the study (n = 474). Children <18 years old (n = 98), recurrent BSI (n = 34), polymicrobial BSI (n = 121) and patients treated in outpatient settings (n = 29) were excluded. Patients with hospital-acquired BSI (n = 126) were also excluded as HLOS may be dictated by the primary hospital admission diagnosis rather than BSI.

Statistical analysis

Linear regression was used to examine the primary outcome of the study, which is the association between FQ-NS and HLOS in hospitalized patients who survived Gram-negative BSI. The analysis was limited to survivors to avoid accounting for early death as a favourable outcome. Potential co-variates associated with HLOS were examined using univariate linear regression. To identify factors that were independently associated with HLOS, variables were included in a multivariate linear regression model if the p value for a univariate association with HLOS was $\leq$0.10. In addition, differences between fluoroquinolone-susceptible (FQ-S) and FQ-NS bloodstream isolates were identified. Chi-squared or Fisher's exact test, as appropriate, was used to examine for associations between categorical variables and fluoroquinolone susceptibility, and Student's t test was used to assess for differences in continuous variables. Factors with a p value $\leq$0.10 were also included as covariates in the final linear regression model. Parameter estimates with 95% CI were presented to demonstrate the strength of association between each risk factor and HLOS.

Kaplan–Meier survival analysis was used to compare 28-day mortality in patients with BSI due to FQ-S and FQ-NS Gram-negative bacilli to allow the censoring of patients who were lost to follow up within 28 days of BSI. Log-rank test was used to calculate the p value for a difference in mortality between the two groups. The association between FQ-NS and need for outpatient intravenous antibiotics at hospital discharge was examined using Chi-squared or Fisher's exact test, as appropriate. In a post-hoc analysis, multivariate logistic regression was used to examine risk factors for receiving inappropriate empirical antimicrobial therapy. Odds ratios with 95% CI were reported to demonstrate the association between each variable and inappropriate therapy.

JMP (version 10.0, SAS Institute Inc, Cary, NC, USA) was used for statistical analysis. The level of significance for statistical testing was defined as $p < 0.05$ (two-sided) unless otherwise specified.

Results

Among 474 patients with community-onset Gram-negative BSI during the 3-year study period, 384 (81%) had BSI due to FQ-S and 90 (19%) had BSI due to FQ-NS isolates. The baseline clinical characteristics of patients are shown in Table 1.

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