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Original Article

Beta-lactam vs Non-Beta-Lactam for the Empiric Treatment of Gram Negative Bloodstream Infections

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ABSTRACT

Background: Historically studies evaluating treatment outcomes for patients with gram negative bacilli (GNB) bloodstream infections (BSI) have been between two beta-lactams. The objective of this study is to determine the rate of clinical failure in patients with GNB BSI when empiric therapy is a beta-lactam (BL) vs. a non-beta-lactam (NBL) with a subgroup analysis of patients with a history of BL allergies. Methods: This single center retrospective cohort study included all adult patients receiving antibiotic therapy for a GNB BSI at a university teaching hospital. Treatment groups were created based on receipt of empiric antibiotic, BL or NBL. The primary outcome of clinical failure was assessed after 72 to 96 hours of antibiotic therapy. Results: The cohort included 598 patients, 104 in the NBL treatment group and 494 in the BL treatment group. Rates of clinical failure were higher for patients receiving NBL empirically compared to receiving a BL (32.7% vs. 23.1%, p=0.028). Mortality rates were higher in the NBL treatment arm compared to the BL arm (20.2% vs. 12.8%, p=0.037). Receipt of appropriate empiric therapy was less likely in the NBL treatment group than BL group (61.5% vs. 72.1%, p=0.023). Length of stay was longer for patients receiving a NBL than BL (41 days vs. 27 days, p=0.040). Logistic regression identified NBL as empiric therapy as a risk factor for clinical failure (odds ratio (OR) 1.6) and death (OR 1.7). Conclusion: Patients with gram negative bacilli bloodstream infections receiving a NBL as empiric therapy are more likely to experience clinical failure, death and longer lengths of stay. These negative outcomes are likely due to the higher frequency of empiric therapy not having *in vitro* activity against the infecting pathogen in the NBL treatment group.

Keywords: Gram negative bacilli, bloodstream infection, beta-lactam, fluoroquinolone, aminoglycoside, empiric therapy

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1. INTRODUCTION

Early and appropriate empiric antibiotic treatment has been found to be a positive predictor of treatment outcomes for patients with bloodstream infections

(BSI) in several studies. [1-5] A review of key aspects of sepsis treatment identified empiric antibiotic therapy as the one intervention clinicians have the most control over to increase the chance of sepsis survival. [6] Neither guidelines nor treatment recommendationsexist for suspected gram negative bacilli (GNB) BSI. The majority of sepsis studies have evaluated differences between two different beta-lactams (BL) or compared a BLto a BL in combination with a non-beta-lactam (NBL) with gram negative coverage.[7] In addition to a favorable safety profile, susceptibility databases show BLs are more likely to have activity against infectingGNB than NBL.[8]

Only one randomized control trial has been published comparing a BL, imipenem/cilastatin, and a NBL, levofloxacin, for the treatment of bacteremia or sepsis. [9]Characteristically similar to a majority of antimicrobial studies, the trial was designed to prove non-inferiority and provided a δ of 15%. The cure rate in the levofloxacin arm at the end of treatment was within 15% of the clinical cure rate of the imipenem/cilastatinarm and therefore was determined to be a non-inferior treatment option for bacteremia or sepsis. A critical difference between the results of randomized controlled trials and the reality of clinical practice is the definition of the primary endpoint, clinical cure. Non-inferiority studies typically assess clinical cure after completion of the assigned antibiotic course, in many cases up to 28 days after completion of therapy. This type of outcome does not represent clinical practice as it isroutine to evaluate clinical response to antibiotic treatment much earlier after initiation of treatment, commonly within 48 to 96 hours after initiation of antibiotics, as recommended in the Surviving Sepsis Guidelines and the American Thoracic Society and Infectious Diseases Society of America (IDSA) Hospital-acquired, Ventilator-associated, and Healthcare-associated Pneumonia guidelines. [10, 11]

The objective of this study is to compare clinical failure rates in patientsempirically receiving aNBLora BLfor the treatment of GNB BSI, with a subgroup analysis of patients with a history of a BL allergy. The primary outcome is clinical failure. Secondary outcomes include receipt of appropriate antibiotics, length of stay, allergic reaction to antibiotic therapy and all cause hospital mortality.

2. METHODS

Setting and Subjects

This is a retrospective cohort study of all patients with gram negative bacilli bloodstream infections at a single institution between August 2008 and August 2011. The study was conducted at University Medical Center of Southern Nevada (UMCSN), a 550 bed academic county hospital. The protocol was approved by the UMCSN Institutional Review Board. Patients enrolled in the study included those with blood cultures positive for GNBand receiving antibiotics with intrinsic activity against GNB. Patients with multiple admissions during the study period had only the most recent admission included. Data collection for each patient included demographic information, baseline comorbidities, empiric antibiotic choice, time to receipt of antibiotic after culture collection, pathogen identification and susceptibilities, BSI source, and severity of illness measures.Modified APACHE II scores, without the inclusion of Glasgow Coma Scale, were calculated based on laboratory and clinical data from the day of antibiotic start. [13] Presence or manifestation of antibiotic allergy and description of reaction was collected prior to receipt of antibiotic and during admission.

Definitions and Outcomes

All definitions were selected a priori. Patients were placed in the BL arm if they received a BL with GNB

activity, regardless of concurrent therapy with NBL, within the first 24 hours after blood culture collection. Patients receivingonly NBLs for a minimum of the first 24 hours after culture collection were included in the NBL arm. BSI was considered to be secondary if the same pathogen was cultured from another site within 24 hours of blood culture collection.

Clinical failure was objectively defined and met if any of the following occurred 72 to 96 hours after initiation of antibiotic therapy: maximum temperature greater than 38.0°C, increase in hemodynamic support in the form of vasopressor agents from day of antibiotic start, increase in respiratory support requiring mechanical ventilation from day of antibiotic start, increase in level of care requirements consisting of a transfer from the floor to the intensive care unit. Appropriate antibiotic was defined as receipt of an antibiotic with in vitro coverage of cultured pathogen within 24 hours of blood culture draw. [14-16] Allergic reaction to received antibiotic was defined as a new allergy documented in the pharmacy database or medical chart.

Statistical Analysis

Primary data analysis compares clinical failure between patients treated with a NBL versus a BL. Variables were classified as either nominal or continuous and $\chi 2$ and independent t-test utilized, respectively. Univariate and multivariate predictive logistic regression analyses were performed using the occurrence of death and clinical failure as the modeled primary outcome. Factors thought to increase the risk of clinical failure were included in the original model with values greater than 0.05 excluded from the final model. A *p* value less than 0.05 was determined to represent statistical significance. The ratio of outcome events to variables allowed into the multivariate analysis was set at 10:1. [17] SPSS (SPSS, Inc., Chicago, IL) version 19.0 was employed for statistical analysis.

3. RESULTS

The four year retrospective review identified 598 patients eligible for analysis. The rate of clinical failure and mortality were 24.7% and 14.0% respectively. A majority of patients received a BL as a part of their empiric therapy (n=494, 83.9%). Patient demographics, comorbidities, severity of illness measures and distribution of infecting pathogens were similar between treatment groups (Table 1). Differences included a higher proportion of patients with a history of BL allergy and secondary BSI in the NBL treatment arm. Significantly more patients were immune compromised and required vasopressors at start of antibiotics in the BL treatment arm.

Patients in the NBL treatment arm were more likely to meet the primary outcome of clinical failure in comparison to patients in the BL treatment arm (32.7% vs. 23.1%, p=0.028) (Table 2). Secondary outcome of in-hospital mortality was also higher in the NBL treatment arm (20.2% vs. 12.8%, p=0.037). Patients in the NBL treatment group were less likely to receive appropriate empiric therapy (61.5% vs. 72.1%, p=0.023) and experienced longer lengths of stay (41.9 vs. 27.7 days, p=0.040).

Logistic regression identified the use of a NBL as an independent risk factor of clinical failure (odds ratio (OR), 95% confidence interval) 1.6, 1.0-2.6) and death (OR 1.7, 1.0-2.9). The NBL odds ratio for clinical failure did not change greater than 10% when other predictive variables were added to the model including APACHE II scores, APACHE II score greater than 15, ICU at start of antibiotics, mechanical ventilation at start of antibiotics, vasopressor support at start of antibiotics, and immune suppression. Empiric therapy resistant to infecting pathogen and inappropriate empiric therapy were not included in the model as the three variables have considerable overlap in patient population. The OR for clinical failure when empiric therapy is resistant to infecting pathogen is 2.2 and 1.5

for inappropriate empiric therapy. The ORs for death are 3.5 when empiric therapy is resistant to infecting pathogen and 3.7 for inappropriate empiric therapy.

An analysis comparing treatment arms subdivided based on infection source was performed to determine if clinical failure rates were similar between multiple sites of infection. Patients with a primary GNB BSI treated with a NBL had higher rates of clinical failure than patients receiving BLs empirically (38.1% vs. 18.3%, p=0.005) (Table 3). Patients with a primary urinary infection receiving a NBL had numerically lower failure rates.

Additional analysis comparing NBL antibiotic classes separately was performed to better assess their individual impact on treatment outcomes (Table 4). Patients treated empirically with a macrolide or tetracycline had significantly higher rates of clinical failure than patients receiving a BL (35.0% vs. 23.1%, p=0.043). Rates of clinical failure were similar between BLs (23.1%) and fluoroquinolones (24.6%) and non-statistically higher in patients receiving aminoglycosides (35.0%). Mortality was higher for patients receiving a macrolide, tetracycline, or other antibiotics (trimethoprim/sulfamethoxazole, colistin). Length of stay was longer for all NBL classes in comparison to patients receiving a BL empirically.

A relative risk analysis was done to identify if patients with specific characteristics had different treatment outcomes in comparison to the whole group. Patient groups with statistically significant relative risks in favor of BLsinclude those with APACHE II scores greater than 15, in the intensive care unit at the start of antibiotics, requiring mechanical ventilation at the start of antibiotics, requiring vasopressor support at the time of antibiotic start, or had *Pseudomonas aeruginosa* as an infecting pathogen (Figure 1).

4. DISCUSSION

This retrospective analysis of a large group of patients with GNB BSI identifies the importance of empiric antibiotic choice. Patients receiving a NBL as their empiric antibiotic experienced a higher rate of both clinical failure and death. This increase in clinical failure and death was seen despite the larger proportion of immune suppressed patients requiring vasopressor support at baseline. It should be noted this difference in severity of illness was not seen in APACHE II scores. The main driver of clinical failure for all patients was either continued or new fever after 72 hours of antibiotics. Initiation of vasopressor support, mechanical ventilation, and upgraded level of treatment requiring critical care unit admission was experienced by few patients in either treatment arm and did not provide additional objective outcome data. Additional secondary outcomes of appropriate empiric therapy and length of stay also favored patients receiving BL as empiric therapy.

Appropriate empiric therapy has been extensively studied in the sepsis literature [1-5] but hasn't been examined when comparing empiric therapy of a BL or a NBL. Multivariate analysis found resistance to empiric antibiotics and use of a NBL for empiric therapy as significant risk factors for both clinical failure and death. Logistic regression identifies the importance of each of these variables individually and indicates that the use of a NBL isn't itself leading to the increase in clinical failure and death but more likely the lack of active empiric therapy is driving this outcome. Therefore the choice of a BL may only be superior based on the increased likelihood of having activity against the infecting pathogen and not the inherent efficacy against the pathogen. To determine the impact of infection source on clinical failure rates, patients were separated by infection source and treatment group. Clinical failure rates were higher for patients receiving a NBL if the patient had a primary

BSI, respiratory and intra-abdominal infection. Patients with primary urinary tract infections had higher failure rates if treated empirically with a BL in this cohort. These results reflect randomized controlled trials in which treatment with a BL for uncomplicated cystitishas been found to be less successful than trimethoprim/sulfamethoxazole or ciprofloxacin. [18, 19] Further analysis of patients with primary urinary tract infections and subsequent BSI is warranted to determine if appropriate empiric therapy is more likely to be achieved with a BL oral NBL.

Table 1: Patient characteristics of patients with gram negative bacilli bloodstream infections based on empiric antibiotic class

	Beta-lactam, n=494	Non-beta-lactam, n=104	P value
Male, n (%)	262 (53.0)	50 (48.1)	0.208
Age, year ± SD	53.7 ± 16.7	55.3 ± 15.0	0.361
Weight, kg ± SD	80.8 ± 25.7	81.5 ± 29.4	0.831
Race, n (%)			0.261
White	224 (45.3)	51 (49.0)	
Hispanic	129 (26.1)	27 (26.0)	
Black	88 (17.8)	11 (10.6)	
Immunosuppressed, n (%)	80 (16.2)	8 (7.7)	0.015
Trauma, n (%)	54 (10.9)	14 (13.5)	0.278
Burn, n (%)	19 (3.8)	3 (2.9)	0.449
Malignancy, n (%)	63 (12.8)	12 (11.5)	0.440
Diabetes, n (%)	162 (32.8)	39 (37.5)	0.208
Cirrhosis, n (%)	15 (3.0)	5 (4.8)	0.258
Transplant, n (%)	14 (2.8)	1 (1.0)	0.233
Chronic kidney disease, n (%)	48 (9.7)	11 (10.6)	0.453
HIV, n (%)	14 (2.8)	6 (5.8)	0.116
Severity of Illness			
Vasopressor at start of antibiotics, n (%)	126 (25.5)	12 (11.5)	0.001
ICU at start of antibiotics, n (%)	256 (51.8)	49 (47.1)	0.222
Mechanical ventilation at start of antibiotics, n (%)	171 (34.6)	40 (38.5)	0.262
Secondary bloodstream infection, n (%)	248 (50.2)	62 (59.6)	0.005
Urine	129 (26.1)	30 (28.8)	
Respiratory	85 (17.2)	24 (23.1)	
Intra-abdominal	20 (4.0)	1 (1.0)	
Other	14 (2.8)	7 (6.7)	
Charleston score ± SD	2.2 ± 2.3	2.2 ± 2.3	0.968
APACHE II ± SD	13.7 ± 6.1	12.9 ± 5.3	0.230
Infecting Pathogens, n (%)			
E. coli	178 (36.0)	35 (33.7)	0.366
Klebsiella sp.	106 (21.5)	28 (26.9)	0.139
Enterobacter sp.	60 (12.1)	11 (10.6)	0.399
Pseudomonas sp.	51 (10.3)	12 (11.5)	0.413
Acinetobacter sp.	51 (10.3)	11 (10.6)	0.528
Proteus sp.	26 (5.3)	3 (2.9)	0.226
Citrobacter sp.	11 (2.2)	1 (1.0)	0.354
Serratia sp.	10 (2.0)	0 (0)	0.146
Other GNB	23 (4.7)	7 (6.7)	0.254

HIV = human immunodeficiency virus, ICU = intensive care unit, GNB = gram negative bacilli

Table 2: Outcome measures of patients with gram negative bacilli bloodstream infections based on empiric antibiotic class

	Beta-lactam, n=494	Non-beta-lactam, n=104	P value
Clinical failure, n (%)	114 (23.1)	34 (32.7)	0.028
Fever after 72 hours of antibiotics	105 (21.3)	33 (31.7)	0.017
Vasopressor initiation	11 (2.2)	2 (1.9)	0.600
Mechanical ventilation initiation	7 (1.4)	2 (1.9)	0.482
Intensive care unit admission	5 (1.0)	0 (0)	0.383
Secondary Outcomes			
Death, n (%)	63 (12.8)	21 (20.2)	0.037
Appropriate empiric therapy, n (%)	356 (72.1)	64 (61.5)	0.023
Length of stay, days ± SD	27.7 ± 36.6	41.9 ± 68.2	0.040

Table 3. Clinical failure in patients with gram negative bacilli bloodstream infection according to primary source of infection

	Beta-lactam, n (%)	Non-beta-lactam, n (%)	P value
Blood, n=288	45 (18.3)	16 (38.1)	0.005
Respiratory, n=109	31 (36.5)	11 (45.8)	0.274
Urine, n=159	29 (22.5)	4 (13.3)	0.197
Intra-abdominal, n=21	4 (20.0)	1 (100.0)	0.238
Other, n=21	5 (35.7)	2 (28.6)	0.572

Table 4. Outcome measures of patients with gram negative bacilli bloodstream infections based on specific non-beta-lactam antibiotic class

	BL, n=494	AG, n=20	FQ, n=57	Mac/tet, n=19	Other, n=8	P value

Clinical failure, n (%)	114 (23.1)	7 (35.0)	14 (24.6)	9 (47.4)*	4 (50.0)	0.043
Death, n (%)	63 (12.8)	3 (15.0)	5 (8.8)	9 (47.4)*	4 (50.0)*	<0.001
Appropriate empiric therapy, n (%)	356 (72.1)	12 (60.0)	40 (70.2)	9 (47.4)*	3 (37.5)*	0.031
Length of stay, days ± SD	27.7 ± 36.6	67.5 ± 102.5*	34.2 ± 64.9*	39.2 ± 30.9*	39.0 ± 37.0*	0.001

* indicates statistical significance in comparison to beta-lactam treatment group
BL = beta-lactam, AG = aminoglycoside, FQ = fluoroquinolone, Mac = macrolide, Tet = tetracycline

When the NBL treatment group was divided into separate antibiotic classes, clinical outcomes did not show statistical differences between BL, aminoglycoside or fluoroquinolone treatment groups. Similar to whole group findings, appropriate empiric therapy was inversely related to clinical failure rates. Fluoroquinolones and aminoglycosides were numerically just as likely to provide appropriate empiric antibiotics as BLs. However the length of stay was significantly longer for all NBL treatment groups in comparison to patients receiving BLs. This outcome may indicatea quicker recovery of infectious process for patients receiving BL sregardless of appropriate NBL empiric therapy.

This study's findings cannot be directly compared to randomized trials comparing BLs to NBLs. The outcomes for infectious disease studies are most commonly test of cure or end of therapy measurements which can take place weeks after the last day of antibiotic therapy. This study aimed to mimic decisions seen in clinical practice and evaluate patient response to therapy after receipt of 72 to 96 hours of antibiotics. However, the findings support the trends found in the medical literature when BLs have been compared to NBLs. Several randomized controlled trials including patients with pulmonary and intra-abdominal bacterial infections yielded cure rates ranging from 77-81% for NBL to 89-91% for BLs. [20-25] Even though BLs were numerically superior to their NBL comparators, all studies were non-inferiority trials and cure rates were not directly compared. Superiority was found in a meta-analysis of secondary gram negative BSI comparing tigecycline to multiple comparators, primarily aztreonam. The clinical cure rate was 81% (n=17/21) for tigecycline versus 91% (n=20/22) in the comparator arm. [26] The theory for the decrease in efficacy is the large volume of distribution of tigecycline, 7-9 L/kg, and the resulting low serum concentrations, similar to tetracyclines and macrolides. [27]

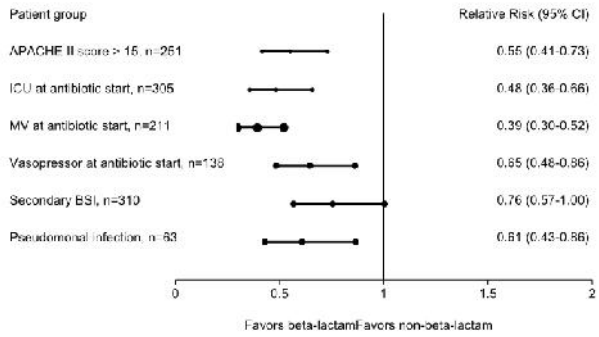

Fig 1: Relative risk of combined outcome of clinical failure and death for patients with gram negative bacilli bloodstream infections based on patient characteristics.
Horizontal bars represent 95 percent confidence intervals.
ICU = intensive care unit, MV = mechanical ventilation, BSI = bloodstream infection

The present study has several limitations related to the retrospective study design. The potential for bias exists as some information that may be necessary to analyze patient cases is not always available. In order to decrease systematic error in data gathering, the outcome measures were modified from previously published retrospective infectious diseases studies to make all outcomes objective and measureable. [28] This is a single-center analysis in a tertiary care hospital and may not be generalizable to all patient populations. Specifically, patients receiving a BL were not compared based upon receipt of specific BL. While the antibiotic stewardship program at the study hospital

does not restrict empiric antibiotic choice, a majority of patients received cefepime in comparison to other BLs. Findings may differ in institutions using an alternative primary BL or have an even distribution of empiric BL between multiple options. Despite the limitations of this study, the results provide insight to the clinical dilemma regarding choice of empiric therapy in patients with GNB BSI. This hypothesis generating study identifies future areas of research needed in the understudied patient population.

5. CONCLUSION

The use of non-beta-lactams is associated with poor treatment outcomes compared to beta-lacatms. This is likely due to a higher rate of inappropriate empiric therapy in the non-beta-lactam group. Clinicians should be aware of this risk when choosing empiric therapy for patients with suspected gram negative infections.

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