Mortality and Length of Stay in Patients with Bloodstream Infections Due to Drug-Susceptible Versus Drug-Resistant Gram-Negative Bacteria

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Abstract: A prospective patient surveillance and analysis in three urban hospitals with the objective of comparing the mortality rates among patients with antimicrobials-sensitive versus -resistant gram-negative bacterial bloodstream infections. The analysis focused on the rates of in-hospital and 28-days mortality. There were 189 patients with BSI, drug-susceptible gram-negative bacteria (DSGNB) 40.7%, multi-drug resistant bacteria (MDRGNB) 42.3% and extensive-drug resistant bacteria (XDRGNB) 16.9%. The mean age, gender, SOFA score on the initial evaluation, APACHE II score, comorbidities, identified bacterial species, and BSI-associated diagnoses were not statistically different except for VAP (P = 0.000) in the XDRGNB infected patients. In-hospital and 28-days mortalities were significantly higher in the XDRGNB-BSI group (P = 0.000), and ICU length of stay (P = 0.000). XDRGNB-BSI was significantly higher in inappropriate and delayed treated patients (P < 0.05). Logistic regression analysis demonstrated no significant interaction for the 28 days mortality neither with the admission diagnoses, the antimicrobial class (except aminoglycosides), the comorbidities (except for solid tumors) (P > 0.05, Nagelkerke R² < 0.4). In conclusion, BSI due to multiple class antimicrobial resistance has higher mortality and ICU length of stay.

Keywords: Multidrug-resistant Bacteria, Extensive Drug-resistant Bacteria, Bloodstream Infection, Appropriate Therapy, ICU Length of Stay

1. Introduction

Rug (Antimicrobials)-resistant gram-negative bacterial infections (DRGNB), especially pathogens included in the mnemonic “ESKAPE” (Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumonia, Acinetobacter baumannii,
2. Materials and Methods

2.1. Study Setup and Location

Prospective patient surveillance and data collection in three urban hospitals: Al Khalidi Hospital and Medical Center, the Specialty Hospital, and Jordan Hospital and Medical Center, the last two are Jordan Medical Council- and the Arab Board of medical Specialities-accredited residency teaching hospitals, all located in Amman, Jordan. The three hospitals encompass around 650 beds with 53 ICU beds, they provide primary care and referral services for Amman residents, as well as referral from other Arab Countries. The study was between January 2017 to February 2019. No consent was obtained due to the nature of the study, no suggestions or changes were made during patients care.

2.2. Data Recruitment

Data was collected with the cooperation among Internists, ICU specialists, Medical residents, clinical pharmacists, and microbiologists. The working teams prospectively evaluated the appropriateness of the treatment regimens for the patients; appropriateness of the prescribed antimicrobial agent(s) for the clinical management of patients, appropriateness of dose and frequency. Information was obtained by following patients as they are admitted through the emergency room, blood cultures from hospitals' microbiology laboratories, admission office, morning reports, and infection control offices. Twenty-eight days after discharge, patients were followed up by phone calls. Patients were included if they were newly admitted with the diagnosis of BSI or develop BSI during their hospital stay, and were diagnosed or suspected to have pneumonia with bacteremia, bacteremic pneumonia, abdominal infection with bacteremia, bacteremic abdominal infection, urinary infection with bacteremia, bacteremic urinary tract infections, SSTI (skin and soft tissue infection) with bacteremia, bacteremic SSSI and CNS infection with bacteremia, and were ≥ 18 years old. Patients were excluded if pregnant, were treated with an antimicrobial outside its labeled indication, e.g. tigecycline and ertapenem (both are not labeled for patients with BSI), no bacterial growth available and imminent mortality. The study was conducted in full confidentiality, treating teams were not informed of the study conduct. Study approval from the internal review boards of the participating hospitals was obtained (Data are available on request as excel and SPSS formats on request). Participating members were urged to review the “The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: Guidelines for Reporting Observational Studies” found on https://www.strobe-statement.org/index.php?id=strobe-home.

2.3. Definitions

The clinical outcomes for patients were defined as the following: mortality (death), Improved: subsidence of parameters (SIRS) that diagnosed BSI, and patients did not have a sequelae like an organ damage or failure upon hospital discharge. Appropriate antimicrobial therapy: the antimicrobial agent used for treatment was covering the causative agent of BSI. Inappropriate antimicrobial therapy is defined as either the antimicrobial agent that has been used for the treatment in patients with BSI was not covering the isolated bacteria at the time of microbiological diagnosis, or delay in starting the appropriate antimicrobial agent [8-10]. Sepsis and severe sepsis syndrome definitions used for this study is according to what was described and reported elsewhere [11].

Definition for DSGNB, MDRGNB, DRGNB, and Pandrug-resistant GNB (PDRGNB): MDRGNB defines as resistant to three or more classes of antimicrobials. XDRGNB defined as extensively drug-resistant (i.e. resistant to all but one or two classes). PDRGNB defined as resistant to all available classes. DSGNB: The isolate susceptibility is not included in MDR or XDR, and susceptible to most tested agents [7]. The outcome sought in this study if there were differences in in-hospital mortality and 28 days mortality, ICU length of stay and hospital length of stay among patients with DSGNB-BSI, MDRGNB-BSI or DRGNB-BSI, no PDRGNB was isolated in our current patients.

2.4. Statistical Analysis

Continuous variables were calculated as mean ± SD. Multiple
Means comparison were analyzed by ANOVA and post hoc analysis by Tukey HSD assuming equal variances. Fischer exact test and Chi-square test ($\chi^2$) was used to analyze the proportions of differences among the three tested resistance patterns. P-value was considered significant for < 0.05. Multicollinearity was assessed among CRE, ESBL-producing GNB, DSGNB, MDRGNB, and XDRGNB: the Tolerance was adequate for all and ranged 0.773 – 0.850 with low Variance Inflation Factor (VIF) 1.294 - 1.314, sensing no multicollinearity and outcomes can be analyzed for the three resistance patterns without redundancy. Data processing was by SPSS (Statistical Package for Social Sciences, version 22. IBM Corporation). Calculations of APACHE 2 score was by a web paste application found on http://reference.medscape.com/calculator/apache-ii-scoring-system. And SOFA Score calculation found on http://www.mdcalc.com/sequential-organ-failure-assessment-sofa-score/.

3. Results

There are 189 patients with BSI distributed as DSGNB 77 (40.7%), MDRGNB 80 (42.3%) and XDRGNB 32 (16.9%). Among the three resistance patterns, the mean ages (P = 0.332) and gender distribution (P = 0.066) were not statistically different. On the initial evaluation patients were risk stratified by SOFA scores to assess the initial likelihood of mortality and statistically were not different (P = 0.152), neither their health evaluation status measured by the APACHE II score (P > 0.05) for all subcategories. The BSI-associated admission diagnoses were not different (P ≥ 0.138) except for more VAP patients (P = 0.000) in the XDRGNB-BSI patients. Comorbidities including diabetes mellitus, immunosuppressive treatments and states, hematological and solid malignancy, kidney transplants, abdominal and other surgeries, and other chronic medical diseases were not different (P > 0.05) among the three resistant patterns. The isolated Enterobacteriaceae, Acinetobacter and Pseudomonas species (P = 0.572) (Figure 1), the distribution of ESBL-producing GNB, CRE, lactose fermenters and lactose non-fermenters among the three resistance patterns (DSGNB, MDRGNB, and XDRGNB) were not significantly different P = 1.0), (table 1).

### Table 1. Demography and characteristics of patients diagnosed as Gram-negative Bacterial Blood Stream Infection with drug-susceptible, multidrug resistant and extensive drug resistant bacteria.

| Characteristic | DSGNB-BSI | MDRGNB-BSI | XDRGNB-BSI | P-Value** |
|---------------|-----------|------------|------------|-----------|
| Total number of patients with GNB-BSI (%) | 77 (40.7) | 80 (42.3) | 32 (16.9) | --- |
| Age Mean (± SD) | 65 (19) | 64 (18) | 65 (14) | 0.332* |
| Gender | | | | |
| Males | 37 | 41 | 23 | 0.066 |
| Females | 40 | 39 | 9 | |
| APACHE II Score | | | | |
| (< 11) | 1 | 9 | 0 | |
| (11 - 20) | 27 | 20 | 7 | >0.05 |
| (21 - 30) | 17 | 11 | 9 | |
| (31 - 40) | 4 | 9 | 7 | |
| (>40) | 1 | 1 | 2 | |
| Initial SOFA Score | | | | |
| (< 5) | 14 | 19 | 3 | 0.152 |
| (5 - 9) | 44 | 42 | 14 | |
| (10-14) | 14 | 17 | 3 | |
| (>14) | 2 | 2 | 2 | |
| Admission Diagnoses with BSI | | | | |
| Primary BSI | 24 | 20 | 10 | 0.648 |
| Ventilator-Associated Pneumonia | 2 | 4 | 9 | 0.000 |
| Community-Associated Pneumonia | 14 | 11 | 5 | 0.749 |
| Urinary Tract Infection | 26 | 33 | 8 | 0.247 |
| Surgical Site Infection | 2 | 3 | 0 | 0.535 |
| Skin and soft tissues infections | 6 | 6 | 2 | 0.961 |
| Intra-Abdominal Infection | 6 | 9 | 0 | 0.138 |
| Other Diagnoses | 1 | 2 | 2 | 0.339 |
| Co-Morbidities | | | | |
| Diabetes mellitus | 35 | 32 | 14 | 0.783 |
| Immunosuppressive treatment | 9 | 12 | 4 | 0.822 |
| Immunosuppressive states | 6 | 10 | 5 | 0.433 |
| Hematological malignancy | 3 | 6 | 5 | 0.104 |
| Solid tumor | 14 | 18 | 7 | 0.785 |
| Kidney Transplant | 1 | 1 | 0 | 0.813 |
| Abdominopelvic surgery | 8 | 10 | 2 | 0.622 |
| Other surgeries | 3 | 9 | 5 | 0.097 |
| Chronic Skin Diseases | 6 | 4 | 1 | 0.089 |
| Chronic Kidney Disease | 0 | 3 | 41 | 0.115 |
| Chronic Liver Disease | 0 | 1 | 11 | 0.695 |
Other GNB: other gram-negative bacteria. Pseudomonas spp: including \textit{P. aeruginosa}

| Characteristic                           | DSGNB-BSI N | MDRGNB-BSI N | XDRGNB-BSI N | P-Value** |
|-----------------------------------------|-------------|--------------|--------------|-----------|
| Other conditions                        | 31          | 46           | 17           | 0.089     |
| Microbiological Diagnosis               |             |              |              | 0.572     |
| \textit{E. coli}                        | 37          | 47           | 3            |           |
| \textit{Klebsiella pneumoniae}          | 16          | 18           | 8            |           |
| Enterobacter spp.                       | 7           | 4            | 1            |           |
| Acinetobacter spp.                      | 3           | 4            | 18           |           |
| \textit{Pseudomonas aeruginosa} and spp.| 7           | 3            | 1            |           |
| Other GNB\*                            | 7           | 4            | 1            | 1.0       |
| Other Resistance patterns               |             |              |              |           |
| ESBL-producing GNB                     | 25          | 53           | 6            |           |
| CRE                                    | 0           | 0            | 5            |           |
| Lactose fermenter                      | 60          | 69           | 12           |           |
| Lactose non-fermenter                  | 10          | 7            | 19           |           |

\*Other GNB: \textit{Citrobacter freundii}, Enterobacter spp., \textit{Klebsiella} spp., \textit{Morganella}, \textit{Proteus} spp., and \textit{Serratia} spp.

BSI: bloodstream infection. DSGNB: drug susceptible gram-negative bacteria. MDR: multidrug resistant. XDR: extensive drug resistant. ESBL—GNB: extended spectrum beta-lactamases producing gram-negative bacilli. CRE: Carabapenem-resistant Enterobacteriaceae.

** Significance was tested by Chi square ($X^2$)

*Significance was tested by ANOVA.

$^\dagger$ Including non-CAUTI.

The outcomes; in-hospital and 28-days mortalities were significantly higher in the XDRGNB-BSI patients ($P = 0.000$), even after adjusting for appropriateness of the antimicrobial therapy mortalities were higher with XDRGNB-BSI patients for both endpoints ($P = 0.005$ and $P = 0.003$ respectively). The length of the ICU stay was longer for XDRGNB-BSI patients than patients with the other two resistance patterns ($P = 0.000$), but the length of hospital stay was not different for the three resistance patterns ($P = 0.413$). Delay in antimicrobial therapy resulted in an increase in the length of hospital stay ($P = 0.025$) and ICU stay ($P = 0.001$) for only DSGNB-BSI patients, but not for patients with MDRGNB-BSI and XDRGNB-BSI ($P \geq 0.422$), (Table 2). Logistic regression analysis demonstrated no statistically significant interaction neither with the admission diagnoses ($P > 0.3$, Nagelkerke $R^2 = 0.169$) the antimicrobial class used ($P > 0.170$, Nagelkerke $R^2 = 0.444$, except for Aminoglycosides $P = 0.02$), and the comorbidities ($P > 0.263$, Nagelkerke $R^2 = 0.165$, except for solid tumor $P = 0.026$) with the 28 days mortality.
The frequency of the inappropriate use of antimicrobials therapy was significantly more in patients with XDRGNB-BSI than patients in the other two resistance patterns \((P = 0.000)\), and improper indications like using aminoglycosides and quinolones as monotherapy \((P = 0.001)\), but not between DSGNB-BSI and MDRGNB-BSI patients \((P = 0.931)\). There was a significant difference in the delay of the antimicrobial therapy in patients with XDRGNB-BSI compared with DSGNB-BSI patients \((P = 0.031)\) but not versus MDRGNB-BSI \((P = 0.392)\). There were five CREs all in the XDRGNB-BSI category. ESBL-producing bacteria were 63.1\% in patients with the MDRGNB-BSI, 29.8\% in the DSGNB-BSI and 7.1\% in the XDRGNB-BSI patients. In this group neither ESBL or CRE showed a significant statistical difference within the DSGNB, MDRGNB, and XDRGNB resistance patterns when were selected to test for in-hospital death, 28-days death, length of ICU stay, hospital stay, appropriateness of therapy and improvement \((P > 0.05)\) (Table 3).

### Table 3. Appropriateness of antimicrobial therapy classified according to drug susceptibility patterns for patients with GNB-BSI.

| Antimicrobial Therapy | DSGNB-BSI | MDRGNB-BSI | XDRGNB-BSI | P-Value |
|-----------------------|-----------|------------|------------|---------|
| Appropriate           | 71        | 63         | 4          | 0.000   |
| Improper in indication| 1         | 2          | 6          | 0.001   |

BSI: blood stream infection. DSGNB: drug susceptible gram-negative bacteria. MDRGNB: multidrug resistant gram-negative bacteria. XDRGNB: extensive drug resistant gram-negative bacteria.

**4. Discussion**

Despite several studies that address mortality and length of hospital stay contrasted with inappropriate therapy \([12, 13]\), few studies either focused on monomicrobial resistance like Acinetobacter and Pseudomonas as a cause of inappropriate empiric therapy and mortality, while another study invited to look at resistance as a major part of inappropriate therapy \([14, 15, 9]\). Our study directly assesses resistance patterns according to an international experts proposal classification for the definition of XDR and MDR gram-negative bacteria (excluding the pan drug-resistant bacteria PDRGNB for being not present in our patients) and their impact on mortality and length of ICU and hospital stay \([3, 7]\). In the quest to analyze our data based on the unique resistance patterns in relation to the outcomes, we tried our best to adjust for several confounders and lurking variables like age, gender, SOFA and APACHE II scores, initial admission diagnoses, comorbidities, the infecting bacterial species, other classified resistance patterns like ESBL, CRE, and types of bacteria based on lactose fermentation. We found that all were statistically not different among the three groups \((P > 0.05)\) except significantly few more cases in VAP were in the XDRGNB-BSI patients, nonetheless their absolute numbers were modest, this was to some extent reassuring that the bulk of the studied outcomes were dominantly correlated with the three resistance patterns under study i.e XDRGNB, MDRGNB and DSGNB.

Despite the XDRGNB-BSI patients did have more inappropriate initial empirical coverage due to resistant...
bacteria, but the inappropriate therapy may affect mortality independent of the resistance pattern [16, 17]. In our patients, those with XDRGNB-BSI infection carried significantly higher mortality compared with DSGNB-BSI and MDRGNB-BSI patients (P = 0.000), even after adjusting for patients receiving appropriate therapy for their resistant bacteria the hospital mortality was higher (P = 0.005) and the 28-days mortality (P = 0.003). Those who were discharged home, the clinical improvement was significantly less in patients with XDRGNB-BSI compared with patients in the other two resistance patterns (P = 0.000).

Like what was found in other studies, resistance is a cause for a longer hospital stay. Here, XDRGNB-BSI subset of patients have longer ICU length of stay (P = 0.000) but not the overall hospital stay (P = 0.413), this may be due to the nature of the most uninsured patients in the private costly hospitals, patients and families tend to discharge their patients as soon as they become reasonably stable [18]. Other studies did not show that resistance is a cause for longer hospital length of stay, but their definition of resistance in their patients was based on cephalazidine resistance in gram-negative bacteria [19]. The delay in the antimicrobial therapy resulted in the increase in the length of hospital stay (P = 0.025) and ICU stay (P = 0.001) for only DSGNB-BSI patients, but not for patients with MDRGNB-BSI and XDRGNB-BSI (P ≥ 0.422), possibly due to a concealed effect of the longer stay for patients with resistance patterns, reflecting their comorbid status [20]. Newly introduced automated testing systems such as MALDI-TOF MS proved useful in reducing mortality and hospital length of stay, especially in patients with gram-negative sepsis [21].

5. Conclusion

Patients with BSI due to XDRGNB have higher mortality and ICU length of stay. Delayed antimicrobial therapy caused an increase in the length of hospital stay and ICU stay in patients with DSGNB, but not XDRGNB and MDRGNB, possibly due to their comorbid conditions. Multiclass antimicrobials resistance adds more outcome-adverse effect on patients, and this phenomenon is not unique for ESBL-producing gram-negative bacteria and CRE as usually reported.

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