Bacteremia Associated with Pressure Ulcers at Alyarmuk Teaching Hospital in Baghdad

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Abstract
Fifty patients (24 female and 26 male) with pressure ulcers associated with different diseases and attending AL-yarmouk Teaching Hospital in Baghdad were selected in this study. The duration of sample collection was from March to December 2018. All blood samples collected from patients were submitted to a blood culturing technique to examine bacteremia. The results showed that 12 blood bacterial isolates were obtained. The isolated bacteria were subjected to Vitek-2, which is an accurate identification technique. The results of the blood culturing technique revealed that 33.3% were Gram negative bacteria, while 66.6% were Gram positive. Diagnosis by Vitek-2 showed that 33.3% were Staphylococcus spp., 33.3% were Enterococcus spp., 25.1% were Serratia marcescens and 8.3% comprised Acinetobacter baumannii. The results of minimum inhibitory concentration (MIC) by Vitek-2 showed that Trimethoprime – Sulfamethazole concentration at 320 µg/ml was the MIC for Acinetobacter baumannii, while piperacillin, Ticarcillin, and Ticarcillin-Clavulanic acid at 128 µg/ml were the MIC for Serratia marcescens. Acinetobacter baumannii showed 100% resistance to all antimicrobial agents, while for the Serratia marcescens resistance values were 54.55%, 54.55%, and 45.45% for isolate numbers 1, 2, and 3, respectively. Gram positive bacteria recorded Nitrofurantoin MIC of 256 µg/ml against Staphylococcus epidermidis and Enterococcus spp., with both species showing high resistance compared with the others which had a value of 87.50%.

Keywords: Pressure ulcers, bacteremia, Blood culture.
Introduction
Pressure ulcers (PUs) are an injury to the skin or underlying tissue due to unrelieved pressure [1]. It is a serious health problem for the world, specifically to weakened geriatric or bed-bound patients in hospital [2]. The symptom typically range from skin redness to serious injuries to the bones or attached tissues, raising significant threat to patients with restricted mobility [3]. The prevalence of developed pressure sore is high in elderly people, appearing within those between the 70s and 80s decades. These ulcers appear in community setting, nursing homes and hospitals, with an incidence varying from 1.2% to 11.2% [4]. Pressure ulcers are generally followed by an inflammatory response and mostly by local bacterial colonization or systemic disease[5].

Risks of pressure ulcers are correlated with remarkable morbidity and mortality with bacteria, which are the most prevalent complicating factors related with pressure ulcers[6]. Pressure ulcers can serve as foci for blood infection as the most prevalent considerable Infected PUs complication. Patients are often more probable to develop bacteremia[7].

The association between PUs and bacteremia was related with 50 percent mortality rate in hospitalized patients[8]. Septicaemia or secondary bacteremia can represent complications of the pressure ulcer where both of these are correlated with increased death[9]. Precise identification of bacterial isolates from blood at species level as well as accurate identification of portal of entry and/or the source of infection are essential for the ideal management of such infections[10].

From 1995 to 2002, a database of a hospital in the United States recognized coagulase negative staphylococcus (CoNS) as the most prevalent cause, responsible for 31 percent of cases[11]. In recent years, the prevalence of Acinetobacter baumannii bacteremia has increased significantly, particularly in immunocompromised populations and intensive care units[12]. Enterococci have recently become one of the most prevalent nosocomial pathogens, with an elevated mortality rate of up to 61% [13]. Serratiamarcescens is considered as an opportunistic bacterium that causes a variety of human infections, including keratitis, bacteremia, as well as urinary tract and wound infections [14].

The aim of this study is to detect bacteremia associated with pressure ulcers, along with testing MIC values of several antibacterial agents.

Materials and methods

Patients
Fifty patients (24 female and 26 male). 40% of patients between 70 and 80 years were included in this study suffering from pressure ulcer and another disease (30% heart disease, 18% lung disease, 16% kidney disease, 16% diabetic patients and the remaining percent for another disease) all these disease with a pressure ulcer were made the patients bed ridden at department of medicine\ AL-yarmouk teaching hospital and the patients diagnosed clinically by a physician for pressure ulcer and bacteremia. The duration of study from the march 2018 to December 2018.

Blood sample collection and bacteremia
The following guidelines were implemented rigidly when samples of blood were obtained for blood culture [15]:
Whenever possible, blood samples were taken for culture before antimicrobial therapy was administered. Nine millilitres of blood was injected into a sterile bottle containing brain heart infusion broth culture. The same method was repeated to another blood sample taken from separate sites over a duration of 10 min. Then, the bottles were incubated for 18-24 hours at 37 °C. The presence of macroscopic alterations such as haemolysis, turbidity, cotton ball like colonies, and gas bubbles were
screened during the next days. Gram staining was performed irrespective to the macroscopic indications of growth, while blind subcultures of blood and Macconkey agar were performed after 1, 3, and 7 days.

Identification of bacterial isolates

Morphological identification was performed by examining the colonies on different media and by gram staining. The precise identification was achieved through diagnosis by vitek-2 system.

Antimicrobial screening of bacterial isolates

Antimicrobial screening test was performed by using vitek-2 system, with the susceptibility card for Gram positive bacteria was AST-P580 and that for Gram negative bacteria was AST-222. Interpretation of the results was carried out using the criteria of the Clinical Laboratory Standards Institute (CLSI, 2018) [16].

Statistical Analysis:

The Statistical Analysis System- SAS (2012) program was used to detect the effects of different factors on study parameters[17]. Least significant difference –LSD- test was used to compare significant differences between means and Chi-square test was used to compare significant differences between percentages.

Results and Discussion

From 50 patients with pressure ulcer, 12 samples (24%) were blood culture positive and different types of bacterial isolates were isolated and stained (33.3%-Gram negative bacteria and Gram positive 66.6%), as shown in Table-1. Accurate diagnosis by vitek-2 revealed 33.3% Staphylococcus sp., 33.3% Enterococcus sp., 25.1% Serratia marescens, and 8.3% Acinetobacter baumannii, as shown in Table-1. Antimicrobial test was performed for bacterial isolates.

Table 1: The results of blood culture and identification by Vitek-2 compact system

| NO. | Blood culture | Vitek-2 |
|-----|--------------|--------|
| 1   | 33.3% of Staphylococcus sp. | 25% of S. haemolyticus |
|     |              | 25% of S. epidermidis |
|     |              | 50% of S. aureus |
| 2   | 33.3% of Enterococcus sp. | 50% of E. faecalis |
|     |              | 50% of E. gallinarum |
| 3   |              | 25.1% Serratia marescens |
| 4   |              | 8.3% of Acinetobacter baumannii |

The results demonstrated a significant difference between bacterial isolates (P<0.05). The highest minimum inhibitory concentration (MIC) achieved using Trimethoprim-Sulfamethazole was against Acinetobacter baumannii was 320 µg/ml, whereas for Serratia marescens, the piperacillin, Ticarcillin and Ticarcillin-Clavulanic acid showed highest MIC (128 µg/ml), as shown in Table-2 and Figure-1.

Table 2: The minimum inhibitory concentration for Gram negative bacteria

| Bacterial isolate | Serratia marescens | Serratia marescens | Serratia marescens | Acinetobacter baumannii |
|-------------------|--------------------|--------------------|--------------------|-------------------------|
| MIC µg/ml         | MIC µg/ml          | MIC µg/ml          | MIC µg/ml          |                         |
| Antimicrobial      |                    |                    |                    |                         |
| Ticarcillin-Clavulanic acid | 128 (R)           | 128 (R)           | 128 (R)           | 128 (R)                |
| Ticarcillin        | 128                | 128                | 128                | 128                    |
| Meropenen         | 16 (R)             | 0.25 (S)          | 0.25 (S)          | 16(R)                  |
| Gentamicin        | 4 (S)              | 16 (R)            | 1 (S)             | 16 (R)                 |
| Ciprofloxidine    | 0.25 (S)           | 0.25 (S)          | 0.25 (S)          | 4 (R)                  |
| Ceftazidime       | 64 (R)             | 16 (R)            | 64 (R)            | 64 (R)                 |
| Cefepime          | 64 (R)             | 8 (S)             | 64 (R)            | 32 (R)                 |
| Gentamicin        | 4 (S)              | 16 (R)            | 1 (S)             | 16 (R)                 |
| Minocycline       | 8 (I)              | 4 (S)             | 8 (I)             | 16 (R)                 |
| Meropenen         | 16 (R)             | 0.25 (S)          | 0.25 (S)          | 16 (R)                 |
| Ticarcillin-Clavulanic acid | 128 (R)           | 128 (R)           | 128 (R)           | 128 (R)                |
| Ticarcillin       | 128                | 128                | 128                | 128                    |
| Ticarcillin-Clavulanic acid | 128 (R)           | 128 (R)           | 128 (R)           | 128 (R)                |
Tobramycin \( 320 \) (R) \( 20 \) (S) \( 20 \) (S) \( 20 \) (S) (R) 16 (I) 16 (R)

Trimethoprim-Sulfamethazoloe \( 1 \) (S) \( 2 \) (S) \( 3 \) (S) \( 4 \) (S) \( 5 \) (S) \( 6 \) (S) \( 7 \) (S) \( 8 \) (S) (R) 16 (I) 16 (R) 320 (R)

LSD value 16.38 * \`18.24 * 16.55 ** 27.93 *

* (P<0.05).

** (P<0.01).

**11 : Is the number of antimicrobial agent used in this study.

There was also a significant difference between bacterial isolates (P<0.05), with the highest MIC using Nitrofurantion against Staphylococcus epidermidis being 256 µg/ml while that for all Enterococcus spp. was 256 µg/ml, as shown in Table-4 and Figure-2.
Table 4-The MIC values for Gram positive bacteria

| Bacterial isolate | S. aureus | S. epidermidis | S. haemolyticus | S. haemolyticus | E. faecalis | E. faecalis | E. gallinarum | E. gallinarum |
|-------------------|-----------|----------------|----------------|----------------|------------|------------|--------------|--------------|
|                   | MIC µg/ml | MIC µg/ml       | MIC µg/ml       | MIC µg/ml       | MIC µg/ml  | MIC µg/ml  | MIC µg/ml    | MIC µg/ml    |
| Levofloxacin      | 0.12 (S)  | 0.12 (S)        | 8 (R)           | 8 (R)          | 12 (S)     | 12 (S)     | 0.25 (S)     | 12 (S)       |
| Erythromycin      | 8 (R)     | 8 (R)           | 8 (R)           | 8 (R)          | 8 (R)      | 8 (R)      | 8 (R)        | 8 (R)        |
| Linezolid         | 2 (S)     | 8 (R)           | 2 (S)           | 8 (R)          | 8 (R)      | 8 (R)      | 8 (R)        | 8 (R)        |
| Ticoplanin        | 0.5 (S)   | 32 (R)          | 4 (S)           | 4 (S)          | 32 (R)     | 32 (R)     | 32 (R)       | 32 (R)       |
| Vancomycin        | 1 (S)     | 32 (R)          | 1 (S)           | 1 (S)          | 32 (R)     | 32 (R)     | 32 (R)       | 32 (R)       |
| Tetracycline      | 1 (S)     | 16 (R)          | 2 (S)           | 16 (S)         | 16 (R)     | 16 (R)     | 16 (R)       | 16 (R)       |
| Tigecycline       | 0.12 (S)  | 1 (R)           | 0.5 (S)         | 0.5 (R)        | 1 (R)      | 1 (R)      | 1 (R)        | 1 (R)        |
| Nitrofurantion    | 16 (S)    | 256 (R)         | 16 (S)          | 16 (S)         | 256 (R)    | 256 (R)    | 256 (R)      | 256 (R)      |
| LSD value         | 6.19 *    | 17.94 *         | 6.55 *          | 6.09 *         | 20.44 *    | 20.44 *    | 17.52 *      | 20.44 *      |

* (P<0.05).

Figure 2-Antibiotic sensitivity variations among Gram negative bacterial isolates (series1 Serratia marescence38; series 2 Serratia marescence15; series3 Serratia marescence7; series4 Acinetobacter bumannii). 1-Cefepime;2-Ceftazidime;3-Ciprofloxacin;4-Gentamicin;5-Meropenem;6-Minocycline;7-piperacilin;8-Ticarcillin;9-Ticarcillin-Clavulanic acid;10-Tobramycin;11-Trimethoprim-Sulfamethazole.

The bacterial isolate that had the highest bacterial resistance was S.epidermidis87.50%, with the same percentage being recorded for Enterococcus spp., as shown in Table-5.

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Table 5-The resistance percentage for Gram negative bacteria

|        | S. aureus | S. epidermidis | S. haemolyticus | S. haemolyticus | E. faecalis | E. faecalis | E. gallinarum | E. gallinarum |
|--------|-----------|----------------|-----------------|----------------|-------------|-------------|---------------|---------------|
| R      | (12.50%)  | (87.50%)       | (25.00%)        | (37.50%)       | (87.50%)    | (87.50%)    | (87.50%)      | (87.50%)      |
|        | (18)      | (78)           | (28)            | (38)           | (78)        | (78)        | (78)          | (78)          |
| S      | (87.50%)  | (12.50%)       | (75.00%)        | (62.50%)       | (12.50%)    | (12.50%)    | (12.50%)      | (12.50%)      |
|        | (78)      | (18)           | (68)            | (58)           | (18)        | (18)        | (18)          | (18)          |
| I      | (0.00%)   | (0.00%)        | (0.00%)         | (0.00%)        | (0.00%)     | (0.00%)     | (0.00%)       | (0.00%)       |
|        | (08)      | (08)           | (08)            | (08)           | (08)        | (08)        | (08)          | (08)          |
| Total  | *8        | *8             | *8              | *8             | *8          | *8          | *8            | *8            |
| Chi^2  | 12.56 **  | 12.56 **       | 10.47 **        | 9.85 **        | 12.56 **    | 12.56 **    | 12.56 **      | 12.56 **      |

** (P<0.01).

*8: Is the numbers of antimicrobial agents used in this study.

Discussion

A study published by Thomas (2006) on 21 sepsis syndrome with a attributable to pressure ulcers revealed that 76% had bacteremia resulted from pressure ulcer [18]. Another study by Braga et al. (2017) revealed that among sixteen patients with infected pressure ulcer, 62.5% developed bacteremia [19]. These results demonstrated higher proportions of bacteremic patients than that recorded in our study, which was 24%.

The Gram negative bacteria associated with bacteremia: (Acinetobacterbaumannii and S. marescens)

In our study, A. baumannii showed resistance to all antimicrobial agents. This result is corresponding with other studies. A study by Yang et al. (2018) showed that 77.8% of the patients were multidrug resistant [20]. In addition, China’s antimicrobial resistance monitoring program has widely identified extensive drug resistance to A. baumannii (XDRAB) [21].

In another study done by Xu et al. (2016) state that 87.7% isolates from bacteremic patients were considered to be XDR [22]. In the same study of Xu et al. (2016) Acinetobacter baumannii isolated from blood was resistant to Ceftipime, Ceftazidime, Ciprofloxacin, Gentamicin and Tobramycin this results correspond the current study results only the different in the isolatetwas immediately resistant to Meropenem, while in a present study was resistant to it [22]. The ability of A. baumannii for the acquisition of genetic resistance determinants is responsible for the development of MDR strains. Other resistance mechanisms include Beta-lactamases, changes in porin canals, efflux pump (responsible for resistance to beta lactams antibiotics), mutations in deoxyribonucleic acid topoisomerase (mediated resistance to quinolone), and genes coding amino-glycoside-modifying enzymes. In addition, oxacillinases and metallo-blactamases (e.g., blaOXA58 and blaOXA24A40, blaOXA23, ) contribute to the resistance of carbapenem [23].

A retrospective cohort study was also previously performed, were 10 patients with one or more positive blood cultures for S. marcescens were recorded in a tertiary care hospital in Seoul, South Korea, from January 2006 to December 2012 [24]. While in the present study, 3 patients with positive blood cultures of S. marcescens were recorded for the period from March 2018 to December 2018.

The majority of the isolates in a study by Kim et al., (2015) were susceptible tomeropenem, cefepime, and ceftazidime [24]. While in this study, only 2 isolates were sensitive to meropenem-sensitive and one isolate was sensitive to cefepime, whereas all isolates were resistant to ceftazidime.
Recent epidemiological analysis demonstrated an increase in the rate of antimicrobial resistance among isolates of *S.* Marcescens. In contrast, the multidrug-resistant (MDR) strains of *S.* Marcescens were linked with severe outcomes [25].

**The Gram positive bacteria associated with bacteraemia**

The most common bacteria associated with pressure ulcers were reported to be *Enterococcus faecalis* and *Staphylococcus aureus* [26]. The incidence of MRSA infections, particularly bacteraemia, varies worldwide. In 2014, the proportion of MRSA isolates in Europe ranged from 0.9% in the Netherlands to 56% in Romania [27]. In a study on patients with coagulase-negative staphylococci (CoNS), three cases out of 56 (5.4%) of bacteremia were associated with pressure ulcers [28], whereas the proportion of those with CoNS was 10.09% [29].

*Enterococcus* spp. was shown to be responsible for 3.6% of bacteremia associated with pressure ulcers [30]. Enterococci have recently become one of the most prevalent nosocomial pathogens, with an elevated death rate of up to 61%. Enterococci are reported as the second most cause of urinary tract and wound infections and the third common cause of bacteraemia [31]. In the UK, there were 7066 cases reported of bacteremia by *Enterococcus* species in 2005, reflecting an increase of 8% from 2004. *E. Faecalis* was responsible for 63% of these cases, whereas 28% were caused by *E. Faecium*. In addition, 80% of all cases were resistant to antibiotics. Also, it was reported that approximately 12 percent of nosocomial infections in the USA are caused by *Enterococcus* species [32].

**Conclusions**

Pressure ulcer is a serious health problem and bacteraemia could certainly be one of its dangerous complications. Appropriate antibiotic treatment should be selected in order to eradicate the infection associated with pressure ulcer and avoid bacteremia.

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