Extensive Drug Resistance in Intensive Care Units, Yemen, 2021: A Cross-Sectional Study

المقاومة الشاملة للمضادات الحيوية في وحدات العناية المركزة، اليمن، 2021: دراسة مقطعية

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Abstract:

The emergence of nosocomial infections (NCI) in Intensive care units (ICUs) that caused by antimicrobial Drug Resistance (AMR) Gram-Negative bacilli (GNB) has become a major public health threat since there is a limited effective treatment. This study is aimed to determine the Prevalence Rate of NCI, and the antibiotic susceptibility pattern of isolates. A cross-sectional study was conducted in six adult ICUs at Al Thawra General hospital, Sana'a, Yemen. A total of 117 admitted patients were included in the study from the period of 1st August to 31st October 2021. A pre-designed questionnaire was used for the collection of socio-demographic and clinical data, various clinical specimens were collected from NCI patients and processed using Vitek 2 automated system to identify the isolates and its susceptibility pattern. Carbapenemase producing was tested by Imipenem-EDTA synergy disc diffusion test according to Clinical and Laboratory Standards Institute (CLSI) guidelines. Data were analyzed using Epi-info version 7.2 statistical software packages (CDC, USA), and the results were presented as descriptive statistics: rates & frequency for categorical variables while, mean ±SD or\medium (minimum –maximum) for quantitative variables. The prevalence of NCI in ICUs was 46%. The most isolates were GNB (88%, 52/59). *K pneumoniae* was the most prevalent (37%, 19/52) while, *P aeruginosa* and *A baumannii* were the most resistant. The resistance for tested antibiotics was 98% (51/52) of isolates; 75% of them showed Extensive Drug Resistance (XDR), and 47% were Carbapenemase producers. However, most AMR-GNB is still susceptible to Polymyxin B and Colistin, the resistance has found to be 10% and 12 % respectively. The high prevalence of AMR-NCI in ICUs calls for an urgent establishment of a stewardship program with strict measures of Infection Prevention Control and regular monitoring of the resistant strains.

Keywords

Antimicrobial Drug-Resistant, Nosocomial Infections, Intensive Care Units, Gram-Negative bacilli, Yemen.

الملخص :

أصبح ظهور عدوى المستشفيات (NCI) في وحدات العناية المركزة (ICUs) والتي تسببها عصيات البكتيريا سالبة الجرام المقاومة للمضادات الحيوية (GNB) تهديدًا كبيرًا للصحة العامة نظرًا لمحدودية وجود العلاج الفعال. تهدف هذه الدراسة إلى تحديد معدل انتشار عدوى المستشفيات (NCI)، ونمط الحساسية للمضادات الحيوية للعزلات البكتيرية. تم اجراء دراسة مقطعية وصفية على ستة وحدات للعناية المركزة في مستشفى الثورة العام، صنعاء، اليمن.

حيث تم تضمين ما مجموعه 117 مريضًا بالغاً في الدراسة للفترة من 1 أغسطس إلى 31 أكتوبر 2021. تم جمع البيانات الاجتماعية والديموغرافية والسريرية باستخدام استبيان تم اعداده مسبقاً، وتم جمع عينات سريرية مختلفة من المرضى المصابين بعدوى المستشفيات (NCI)، حيث تم تعريف البكتيريا المعزولة وحساسيتها للمضادات الحيوية باستخدام نظام Vitek 2 الآلي. تم اختبار إنتاج البكتيريا المعزولة لأنزيم الكاربابينيماز بواسطة اختبار انتشار القرص التآزري Imipe-nem-EDTA)) وفقًا لإرشادات معهد المعايير السريرية والمخبرية (CLSI). تم تحليل البيانات باستخدام البرناامج الإحصائي Epi-info الإصدار 7.2 (CDC، الولايات المتحدة الأمريكية)، وتم عرض النتائج كإحصاءات وصفية: معدلات وتكرار للمتغيرات الفئوية بينما متوسط ±SD أو\الوسيط (الحد الأدنى -الحد الأقصى) للمتغيرات الكمية. بلغ معدل انتشار عدوى المستشفيات (NCI) في وحدات العناية المركزة (46٪)، وكانت أكثر العزلات للبكتيريا سالبة الجرام ((GNB (88٪، 59/52). و كان النوعpneumoniae) (K هو الأعلى نسبة (37%، 52/19)، بينما كان النوعان (P aeruginosa) و A baumannii)) هما الأكثر مقاومة. بلغت مقاومة البكتيريا المعزولة للمضادات الحيوية المختبرة 98% (52/51)، (75%) منها أظهرت مقاومة واسعة النطاق للمضادات الحيوية (XDR)، بينما (47%) كانت منتجة لإنزيم الكاربابينماز. ومع ذلك، فإن معظم البكتيريا سالبة الجرام المقاومة للمضادات الحيوية (AMR-GNB) لا تزال حساسة للبوليميكسين ب والكوليستين فقد وُجد أن المقاومة بلغت (10% و12%) لهما على التوالي. إن ارتفاع معدل انتشار AMR-NCI في وحدات العناية المركزة يدعو إلى إنشاء عاجل لبرنامج يشرف على استخدام المضادات الحيوية في المستشفيات عامة وفي وحدات العناية المركزة خاصة مع اتخاذ تدابير صارمة لمكافحة العدوى وعمل مراقبة منتظمة للسلالات المقاومة.

الكلمات المفتاحية: مقاومة المضادات الحيوية، عدوى المستشفيات، وحدات العناية المركزة، البكتيريا سالبة الجرام، اليمن.

1. Introduction

Intensive care units (ICU) have the highest prevalence of nosocomial infections (NCI) that caused by antimicrobial resistance pathogenic bacteria. However, the emergence of these agents in ICU has become a major public health threat since there is a limited effective treatment [1].

This type of infection is responsible for 5 to 35% of all NCI and for approximately 90% of all outbreaks of diseases in an ICU, and the mortality rates ranging from 9 to 38% and can reach 60% [2].

The highest frequencies of NCIs reported by WHO were from hospitals in Eastern Mediterranean Region (EMRO) 11.8%; however, in low and middle-income countries there is a few data available on the impact of this health problem [3].

According to the Centers for Disease Control and Prevention (CDC), more than 70% of the bacteria causing nosocomial infections are resistant to at least one of the antimicrobial agents. The infections caused by drug-resistant gram-negative bacteria (GNB) in the hospital units are still a significant challenge, however, *Enterobacteriaceae*, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* (Ab) are still the major hospital-acquired drug-resistant GNBs [3].

There are three antimicrobial resistance types presenting in GNB: multidrug-resistant (MDR), extensively drug-resistant (XDR), and pan drug-resistant (PDR) [1]. The emergence of this types of resistance is particularly worrying since clinicians are running out of treatment options and it has been estimated that AMR will cause 10 million deaths per year by 2050 if they fail to take appropriate actions now [4].

The rate of AMR-GNB pattern in ICUs is up to five-fold increase than in general hospital settings contributing 20%–25% of all nosocomial infections [1, 5, 6]. Although, 70% of ICU admitted patients are using antibiotics either as prophylaxis or treatment [7, 8]. In South East Asia MDR-GNB infection is among

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the highest worldwide, especially in relation to ICU stay [9]. The prevalence rate of AMR-GNB in Yemen is still not well studied, therefore this study is aimed to estimate the magnitude of the problem in ICUs, and the antibiotic susceptibility patterns of isolates to help providing a rational protocol for antibiotic using in ICUs rather than empirical therapy.

2. Material and Method

All study methods were carried out according to the relevant guidelines and regulations

2.1. Study Design, Period and Population

A cross sectional study was conducted in Al Thawra Modern General Hospital (TMGH) in Sana'a, the capital city of Yemen, during the period from August to October, 2021. Six ICUs of the hospital were included in the study: Medical Intensive Care Unit (MICU), Surgical Intensive Care Unit (SICU), Cardiac Intensive Care Unit (CICU), Neuro Intensive Care Unit (NICU), Emergency Intensive Care Unit (EICU) and Nephro Intensive Care Unit (Nephro ICU). A total of 117 adult patients admitted to ICUs were enrolled in this study, while the febrile patients on admission were excluded.

2.2. Definitions and selection criteria

The Diagnostic criteria to classify the infections of admitted patients were recommended and implemented by ECDC criteria [2, 3].

- **a.** ***Infection***: An infection was defined as the isolation of GNB in the presence of compatible signs or symptoms [1].
- **b.** ***Nosocomial infection (NCI)***: An infection that is occurring after 48 hours of hospital admission, 3 days of discharge, or 30 days of an operation [2].
- **c.** ***Pneumonia***: was considered if purulent tracheobronchial secretion or new pathogenic bacteria isolated from sputum or tracheal aspirate [3].
- **d.** ***Bloodstream infection (BSI)***: was defined as one positive blood

culture with a recognized pathogen or two positive cultures with the same organism drawn on separate times with one of the following signs and symptoms: (fever (> 38°C), chills, rigor and hypotension [3].

e. ***Urinary tract infection (UTI)***: was defined as a positive urine culture of $\geq 10^2$ colony forming units/ml with no more than two species of microorganisms, and at least one of the following signs or symptoms: fever (> 38°C); dysuria; suprapubic tenderness; costovertebral angle pain or tenderness with no other recognized cause [3].

f. ***Surgical site infection (SSI)***: was defined as infection which occurred within 3-7 days after the operation involving the skin, subcutaneous tissue, or deep soft tissue of the incision and at least one of the following: purulent drainage with or without laboratory confirmation [3].

g. ***Multidrug Resistance (MDR)***: was defined as non-susceptibility to at least one agent in three or more antimicrobial categories. Extensively Drug-Resistant (XDR): was defined as non-susceptibility to at least one agent in all, but two or fewer antimicrobial categories. Pandrug-resistant (PDR): was defined as non-susceptibility to all agents in all available antimicrobial categories [1].

2.3. Data Collection

Demographic and clinical relevant data were obtained from each patient in a predesigned questionnaire after the approval from the Research Ethical Committee at Ministry of Public Health and Population (MoPHP) (NO. 113), and the agreement of hospital administration and head of ICUs. Verbal consent was secured from patients and for those in critical condition (e.g. coma), and it was taken from their companions. Confidentiality was secured throughout the study.

2.4. Specimen Type and Sampling

Various clinical specimens (urine, sputum, blood, CSF and other body fluids) were received from the patients for the investigation of significant pathogen. Urine specimens were collected into sterile containers. Blood specimens were extracted under aseptic conditions and transferred immediately into sterile bottles containing Tryptone Soya broth. The wounds specimens were taken as swabs, then placed in transport media (Cary blair medium) and analyzed as soon as possible. All specimens were inoculated using suitable differential, selective, enriched media and incubated for 24 to 48 hours. Colonies were subjected to gram staining then diagnosed as gram-negative and gram-positive. All specimens that were not be collected under adequate steps or conditions or containing more than 2 organisms were excluded from the study.

2.5. Laboratory Procedures

Laboratory investigations were performed according to stander microbiological techniques [10], and all types of media were prepared according to manufacturers and standard procedures [11]. The identification of GN isolates and its antimicrobial susceptibility pattern were performed using VITEK 2 system GP ID identification cards for gram-negative (AST-GN 87 (lot: 6770912203), AST-GN 72 (lot: 05921083103) and AST-GN 75 (lot: 5951129403), then classified as MDR, XDR or PDR depending on susceptibility pattern result [1], (the reagent of Vitek 2 system was obtained from Biomerieux Marcy-I, Etoile, France [12]). Carbapenemase producing GNB were detected by using Imipenem-EDTA synergy disc diffusion test, and the result was interpreted as positive when the inhibition zone took a characteristic keyhole shape according to Clinical and Laboratory Standards Institute (CLSI) guidelines [11]. All GN isolates were tested for the following antibiotics: Amikacin, Augmentin, Ceftazideme, Ceftriaxone, Cefotaxime, Ciprofloxacin, Colistin Sulphate, Co-Trimoxazole, Imipenem, Levofloxacin, Piperacillin, Pip-Tazobactam, Polymyxin B, and Tetracycline.

2.6. Data Analysis

Data were entered and analyzed using Epi-info version 7.2 statistical software packages (CDC, USA), and the results were presented as descriptive statistics: rates & frequency for categorical variables while, mean ±SD or\medium (minimum –maximum) for quantitative variables.

3. Results

Out of 117 admitted patients in ICUs 18 patients (15%) were febrile on admission and excluded from the study, and the rest 99 (85%) were afebrile, and only 46 (46%) developed fever after ≥ 48 hours of admission and were diagnosed as NCI patients (Figure 1).

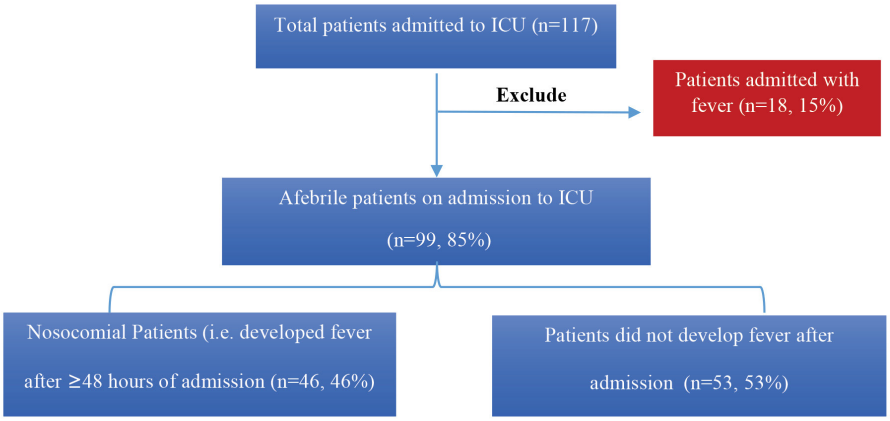

Figure 1 Patients admitted to ICUs

The prevalence rate of NCI per admitted patients was 46/99 (46%), and from NCI patients a total of 80 various clinical specimens were collected, and only 59 (74%) showed a growth. The most specimen that yielded growth was sputum (44%), of the isolates and (52, 88%) were gram negative bacilli, (Table 1).

Table 1. Specimens collected from Nosocomial infected patients ((n=80

Variable	Frequency	Percent (%)
Type of specimen		
Urine	34	42
Sputum	27	34
Blood	16	20
Pus swab	2	3
CSF	1	1
Growth		
Yes	59	74
No	21	26
(Growth by Specimen type (n=59		
Sputum	26	44
Urine	24	41
Blood	6	10
Pus swab	2	3
CSF	1	2
(Type of bacterial growth (n=59		
Gram negative bacilli	52	88
Gram positive cocci	1	2
Fungi	6	10

K pneumoniae was the commonest GN isolates (37%), and 98% of all GN isolates were resistance to the tested antibiotics. Furthermore, nearly three quarters of the resistance isolates were XDR and 24 (47%) were Carbapenemase producers, (Table 2).

Table 2. Gram negative bacterial isolates from Nosocomial infected (patients (n=52

Variable	Frequency	Percent (%)
Type of bacteria isolates		
Klebseilla pneumoniae	19	37
Escherichia coli	13	25
Acinetobacter baumannii	12	23
Pseudomonas aeruginosa	7	13
Citrobacter freundii	1	2
Resistance to antibiotics		
Yes	51	98
No	1	2
(**Type of resistance** (n=51		
**XDR*	38	75
**MDR*	13	25
(**Mechanism of resistance** (n=51		
Carbapenemase	24	47
**ESBL*	13	25
Both	3	6
Other	11	22

***XDR**: **Extensive Drug Resistance**, **MDR**: **Multi Drug Resistance**, **ESBL**: **Extended Spectrum Beta Lactamase**

Pseudomonas aeruginosa and *Acinetobacter baumannii* isolates were resistant (100%) to the following tested antibiotics: Augmentin, Ceftazideme,

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Ceftriaxone, Cefotaxime, Ciprofloxacin, Co-Trimoxazole, Levofloxacin, Piperacillin, Pip-Tazobactam and Tetracycline. Although most AMR-GNB isolates are still susceptible to Polymyxin B and Colistin, the resistance has found to be 10% and 12 % of them respectively, and it was 29% in *Pseudomonas aeruginosa* and 25% in *Acinetobacter baumannii* (Table 3).

Table 3. Resistance pattern for gram negative bacterial isolates ((n=52

Antibiotic	*K pneumoniae* (n=19)	*E coli* (n=13)	*A baumannii* (n=12)	*P aeruginosa* (n=7)	*C freundii* (n=1)	Total (%)
	(%).No	(%).No	(%).No	(%).No	(%).No	
Amikacin	(58)11	(8)2	(83)10	(57)4	(0)0	(52)27
Augmentin	(100)19	(100)13	(100)12	(100)7	(100)1	(100)52
Ceftazideme	(95)18	(92)12	(100)12	(100)7	(100)1	(96)50
Ceftriaxone	(95)18	(92)12	(100)12	(100)7	(100)1	(96)50
Cefotaxime	(95)18	(92)12	(100)12	(100)7	(100)1	(96)50
Ciprofloxacin	(84)16	(69)9	(100)12	(100)7	(100)1	(87)45
Colistin Sulphate	(5)1	(0)0	(25)3	(29)2	(0)0	(12)6
Co-Trimoxazole	(100)19	(92)12	(100)12	(100)7	(100)1	(98)51
Imipenem	(58)11	(46)6	(67)8	(71)5	(0)0	(58)30
Levofloxacin	(84)16	(69)9	(100)12	(100)7	(100)1	(87)45
Piperacillin	(100)19	(100)13	(100)12	(100)7	(100)1	(100)52
Pip-Tazobactam	(84)16	(62)8	(100)12	(100)7	(100)1	(85)44
Polymyxin B	(0)0	(0)0	(25)3	(29)2	(0)0	(10)5
Tetracycline	(63)12	(92)12	(83)10	(100)7	(100)1	(81)42

Discussion

Severe nosocomial infections caused by antibiotic resistant bacteria is associated with risky prognosis for ICU patients since it is associated with dramatic increase in morbidity, mortality and financial burden [13, 14, 38].

Our study reveals that 46% prevalence rate of NCI occurs among afebrile admitted patients in the ICUs, and the result was constant with Nepal (46%) [3], however, it was lower than a previous study in Yemen (65%) [15], Saudi Arabia (60%) [4] and Greece (70%) [16]. Furthermore, it was higher than the rate that recoded in Nigeria (30%) [17], India (33%) [18], Pakistan (25%) [19], Oman (10.8%) [20], Morocco (10.3%) [21], Eastern Ethiopia (6.9%) [22] and developed European and American countries (5-10%) [23].

Previous studies showed that Gram-negative bacterial strains such as *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella spp*., and *Acinetobacter spp* represent the most common nosocomial isolates [14, 24].

Regarding bacterial isolate in this study, *Klebsiella pneumoniae* was the predominant ICUs bacterial isolate; this agrees with results from Nigeria [17], Serbia [25], and Egypt [26]. However, it disagrees with studies from Nepal [3], Saudi Arabia [4], India [14], Yemen [15], China [27], Pakistan [28] and Iran [29]. These differences may be due to the alterations in antibiotic protocols and infection control policies [13].

Highly-resistant (i.e. MDR and XDR) gram-negative bacteria is increasing globally and it is considered a health threat as it is leaving a limited option for treatment since these organisms can be resistant to all currently available antimicrobial agents or only susceptible to more toxic agents [1, 14, 38]. Although in our study no PDR bacterial isolates are found in ICU patients having NCI, it shows 75% of XDR, which is constant with a result from India [30], and Greece [31]. Nonetheless, results from Nepal [3], Saudi Arabia [4], and Egypt [26] showed that the majority of isolates causing NCI in ICUs were MDR.

Increasing antimicrobial resistance in healthcare setting is global burden

particularly among ICUs patients in the developing countries. Although Carbapenems have been the last choice treatment for MDR infected patients in ICU, resistance against this antibiotic has been reported across world, which is a therapeutic challenge [3, 14, 32]. In our study, the most gram-negative isolates found to be Carbapenemase producers, which is similar to studies from Nepal [3], Yemen [15] and India [33]. However, studies in Saudi Arabia [4, 34, 35] and Morocco [21,] showed that the most isolates were ESBL producers.

Previous studies showed that the most frequent multi-drug resistant microorganisms causing NCI were *A baumannii* and *P aeruginosa* since these organisms present in abundance in hospitals environments and largely depend on the epidemiological setting and hygiene levels [14], [24]. In this study, a higher drug resistance was observed among *A baumannii* and *P aeruginosa*. A similar result was found in Nepal [3], Yemen [15], Nigeria [17], Oman [20], Egypt [26], Pakistan [28] and Iran [29].

Drug-resistant GNB infections have been increasingly reported to the degree that developing new antibacterial agents cannot preserve the rapid increasing rate of resistant [4]. In Saudi Arabia [4], Nigeria [17], Oman [20] and China [27] the choice treatment for XDR isolates were Carbapenems, and we found that more than half of isolates are resistant to it.

Therefore, clinicians have to use Colistin and Polymxine B (the last alternative antibiotic used to treat drug resistance GNB), which is also reported from Nepal [3], Yemen [36], India [33] and Italy [37].

4. Conclusion

The study reveals a prevalence of 46% of NCI among ICUs admitted patients; three out of four of GNB isolates causing NCI were XDR and Carbapenemase producers. The highest resistance was observed among *A baumannii* and *P aeruginosa*. Although most AMR-GNB is still susceptible to Polymxine B and Colistin, the resistance has been found to be 10% and 12 % of isolates respectively.

5. Recommendation

The rate of antimicrobial resistance among the GNBs differs significantly worldwide and rapidly changes over time. Therefore, developing a protocol to encourage the rational antibiotic use in ICUs and raise awareness about the importance of antibiotic susceptibility test before antibiotics therapy in order to reduce the selective pressure for resistant microorganisms, hospitalization frequency, treatment costs, as well the death rate. Furthermore, it is essential to assess the effective use of antimicrobial stewardship program particularly in ICUs, infection prevention and control practices in hospital settings together with regular prevalence monitoring of the resistance are recommended.

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