PATTERN OF MULTIDRUG RESISTANT BACTERIA ASSOCIATED WITH INTENSIVE CARE UNIT INFECTIONS IN IBADAN, NIGERIA

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ABSTRACT

Background: **Patients admitted into the intensive care unit (ICU) usually have impaired immunity and are therefore at high risk of acquiring hospital associated infections. Infections caused by multidrug resistant organisms now constitute a major problem, limiting the choice of antimicrobial therapy.**

Objectives: **This study was aimed at determining the antimicrobial resistance pattern of pathogens causing ICU infections in University College Hospital (UCH), Ibadan, Nigeria. The aetiological agents, prevalence and types ICU infections were also determined.**

Methods: **One year hospital associated infections surveillance was conducted in the ICU of UCH, Ibadan. Blood, urine, tracheal aspirate and wound biopsies specimens were collected under strict asepsis and sent to the Medical Microbiology laboratory of the same institution for immediate processing. All pathogens were isolated and identified by standard microbiological methods. Disk diffusion antibiotic susceptibility testing was performed and interpreted according to Clinical and Laboratory Standards Institute (CLSI) guidelines.**

Results: **The overall prevalence of ICU infections was 30.9% out of which 12.9% were bloodstream infections, 31.5% urinary tract infections, 38.9% pneumonia, and 16.7% skin and soft tissue infections. *Klebsiella* species and *Escherichia coli* were the predominant pathogens. Multidrug resistant organisms constituted 59.3% of the pathogens, MDR *Klebsiella* spp and MDR *E. coli* were 70.8% and 71.4% respectively. Resistance to Cefuroxime was the highest (92.9%) while Meropenem had the least resistance (21.4%).**

Conclusion: **There is a high prevalence of multidrug resistant bacteria causing ICU infections. Application of more stringent infection control procedures and institution of functional antimicrobial stewardship are recommended to combat this problem.**

Keywords: Healthcare associated infections, Infection control, Antibiotic resistance, Intensive care unit.

INTRODUCTION

Nosocomial infections, which are now known as hospital-acquired or healthcare-associated infections rank high among important public health problems globally, and developing countries in particular.[1,2] Patients who are admitted into the intensive care unit (ICU) usually have impaired immunity either due to their underlying disease conditions or exposure to invasive procedures which adversely affect their immune mechanisms. They are therefore at high risk of acquiring nosocomial infections. In addition, they are susceptible to secondary infections such as candidiasis and pseudomembranous colitis arising from destruction of protective microbiota by administration of broad spectrum antimicrobials.[3,4,5]

Hospital-associated infection, a serious problem for patients admitted into the ICU, is associated with appreciable cost of care, length of hospital stay, morbidity and mortality.[6,7] It has been documented that acquiring ICU infection is an independent factor associated with hospital mortality and that ICU patients with infections have two times the death rate of those not infected.[7,8] About 40% of the total expenditure in the ICU is related to infections.[7] ICU infections and indeed all healthcare associated infections have also been noted to be much higher in low and middle income countries compared with high income countries.[9] Bloodstream infections, pneumonia, surgical site infections, and other nosocomial infections affect ICU patients more than patients in other areas of the health care setting.[10] Globally, 12 - 49% ICU infection rate has been reported with a median time to infection being 4 days and most patients develop an infection within 6 days of admission.[11,12,13]

Nosocomial infections are often due to resistant organisms which exhibit intrinsic and/or acquired resistance to antimicrobial agents.[14] Multidrug resistant (MDR) organisms are those with acquired non-susceptibility to one or more agents in at least three antimicrobial categories.[15] This antimicrobial resistance is on the rise and multidrug drug resistant organisms are now widespread. However, therapeutic options for these resistant infections are limited thus threatening optimal antibiotic coverage of patients with such infections.[16,17] In addition to therapeutic challenges, multidrug resistant pathogens also have a high potential for acquiring additional resistance and being widely disseminated within the hospital, posing a higher threat to the control of infection.[18] Antibiotic resistance has been reported to be higher among those on prolonged hospitalization which is a frequent finding in ICU patients.[19] There are also reports that patients with MDR pathogens have a higher ICU-mortality than those with non-MDR.[20]

One study reported an overall almost 4-fold increase in MDR gram negative bacteria over their study period with the highest individual increases of 73-fold seen in Enterococci and 14.6-fold in *Klebsiella pneumoniae*.[21] The resistance rates for Gram negative bacteria was 36% while for Gram positive cocci was 51.7%.[21]

The causes of antibiotic resistance and MDR organisms though multifactorial are related to selective pressure that result from inappropriate antibiotic use.[17] Although a general increase in the number of resistant microorganisms is being reported worldwide, there is considerable variation in the specific patterns and rates of MDR across the countries and geographical regions.[17,21] This reiterates the need for locally relevant data which can be used to predict the resistance type and also guide choice of antibiotics when infections occur.[17] The development of proper strategies for combating multidrug resistant pathogens require adequate knowledge of the prevalent pathogens, types of infections and the antimicrobial susceptibility pattern.[22] This study was conducted to determine the resistance pattern of ICU pathogens to antibiotics. We also determined the prevalence of ICU infections, types and pathogens associated with such infections.

MATERIALS AND METHODS

All patients admitted into the ICU of the University College Hospital (UCH), Ibadan, from January 1 to December 31, 2014 were included in the study. University College Hospital, Ibadan, is an 850 bed tertiary care facility in Southwestern Nigeria with a combined medical and surgical ICU. Socio-demographic and clinical data related to these patients were retrieved from the infection control surveillance records using a structured proforma. Ethical approval was obtained from the UI/UCH Ethics Committee.

All patients who developed infections after at least 48 hours of hospitalization were considered to have ICU acquired infections. Appropriate specimens were collected under strict asepsis and sent to the Medical Microbiology laboratory of UCH, Ibadan for immediate processing. The specimens included blood, urine, wound swabs, biopsies and tracheal aspirates. All pathogens were isolated and identified by standard microbiological methods for aerobic bacteria.[23] Antibiotic susceptibility testing was performed using the disk diffusion technique with antibiotics discs containing Augmentin 20+10μg, Cefuroxime 30μg, Ceftazidime 30μg, Ceftriaxone 30μg, Gentamycin 30μg, Amikacin 30μg, Ciprofloxacin 5μg, Pefloxacin 5μg, Levofloxacin 5μg and Meropenem 10μg. It was interpreted according to Clinical and Laboratory Standards Institute (CLSI) guidelines.[24]

Data analysis was done using the Statistical Package for the Social Sciences (SPSS), version 22 software. Data was categorized into appropriate groups and summarized using means, range and proportions and then presented using frequency tables. Differences in proportions were compared using the one sample t-test. Level of significance was set at $p<0.05$

RESULTS

Prevalence of ICU infections

A total of 152 patients were admitted into the ICU during the study period. Of these, 47 developed infections giving a prevalence rate of 30.9%. Seven of

Table 1: Distribution of age groups and sex of patients

Characteristic	Frequency (n= 47)	Percentage (%)	p-v
Age group1 (years)			
0-9	1	2.1	
10-19	3	6.4	
20-29	12	25.5	
30-39	4	8.5	
40-49	10	21.3	
50-59	9	19.2	
60-69	5	10.6	
>70	3	6.4	
Age group2 (years)			
<40	20	42.6	0.3
≥40	27	57.4	
Sex			
Male	27	57.4	0.3
Female	20	42.6	

Table 2: Types of ICU-acquired infections

Site of infection	Frequency (n=54)	Percentage (%)
Blood stream infections	7	12.9
Skin and Soft tissue infection	9	16.7
Pneumonia	21	38.9
Urinary tract infection	17	31.5

these patients had more than one infection therefore there was a total of 54 infections.

Demographic characteristics of patients with infections

The age range of patients was 8 - 85 years with a mean age of 42 (±19) years. Table 1 shows the distribution by age group. The highest number of patients was in the 20-29 age group followed by 40-49 years age group. There was no significant difference in the proportion of the young (<40 years) and the older age group p=0.381. Among the 47 patients with ICU infections, 27 (57.4%) were males while 20 (42.6%) were females) p=0.381.

Types of ICU infections

Table 2 shows the distribution of the types of infections acquired in the ICU. The most common site was the lungs, accounting for about 39% of infections, followed by the urinary tract. Blood stream infections had the lowest prevalence of 12.9%.

Organisms isolated and prevalence of multidrug resistant pathogens

The distribution of isolates is as shown in Table 3. The frequency of Gram-negative organisms was significantly higher than that of Gram-positive (79.7% vs 20.3%, p=0.001). There were 24 isolates of *Klebsiella* spp (*Klebsiella pneumoniae*-21, *Klebsiella oxytoca*-2 and *Klebsiella aerogenes*-1) which was the predominant Gram-negative organism while *Staphylococcus aureus* was the only Gram-positive pathogen isolated. The overall prevalence of MDR organisms was 59.3%. MDR *Klebsiella* spp, *E. coli* and *Proteus spp* constituted 70.8, 71.4 and 20% of the pathogens respectively.

Table 3: Distribution of pathogens isolated in ICU infections

Organism isolated	MDR (%)	Non-MDR (%)
Klebsiella spp	17 (70.8)	7 (29.2)
Escherichia coli	5 (71.4)	2 (28.6)
Pseudomonas aeruginosa	3 (60)	2 (40)
Hafnia alvei	0 (0)	1 (0)
Proteus spp	1 (20)	4 (80)
Acinetobacter baumannii	1 (100)	0 (0)
Staphylococcus aureus	4 (50)	4 (50)
Enterobacter cloacae	1 (33.3)	2 (66.7)
Total	**32 (59.3)**	**22 (40.7)**

MDR- Multidrug resistant organisms

Antibiotic resistance profile of pathogens isolated

Table 4 shows the resistance pattern of the Gram-negative isolates to the tested antibiotics. Antibiotics classes tested included Penicillins (Augmentin 20+10µg), Cephalosporins (Cefuroxime 30µg, Ceftazidime 30µg and Ceftriaxone 30µg), Aminogly-cosides (Gentamycin 30µg and Amikacin 30µg), Fluoroquinolones

Table 4: Antibiotic resistance profile of isolated organisms

	Antibiotic resistance (%)									
Organisms	Augmentin(20+10µg)	Cefuroxime (30µg)	Ceftazidime (30µg	Ceftriaxone (30µg)	Ciprofloxacin (5µg)	Pefloxacin (5µg)	Levofloxacin (5µg)	Gentamycin (30µg)	Amikacin (30µg)	Meropenem (10µg)
Klebsiella spp	72.7	100	66.7	92.3	69.2	71.4	0.0	83.3	38.5	16.3
Escherichia coli	80.0	100	83.3	80.0	75.0	75.0	NT	100	0.0	0.0
Enterobacter spp	50.0	100	100	NT	100	100	50	100	0.0	100
Hafnia alvei	100	0.0	0.0	NT	100	NT	NT	NT	NT	NT
Acinetobacter baumannii	100	100	0.0	NT	100	NT	NT	0.0	NT	NT
Proteus spp	25.0	80.0	50.0	0.0	33.3	100	NT	33.3	0.0	0.0
Pseudomonas aeruginosa	NT	100	100	66.7	100	0.0	100	50.0	25.0	50.0
Overall resistance to antibiotic (%)	**66.7**	**92.9**	**67.7**	**81.8**	**68.0**	**70.0**	**50.0**	**71.4**	**28.6**	**21.4**

** NT- Antibiotic was not test*

(Ciprofloxacin 5µg, Pefloxacin 5µg and Levofloxacin 5µg) and Carbapenem (Meropenem 10µg). There was high level of resistance to most of the antibiotics especially the Cephalosporins. Resistance to Amikacin and Meropenem was low except among *Pseudomonas* and *Enterobacter* isolates.

DISCUSSION

ICU-acquired infections result in increased cost of hospitalization among patients who develop these infections and has been reported to account for close to half of total expenditure of the hospital stay.[7] It is a predictor of mortality and is associated with high mortality rate in the range of 10-60%.[7,13,25] We found a prevalence of 31% of ICU acquired infections. This is a high rate signifying that one out of every three patients developed infections during the study period. This value is much higher than 15% reported by a study done a few years earlier in the same setting, implying an increasing rate of infection. That study however did not include the antibiotic profile of isolated pathogens.[26] Our result is comparable to findings of other studies where high rates of 26-39% were recorded in Turkey, Brazil, Argentina and other environments.[6,22,27,28] Our finding is not surprising as this is a resource-limited setting where it has been reported that high infection rates may be related to inadequate funding, limited manpower, suboptimal application of infection control procedures and non-availability of guidelines and policies.[9,29,30] As with other studies, despite the higher proportion of men with ICU infections and the higher number of infections in the age group 20-29, we did not find a significant difference in the incidence of infections when the gender and age groups were compared.[22,31]

In general, urinary tract infections, pneumonia and blood stream infections appear to be the most common ICU infections.[13,27,32] Our study found the lungs to be the most affected site in the ICU patients. Similar findings have been reported by Erbay *et al* and Meric *et al* and also corroborated by large multicenter studies.[7,22,27,33] Pneumonia secondary to mechanical ventilation is one of the most common causes of nosocomial infections.[3] Our study population consisted of patients on mechanical ventilation and the foreign device employed in the process could therefore have predisposed them to infection. Although blood stream infections are reported to be common in many ICU infections constituting either the most common or second most common infection, it was however noticed to be low in our cohort as it was reported in less than 15% of those with ICU acquired infections; and was the infection with the lowest prevalence.[6,27,28] We observed that there was no similarity in the distribution of infections seen in a study carried out in the northern part of the country where skin and soft tissue infections were the most common infections.[34] One reason for this disparity may be because most of the patients in that study were admitted on account of road traffic accidents.

More than half of the infections occurring in the ICU are noted to be caused by Gram-negative bacteria and our data was consistent with these findings.[22,35,36] Although there is a wide variation in the distribution of these Gram-negative organisms, *Pseudomonas* spp appears to predominate globally.[7,27,36] We found a preponderance of *Klebsiella* spp, especially *Klebsiella pneumoniae,* which accounted for close to half of the isolated organisms. *Klebsiella* is a common nosocomial pathogen whose rates of colonization and therefore likelihood of infection rises dramatically with hospitalization.[37] *Acinetobacter baumannii* has emerged as a cause of nosocomial infection and is increasingly being reported as a cause of ICU infection especially in immunocompromised patients.[38] It has even been reported as the most common isolate in some studies on ICU infections.[36,39] In this study however, only one isolate of *Acinetobacter* was identified during the period accounting for about 2% of infections. Acinetobacter infection is often reported as outbreaks and non-occurrence of outbreaks may explain the low prevalence we found in the study period.[14] In spite of the widespread predominance of Gram-negative pathogens in ICU infections, a contrasting higher prevalence of Gram-positive organisms was found in a local study where over 40% of the pathogens were *Staphylococcus aureus.*[39] *Staphylococcus aureus* was the second most common organism identified, and the only Gram-positive organism found in this study. Our result is comparable to findings from most studies on nosocomial infections where *Staphylococcus aureus* is usually the predominant Gram-positive pathogen recovered in healthcare associated infections.[27,39,40]

The prevalence of antibiotic resistant organisms in our study population was high. These multidrug resistant organisms pose a serious concern in the hospital environment.[14] The emergence of resistant pathogens in the hospital environment has resulted in part from extensive and also inappropriate use of antibiotics and options for treating infections caused by these organisms are becoming limited.[17,41] These resistant pathogens have emerged in the last two decades as a major infection control issue.[36] The scenario is worse in the ICU where there is extensive antibiotic use and such resistance affects the outcome for hospitalized patients.[11,13,41] A study carried out in a similar low middle income country found that 25% of their isolates were MDR and the risk for infection with these MDR

organisms was related to inappropriate antibiotic use, mechanical ventilation and long ICU stay.[42]

Pathogens recovered from ICU have been noted to be more resistant to antibiotics when compared to isolates from other areas of the hospital.[43] A study comparing developing countries to developed ones noted a striking higher prevalence of ICU infections and also of resistant pathogens in developing countries despite similar device utilization rates.[44] According to our results, there was a very high level of resistance to antibiotics as virtually most isolated pathogens exhibited resistance to multiple antibiotics. Only *Proteus* species was susceptible to a wide range of antibiotics. There is an apparent global trend of increasing MDR Gram negative bacteria in the ICU when compared to the gram positive pathogens. These organisms, *Escherichia coli* and *Klebsiella pneumoniae* in particular, have their resistance genes on plasmids which are easily transferable allowing strains such as Extended Spectrum Beta Lactamase (ESBL) producers to spread rapidly.[45]

More than 70% of the *Klebsiella* spp, the most prevalent isolate, in our study were multidrug resistant. Although the frequency of isolation of this organism differs in various studies, the high prevalence of multidrug resistance is a common occurrence.[36,39,43,] It is however interesting to note that despite the level of resistance of the *Klebsiella* isolates, all were susceptible to levofloxacin. This might be due to the relative infrequent use of Levofloxacin in this setting, sparing it of selective pressure compared to the more commonly used fluoroquinolone- Ciprofloxacin.

Antimicrobial resistance has been noted to be very common in non-fermenting gram negative bacilli such as *Pseudomonas* and *Acinetobacter* in the ICUs in particular. A recent report from the United States found a third of their *Pseudomonas* isolates were resistant to fluoroquinolones, 13-19% were resistant to ceftazidime, resistance to amikacin was 6% and the overall MDR rate was 10%.[14] A contrasting much higher picture of 100%, 100% and 25% resistance to fluoroquinolones, ceftazidime and amikacin respectively were observed in Pseudomonas isolates in our study while the MDR rate was 60%. This indicates a high burden of resistance which requires urgent intervention. A similar high burden of MDR *Pseudomonas* in developing countries has been reported.[44] In comparison to other gram negative bacilli, a remarkably low prevalence of 20% MDR *Proteus* spp was found in this study. A similar pattern of antibiogram was observed in a study carried out elsewhere in the country where the isolates were generally susceptible to fluoroquinolones, cephalosporins, aminoglycosides and carbapenems.[34] *Proteus* spp is not commonly implicated in ICU infections hence data on its resistance pattern is scarce. However, a few studies have demonstrated its potential to exhibit multidrug resistance.[46,47]

With the exception of *Hafnia alvei* and a few *Proteus* spp, all isolates were resistant to cefuroxime, and the pattern was similar for ceftazidime. Only Amikacin and Meropenem exhibited generally good activity against these Gram-negative organisms which is similar to other recent reports by Sader *et al.*[43] Aggressive efforts however need to be instituted to retain the relevance of these antibiotics as the level of resistance of over 20% to both antibiotics is worrisome and may escalate to high level of resistance as recently reported by Qadeer *et al.* [36]

CONCLUSION AND RECOMMENDATION

The prevalence of ICU acquired infections is high with pneumonia predominating. Our study shows a high prevalence of multidrug resistant bacteria associated with these infections and may adversely affect patient outcome. This reiterates the importance of a continuous collaboration between ICU care specialists, medical microbiologists and the infection control team in the care of these patients.[14] Improved health care funding coupled with better adherence to infection control procedures are strategies to improve the current healthcare preventive measures.[14,29] A functional antimicrobial stewardship programme will ensure optimal use of antimicrobials and limit development of resistance. Evaluation of surveillance data should also be carried out regularly to monitor the trends and institute appropriate actions.[16]

LIMITATIONS OF THE STUDY

The study was limited by small sample size which resulted from the short duration of data collection. A larger sample size spanning several years would have been more robust for more statistical conclusions to be made.

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