



Antibiotic Audit in Cases of Septicemia in Medical Intensive Care Unit (MICU) in a Tertiary Care Hospital in Mumbai

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Abstract

Introduction: Intensive care units (ICU) are epicenters for the emergence of antibiotic resistance. Overprescribing and misuse of antibiotics are contributing to the development of multidrug resistance (MDR). Hence, this study was carried out to ensure the best clinical outcome for the patient while lowering the risk of antimicrobial resistance.

Aim and Objectives: To identify microorganisms from clinically suspected cases of septicemia in MICU, their antimicrobial susceptibility pattern and to evaluate the rational use of antibiotics.

Materials and Methods: A retrospective study was carried out in a tertiary care hospital for a period of one and a half years. Blood samples were processed in BACTEC 9120 system. Flash positive samples were further processed to identify the organisms by standard techniques and antimicrobial susceptibility test (AST) was performed by Kirby Bauer Disc Diffusion Method on Mueller Hinton Agar.

Results: Total blood cultures received were 309, of which 22.6% showed growth. Commonest species isolated was *Acinetobacter* spp. (34.3%), followed by *Staphylococcus aureus* (14.3%) and *Escherichia coli* (12.9%). MDR and carbapenem resistance were seen in 25% *Enterobacteriaceae*. MDR in non-fermenters was 50%, whereas carbapenem resistance was 63.3%. Fifty percent *Staphylococcus* spp were Methicillin resistant and 25% of *Enterococci* were Vancomycin resistant. On admission, the patients were empirically started on ceftriaxone and amoxicillin-clavulanic acid. 63% of these patients were later escalated to Carbapenem/Vancomycin, based on the AST reports.

Conclusion: Prospective audit with feedback gives the proper direction to the clinicians and also helps us in formulating antimicrobial policy and revising the policy from time to time.

Keyword: Antibiotic audit, sepsis, antimicrobial resistance, MICU.

Introduction

The intensive care unit (ICU) is often regarded as an epicenter of infections, with sepsis being one of the

commonest cause of morbidity and mortality.

Patients in ICU are critically ill and suffer from debilitated physical conditions, underlying

comorbidities like hypertension, diabetes, Chronic Obstructive Pulmonary Disease (COPD), chronic kidney disease and immunodeficiencies. Also, various other factors like use of mechanical ventilators, urinary catheters and central line use, contribute to increased infections in ICU compared to wards. Owing to their critical status, patients in ICU require intense and broad spectrum antibiotic therapy for longer periods^{[1],[2]}

Sepsis is defined as the combination of an infection with 2 or more criteria of 'Systemic Inflammatory Response Syndrome'(SIRS), which includes body temperature $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$, heart rate >90 beats/min, respiratory rate >20 breaths/min (or arterial $\text{pCO}_2 <32$ mmHg, indicating hyperventilation), white blood cell count $>12.0 \times 10^9/\text{L}$ or $<4.0 \times 10^9/\text{L}$ (or $>10\%$ immature forms), sepsis is infection plus SIRS, severe sepsis is sepsis plus evidence of organ dysfunction^[3]

The global epidemiological burden of sepsis is difficult to ascertain. It is estimated to affect more than 30 million people worldwide every year, potentially leading to 6 million deaths. The burden of sepsis is most likely highest in low and middle income countries^[4]. Mortality for severe sepsis is between 15% and 30% in high income countries; it is 50% or higher in low income countries^[5]

It is caused by a combination of factors related to the particular invading pathogen(s) and to the status of the immune system of the host as well as the comorbidities. Infection triggers pro-inflammatory and anti-inflammatory response that contribute to the control of infection as well as the tissue damage. This may lead to organ damage and other complications^[6]. Symptoms are produced by microbial toxins and cytokines produced by inflammatory cells^[7]. Hence, it becomes necessary to identify the causative organism and to start the patients on broad spectrum antibiotics to decrease the morbidity and mortality.

The total antibiotic consumption is approximately tenfold greater in ICUs than in general hospital wards^[2]. This high density of antibiotic use, overprescribing and misuse of antibiotics contribute to multidrug resistance. So, optimal antibiotic use is crucial in the critical care setting, especially in an era of rising antibiotic resistance and lack of newer

antibiotics^[8]. This will help us to ensure the best clinical outcome for the patient while lowering the risk of subsequent development of antimicrobial resistance. Hence, this study was intended to identify microorganisms from clinically suspected cases of sepsis in MICU, to study their antimicrobial susceptibility pattern and to evaluate the rationale use of antibiotics.

Material and Methods

A retrospective observational study of one and a half years (January 2016 - June 2017) was undertaken in the MICU of this tertiary care hospital after approval from Institutional Ethics Committee (IEC). All patients admitted in MICU clinically suspected of sepsis were included and immunocompromised patients were excluded from this study.

Blood was collected under aseptic conditions in Aerobic BACTEC bottles and processed in BACTEC 9120 system. Subcultures were done on Blood agar and MacConkey agar plates from flash positive bottles and the plates were incubated overnight at 37°C . Organisms were identified by standard biochemical tests^[9]. Antimicrobial susceptibility test (AST) was performed by Kirby Bauer Disc Diffusion Method (KBDDM) on Mueller Hinton Agar (MHA), according to CLSI guidelines 2016^[10]. A proforma of all patients included in the study was filled up.

The antimicrobial agents tested for Gram negative bacilli (GNB) were amoxicillin plus clavulanic acid (20/10 μg), Cefuroxime (30 μg), Cefotaxime (30 μg), Ciprofloxacin (5 μg), Amikacin (30 μg), Imipenem (10 μg), Meropenem (10 μg), Piperacillin-tazobactam (100/10 μg). Colisitin MIC E strip was used for *Acinetobacter* spp. For *Pseudomonas* spp., Piperacillin (100 μg), Ceftazidime (30 μg), Aztreonam (30 μg) and Polymixin B (300U) were used.

For Gram positive cocci (GPC), the antibiotics tested were Penicillin (10U), Cefoxitin (30 μg), Cefazolin (30 μg), Erythromycin (15 μg), Clindamycin (2 μg), Gentamicin (10 μg), Ciprofloxacin (5 μg), Co-trimoxazole (1.25/23.75 μg), Linezolid (30 μg), and Vancomycin

MIC E strip. For *Enterococcus* spp., Ampicillin (10µg) and High level Gentamicin disc (120µg) were used. *Escherichia coli* (ATCC 25922), *Staphylococcus aureus* (ATCC 25923) and *Pseudomonas aeruginosa* (ATCC 27853) were used as standard strains. All the discs and MIC strips were purchased from Himedia Labs Pvt. Ltd., Mumbai.

Results

Total blood culture samples received during this period were 309, out of which 22.6% (70/309) showed growth as shown in Figure 1. Figure 2 shows percentage distribution of Gram positive and Gram negative organisms.

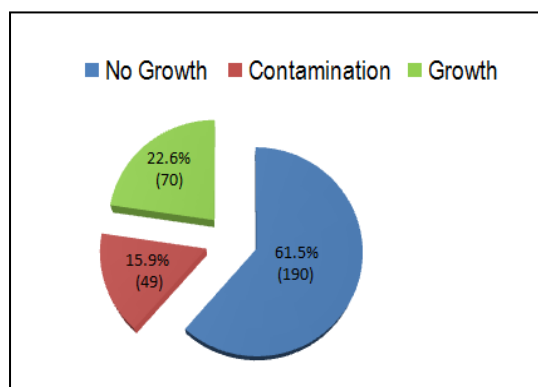


Figure 1: Growth pattern in blood culture isolates (n=309)

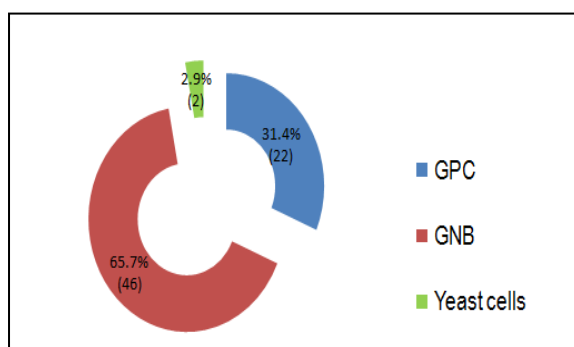


Figure 2: Percentage distribution of gram positive and gram negative organisms

Figure 3 shows overall percentage of organisms isolated. *Acinetobacter* (34.3%) was the commonest isolate, followed by *Staphylococcus aureus* (14.3%). Methicillin resistance was seen in 50% of *Staphylococcus* spp. Out of total *Staphylococcus aureus*, 60% (6/10) were Methicillin sensitive

Staphylococcus aureus (MSSA) and 40% (4/10) were Methicillin Resistant *Staphylococcus aureus* (MRSA). Among the Coagulase negative *Staphylococcus* (CONS), 75% (3/4) were MRCONS and 25% (1/4) were MSCONS. Two *Candida glabrata* were isolated.

Figure 4 shows the percentage antibiotic susceptibility pattern in *Acinetobacter* spp. *Burkholderia* spp shows 100% sensitivity to Cotrimoxazole, Ceftazidime and Meropenem. Figure 5 shows the percentage antibiotic susceptibility pattern in *Enterobacteriaceae*.

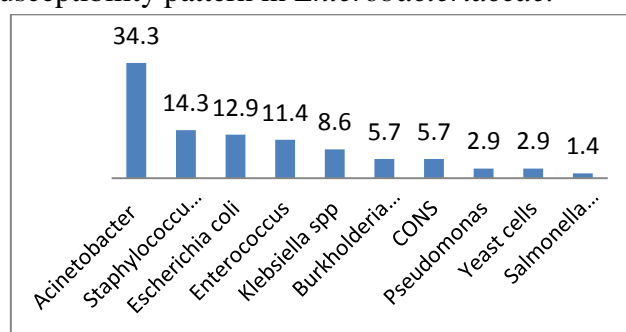


Figure 3: Percentage of organisms isolated

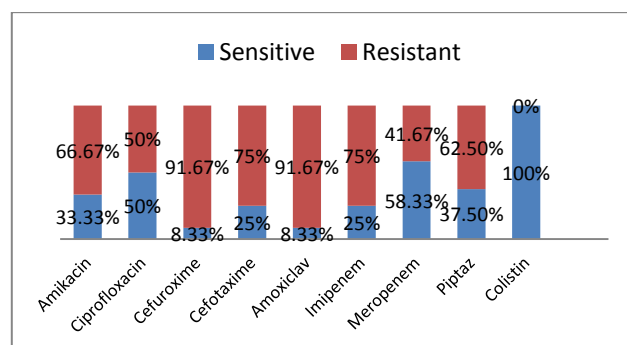


Figure 4: Percentage antibiotic susceptibility pattern in *Acinetobacter* spp.

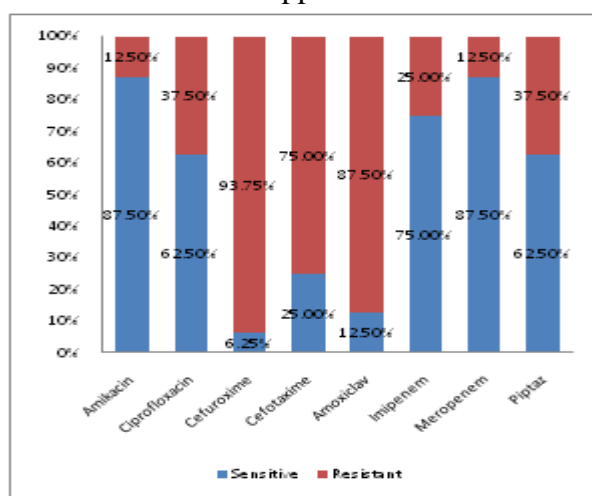


Figure 5: Percentage antibiotic susceptibility pattern in *Enterobacteriaceae*.

Figure 6 shows MDR and carbapenem resistance in GNB.

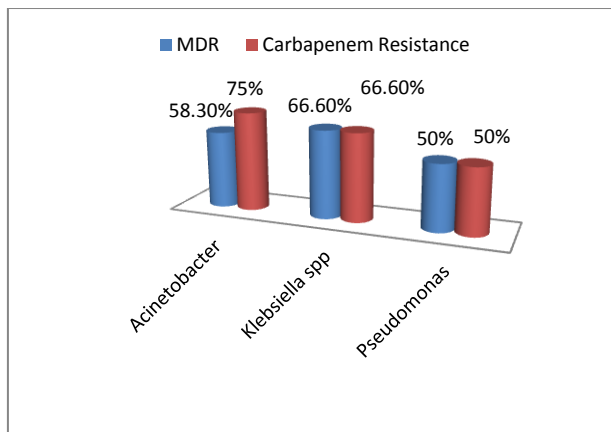


Figure 6: Percentage of MDR and Carbapenem resistance in GNB.

Figures 7 and 8 show the antibiotic susceptibility pattern in *Staphylococcus aureus* and *Enterococcus* spp respectively. 20% *Staphylococcus aureus* (2/10) and 50% CONS (2/4) showed Inducible Clindamycin Resistance (ICR). Among *Staphylococcus aureus*, ICR was seen in 25% MRSA (1/4) and 16.7% MSSA (1/6). ICR was seen in 66.7% MRCONS (2/3). Vancomycin resistance and High level Gentamicin Resistance (HLGR) was seen in 25% (2/8) and 50% *Enterococci* (4/8) respectively.

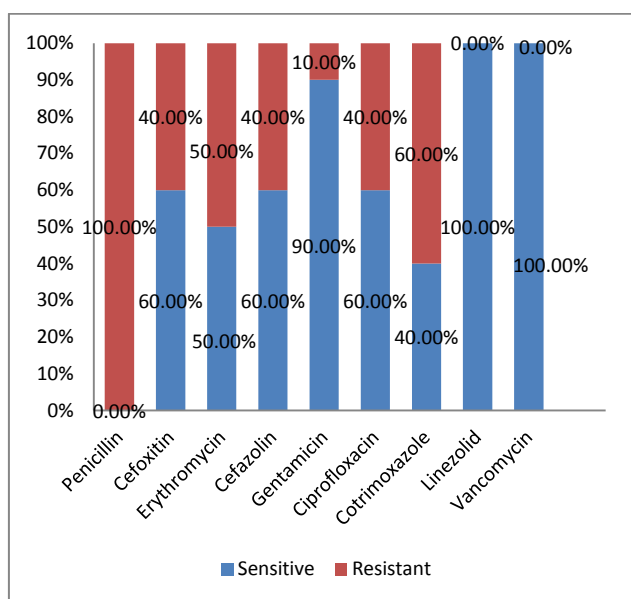


Figure 7: Percentage antibiotic susceptibility pattern in *Staphylococcus aureus*.

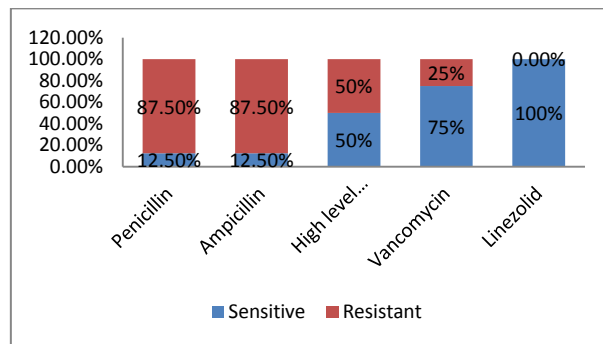


Figure 8: Percentage antibiotic susceptibility pattern in *Enterococcus* spp.

Ceftriaxone and amoxicillin-clavulaunic are the empirical treatment given in this hospital in MICU patients. In 63% of the patients, antibiotics were changed after antibiotic susceptibility report from the laboratory. Amoxicillin-clavulaunic acid was discontinued in these patients and they were escalated to Carbapenems/Vancomycin. In the remaining 37% patients empiric treatment was continued as they responded.

Discussion

As rightly said by Paul Erhlich, “Drug resistance follows the drug like a faithful shadow”. Antimicrobial resistance has become an alarming problem. Various reasons contribute to the emerging drug resistance like self medication and poor compliance, inappropriate selection of antibiotics and multiplication of resistant strains, accumulation of resistance to multiple antibiotics, continuous natural evolution of resistance in bugs and weak surveillance and regulatory systems^[11]. Hence, it has become the need of the hour to control this rising and spreading antimicrobial resistance. Multidrug resistance emergence in ICU is a crisis as ICUs have the patients requiring immediate and timely attention with proper selection of antibiotics. Owing to this antimicrobial resistance, septicemic patients in ICUs require broad spectrum antibiotics to be started as the initial empirical treatment before the culture and antibiotic susceptibility report are received.

There is a decrease in the percentage distribution of GPC (37.5% to 31.4%) and increase in GNB (62.5% to 65.7%) from 2013 study by De et al^[12] to the present study.

Table 1 shows the distribution of isolates in cases of sepsis in different Indian studies. In the present study, *Acinetobacter* spp was the commonest isolate found in MICU, similar to the finding reported in Mumbai in 2013^[12]. However *Pseudomonas* spp was the commonest isolate in 2017, reported by Moolchandani et al^[11]. Over a period of 4 years, prevalence of *Acinetobacter* spp in Mumbai increased from 17.3% in 2013^[12] to 34.3% in the present study. Similarly, prevalence of *Escherichia coli* increased from 4.8%^[12] to 12.9% over the same period.

In the present study, among the Gram positive cocci, prevalence of *Staphylococcus aureus* decreased from 44.0% (Pawar et al^[13]) to 14.3% in this study (Table 1)

“A general principle to start broadly, narrow quickly, if they don't need it get rid of it” has been proposed for

antibiotic management in sepsis^[14]. MDR in *Enterobacteriaceae*, in the present study was 25%, whereas it was reported 31.1% in 2013^[12]. MDR in Non-fermenters shows almost a steady prevalence over these four years being 49.5% in 2013^[12] and 50% in the present study (Figure 6).

Over a period of four years, Carbapenem resistance in both *Enterobacteriaceae* and Non-fermenters increased from 2.6% and 5.8% in 2013^[12] to 25% and 63.3% in the present study respectively (Figure 6). Colistin is the only available option after the increase of carbapenem resistance in ICUs but it has its own limitations due to its side effects.

Over a period of 8 years in Mumbai, GNB resistance to amikacin increased from 20.5% in 2010^[15] to 45% in the present study. Similarly ciprofloxacin resistance increased from 26.7% in 2010^[15] to 45% in the present study. However, in contrast, amikacin resistance among *Enterobacteriaceae* decreased from 15.7% in 2010^[15] to 12.5% in the present study. Similarly, there was a decrease in resistance to amoxicillin-clavulanic acid and cefotaxime from 92.6% and 87% in 2010^[15] to 87.5% and 75% respectively in the present study (Figure 5).

Also, *Acinetobacter* resistance to third generation cephalosporin that is cefotaxime decreased from 94.6% in 2010^[15] to 75% in the present study (Figure 4), whereas an increase in resistance to fluoroquinolones from 33.3% in 2010^[15] to 50% (Figure 4) in the present study was seen. In Mumbai, *Acinetobacter* resistance to imipenem was only 18% in 2010^[15] whereas it was drastically increased to 75% in the present study (Figure 4). This shows that there has been nonjudicious use of imipenem thereby leading to increased imipenem resistance.

In Gram positive cocci, Methicillin resistance to *Staphylococcus* species has increased in recent times. Over a period of 4 years it has increased from 13.3% reported by De et al^[12] to 50% in the present study. Linezolid and vancomycin showed 100% susceptibility to all the isolates (Figure 7). In the present study, ICR was seen in 25% in *MRSA* and 16.7% *MSSA*, whereas De et al^[12] reported 33.86% and 8.59% ICR in *MRSA* and *MSSA* respectively. Among *CONS*, only *MRCONS* showed ICR. Vancomycin resistance was not encountered in *Staphylococcus aureus*. Over a period of 8 years, penicillin resistance of *MSSA* increased from 91.02% in 2010^[15] to 100% in the present study (Figure 7).

There is a steady increase of Vancomycin resistant *Enterococci* over the past 8 years- 12.5% in 2010^[15] to 25% in the present study (Figure 8). Sachan et al^[16] reported 63.6% HLGR whereas in the present study it reduced to 50% (4/8). Linezolid resistance was not encountered in any Gram positive cocci.

Ceftriaxone and amoxicillin-clavulanic acid were used as the empiric treatment followed by other cephalosporins in these patients on admission in this hospital. Amoxicillin-clavulanic acid was stopped in 63% patients and they were escalated to Carbapenem/Vancomycin along with third generation Cephalosporins (cefotaxime), depending upon the antibiotic susceptibility report from the laboratory. This led to narrowing of the empirical therapy and starting of proper antibiotics based on the antibiotic susceptibility report from the laboratory.

Table 1: Percentage distribution of isolates in cases of sepsis in different Indian studies

Organism	De et al ⁽¹³⁾ (2013)	Pawar et al ⁽¹⁴⁾ (2016)	Moolchandani et al ⁽¹⁾ (2017)	Present study (2017)
<i>Acinetobacter</i> spp	17.3%	15.5%	18.9%	34.3%
<i>Escherichia coli</i>	4.8%	16.7%	---	12.9%
<i>Klebsiella</i> spp	12.9%	8.3%	14.9%	8.6%
<i>Pseudomonas</i> spp	4.7%	3.6%	24.8%	2.9%
<i>Staphylococcus aureus</i>	24.1%	44.0%	8.5%	14.3%
<i>Enterococcus</i> spp	29.8%	1.2%	12.4%	11.4%
<i>Candida</i> spp	----	----	12.6%	2.9%

Conclusion

This study would be helpful for optimal antibiotic use, better empirical treatment selection, de-escalation once culture report becomes available and shortening therapy duration which is crucial in ICU settings. De-escalation of antibiotics after the antimicrobial susceptibility report stops the unnecessary antibiotic use in the ICU patients and thus helps in preventing the emergence of drug resistance. Antibiotics can then be started therapeutically according to gram positive or gram negative organisms.

Regardless of the diagnostic strategy/protocol, serial clinical and microbiological evaluations are highly relevant to re-assess therapy after 48-72 hours or to stop it, if infection is unlikely. Therapy can be de-escalated once blood culture results become available, if no resistant organism is recovered or if the isolated pathogen is sensitive to a narrow-spectrum antibiotic than that prescribed empirically, for a better outcome and to shorten the period of morbidity.

Prospective audit with feedback gives a proper direction to the clinicians and also helps us in formulating antimicrobial policy and revising it from time to time. Also, AMR data helps in empirical therapy, antimicrobial policy development, hospital infection control, monitoring resistance trends, data comparison, research and hypothesis development.

Conflict of interest

There is no conflict of interest

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