



ANALYSIS OF APPROPRIATENESS OF RESERVE/RESTRICTED ANTIMICROBIALS USAGE IN THE ADULT ICU PATIENTS OF DIFFERENT DEPARTMENTS OF THE HOSPITAL AS A PART OF ANTIMICROBIAL STEWARDSHIP PROGRAM- A PROSPECTIVE OBSERVATIONAL STUDY.

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ABSTRACT

Introduction: In the past few years there has been a steep rise in the antimicrobial resistance (especially to carbapenems) globally which has resulted in antimicrobial therapy failure leading to increase in patient morbidity and mortality rates. The limited effective available reserve/restricted antimicrobials surveillance has become important to ensure their judicious use and prevent their resistance development. Therefore, the hospital has Antimicrobial Stewardship Program which monitors the appropriateness of usage of the last resort Reserve/Restricted antimicrobials being prescribed to the patients. **Method:** Prospective data of 320 ICU admitted adult patients who were prescribed Reserve/Restricted antimicrobials was collected in Restricted Antimicrobial Usage Form during 6 months period from different medical and surgical specialties to monitor the appropriateness of the restricted antimicrobials prescribed empirically in accordance to Indian Council of Medical Research (ICMR) treatment guidelines for antimicrobial use in common syndromes 2022. **Result:** In our study maximum number of patients admitted in ICU were male (63%) and mostly belonged to 51-60 year followed by 61-70 year of age group. Out of 320 admitted patients, Type 4 category (very high risk) were 47 %, Type 3 (high risk) were 44%, Type 2 (moderate risk) were only 9 % and Type 1 (low risk) were none. Patients were prescribed restricted antimicrobials empirically (71%) and definitively (29%). Patients were found to have infection in lungs (34%) followed by intra-abdominal (25%) and renal (25%) then central nervous system (14%), musculoskeletal system (9%), blood (8%) and skin (7%). The top five intermingled clinical reasons for giving empirical restricted antimicrobials were high Total Leucocyte Count (68%),

ventilator support (41%), comorbidities (diabetes, hypertension, asthma, cancer, kidney failure, liver failure) (35%), sepsis/septic shock (26%) and invasive lines (17%). To treat gram negative infections intravenous administered restricted antimicrobials Polymyxin B was given to 129 patients (40 %), Tigecycline to 45 patients (14%), Ceftazidime Avibactam + Aztreonam to 39 patients (12%), , Colistin to 35 patients (11%), Ceftazidime Avibactam to 20 patients (6%), Minocycline to 10 patients (3%), and Fosfomycin to none and to treat gram positive infections Linezolid was given to 64 patients (20%) followed by Vancomycin to 38 patients (12%) and then Daptomycin to 3 patients (1%). **Conclusion:** We found that Type 4 and Type 3 patients altogether constituted 91% but 71% patients received restricted antimicrobials empirically and in appropriate doses as prescribed by the ICMR 2022 guidelines to cover the Extensive drug resistance (XDR) as well as Difficult to treat (DTR) *A. baumannii* and *K. pneumoniae* and Multi drug resistance (MDR) *E. Coli*, *P. Aeruginosa*, Methicillin-Resistant *Staphylococcus Aureus* (MRSA), Vancomycin Resistant enterococci (VRE) organisms prevalent in the hospital ICUs. The complex critical patients with very high-risk/high risk were managed well within timelines with limited rapid microbial diagnostic methods with varied Pharmacokinetic / Pharmacodynamic index parameters of available limited effective restricted antimicrobials influenced by patients' dynamic pathophysiology changes and expected adverse drug reactions based on patient clinical diagnosis. Highest level of wisdom was implied while choosing the antimicrobial to be given empirically against resistant bugs in correct loading and maintenance doses delivered via prolonged /continuous infusions if required for dose optimization in order to reduce the patient morbidity and mortality. Newer rapid microbial diagnostic tests and newer effective and safe antimicrobials are need of the hour to shoot down the resistant hospital bugs and improve the health and survival of the critically ill patients.

Key words: restricted antimicrobials, antimicrobial stewardship, antimicrobial resistance, pk/pd index, dose optimization

INTRODUCTION: GLOBAL SITUATION

In 2021, it was estimated that worldwide 4.71 million deaths were associated with bacterial antimicrobial resistance (AMR), including 1.14 million deaths attributable to bacterial AMR.

Trends in AMR mortality over the past 31 years varied substantially by age and location. From 1990 to 2021, deaths from AMR increased by over 80% for adults 70 years and older.

For both deaths associated with and deaths attributable to AMR, Methicillin-resistant *Staphylococcus aureus* (MRSA) increased the most and among Gram-negative bacteria, resistance to carbapenems increased more than any other antibiotic class.¹

Forecasts show that an estimated 1.91 million (1.56–2.26) deaths attributable to AMR and 8.22 million (6.85–9.65) deaths associated with AMR could occur globally in 2050. Super-regions with the highest all-age AMR mortality rate in 2050 are forecasted to be South Asia and Latin America and the Caribbean. Increases in deaths attributable to AMR will be largest among those 70 years and older (65.9% [61.2–69.8] of all-age deaths attributable to AMR in 2050).¹

Under the better care scenario, across all age groups, 92.0 million deaths (82.8–102.0) could be cumulatively averted between 2025 and 2050, through better care of severe infections and improved access to antibiotics, and under the gram-negative drug scenario, 11.1 million AMR deaths (9.08–13.2) could be averted through the development of a gram-negative drug pipeline to prevent AMR deaths.¹

Recently, in 2024, WHO has revised the priority pathogen list, for which new antimicrobials are urgently needed.² (Table 1)

Table 1-WHO priority pathogen list (2024)

WHO GROUP NAME	ORGANISM NAME
CRITICAL	Carbapenem-resistant <i>A. baumannii</i> (CRAB), Carbapenem-resistant Enterobacterales (CRE),

	Third-generation cephalosporin-resistant Enterobacterales
HIGH PRIORITY	Fluroquinolone-resistant <i>S. typhi</i> , Fluroquinolone-resistant <i>Shigella</i> spp., Fluroquinolone-resistant non-typhoidal <i>Salmonella</i> , Carbapenem-resistant <i>P. aeruginosa</i> , Third generation and/or fluroquinolone-resistant <i>N. gonorrhoeae</i> , MRSA
MEDIUM PRIORITY	Group A Streptococci, Macrolide-resistant <i>S. pneumoniae</i> , Ampicillin-resistant <i>H. influenzae</i> , Penicillin-resistant Group B Streptococci

The 21st century has witnessed alarming trends in antimicrobial resistance, with the emergence of Multidrug-resistant (MDR) pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA), extended-spectrum β -lactamase-producing Enterobacteriaceae (ESBL) and MDR *Pseudomonas aeruginosa*.

The **ESKAPE** pathogens (*E. faecium*, *S. aureus*, *K. pneumoniae*, *A. baumannii*, *P. aeruginosa*, and *Enterobacter* species), along with *Clostridioides difficile*, are responsible for most nosocomial infections worldwide. Several pathogens of concern for infection prevention and control (IPC) can persist on inanimate surfaces for periods of time that range from weeks to almost two years (*K. pneumoniae*: 600 days; *S. aureus*: 318 days; *C. difficile*: 140 days; *Acinetobacter* spp. 90 days; *E. coli*: 56 days).³

Bacterial recalcitrance was observed in *Staphylococcus aureus*. Importantly, *S. aureus* has the capacity to survive and proliferate intracellularly, which makes the access to bacteria more difficult for antimicrobials. This intracellular localization combined with recalcitrance can lead to antimicrobial treatments failure. In fact, biofilms create a microenvironment in which certain bacteria live in nutrient-poor, anaerobic conditions, especially at the core of the biofilm.⁴

AMR poses substantial health threats to the young (<5 year), the old (>65 years), and weak or immune compromised patients (eg, those with cancer or diabetes), for whom the emergence of drug-resistant infections is accelerated by the use of prophylactic antibiotics and need for extended antibiotic treatments.⁵

INDIAN SCENARIO

In India, the burden of Hospital Acquired infection (HAI) is high, with an estimated pooled prevalence of 15.5 per 100 patients. Amongst the gram- negative organisms, in the past 6 years, carbapenem resistance has substantially increased in hospital-acquired isolates of both *E. coli* (from 19% in 2017 to 34% in 2022) and *K. pneumoniae* (from 41% in 2017 to 58% in 2022). More than 30% of *P. aeruginosa* isolates and >80% of *A. baumannii* isolates are resistant to carbapenems as reported by Indian Council of Medical Research (ICMR) and National antimicrobial resistance surveillance network (NARS-NET) for the 2022 year.² (Table 2)
Over 50% of infections in most ICUs in tertiary care centers in India are caused by difficult-to-treat (DTR) gram-negative pathogens. Carbapenem resistant *A. baumannii* is the leading cause of ventilator-associated pneumonia in Indian intensive care units (ICUs).²

Table 2- ICMR and NARS-NET AMR surveillance network (2022)

	% of cephalosporin-resistant gram negative pathogens			
	<i>E. coli</i>	<i>K. pneumoniae</i>	<i>P. aeruginosa</i>	<i>A. baumannii</i>
ICMR	81	81	41	91
NARS-Net	76	83	44	73
	% of carbapenem resistance in gram negative pathogens			
	<i>E. coli</i>	<i>K. pneumoniae</i>	<i>P. aeruginosa</i>	<i>A. baumannii</i>
ICMR	30	56	36	86
NARS-Net	35	47	27	59
	% of colistin resistance in gram negative pathogens			
	<i>E. coli</i>	<i>K. pneumoniae</i>	<i>P. aeruginosa</i>	<i>A. baumannii</i>
ICMR	3	6	3	5
NARS-Net	0	< 1 (0.4)	< 1 (0.1)	< 1 (0.4)

AMR: Antimicrobial resistance, ICMR: Indian Council of Medical Research, NARS: National Antimicrobial Resistance Surveillance Network (NARS-Net India)

Among carbapenem resistant *E. coli*, New Delhi metallo- β -lactamase (NDM-1) was seen in >95% of the isolates. In carbapenem-resistant *K. pneumoniae*, dual carriage of both NDM and OXA-48-like carbapenemases was found in 60% of the isolates, while OXA 48-like carbapenemases alone was seen in 40% of the isolates.²

In *P. aeruginosa* isolates, NDM (41%) is predominant, followed by Verona Integron-encoded Metallo-beta-lactamase (VIM) (9%). Interestingly, dual carbapenemase producers of NDM with VIM or Imipenemase (IMP) is also noticed among carbapenemase-producing *P. aeruginosa* isolates. NDM being the predominant carbapenemase in >95% of *P. aeruginosa* isolates in many hospital settings.²

Among carbapenem resistant *A. baumannii*, 40% of the isolates have an OXA-23 like gene and dual carbapenemase production of OXA- 23 like and NDM are identified in 60% of the isolates.

Polymyxin and tigecycline-based combinations are most often deployed as first-line therapy for treating DTR gram-negative infections. Emergence of resistance to colistin is less than 10%. In addition, emerging new resistance mechanisms such as Penicillin Binding Protein 3 insert in *E. coli* and mutation in the siderophore iron transport channels contributing to the development of Pan drug resistance (PDR) are of great concern.²

Among gram-positive pathogens, there is an incremental increase in the trend of MRSA, 33% in 2017 to 44.5% in 2023. Similarly, there is a noticeable increase in the proportion of vancomycin resistance in *Enterococcus* sp., which is five times higher in *E. faecium* than *E. faecalis*. In *Staphylococcus aureus*, > 40% of isolates are identified as MRSA as reported by ICMR and NARS-NET for the 2022 year.² (Table 3)

Table 3- ICMR and NARS-NET surveillance network (2022)

Resistant pathogens	% reported by ICMR	% reported by NARS-Net
MRSA	44.5	59%
Vancomycin resistant <i>E. faecium</i>	27%	-
Vancomycin resistant <i>E. faecalis</i>	5%	-
VRE	-	13%

MRSA: Methicillin resistant staphylococcus aureus; VRE: Vancomycin resistant enterococci; NARS: National Antimicrobial Resistance Surveillance Network (NARS-Net India), ICMR: Indian Council of Medical Research.

Vancomycin resistance—encoding gene, *vanA*, is identified in >99% of Vancomycin resistant enterococci (VRE) isolates. In the past 6 years, the proportion of *E. faecium* and *E. faecalis* isolates resistant to vancomycin has substantially increased. In addition, resistance to linezolid is identified in 6% of *E. faecium* and 2% of *E. faecalis* isolates.²

In the given antimicrobial resistant era in India, the clinical outcome in terms of 28-day mortality in patient where isolates were resistant to empirical antimicrobials was 29.6%, in carbapenem resistant patients was 32% and in colistin resistant patients was 27%.⁶

HOSPITAL CURRENT ANTIBIOGRAM SCENE

In our hospital, the latest 2024-25 antibiogram suggest an alarming situation of presence of extensive drug resistance (XDR), difficult to treat (DTR), multi-drug resistance (MDR), Cephalosporin resistant entrobacteriaceae amongst the gram-negative organisms. (Figure1,2,3,4) and MDR MRSA, MDR VRE amongst the gram-positive organisms. (Figure 5,6) as per below Table-4.

Table-4. Types of micro-organism in the hospital antibiogram

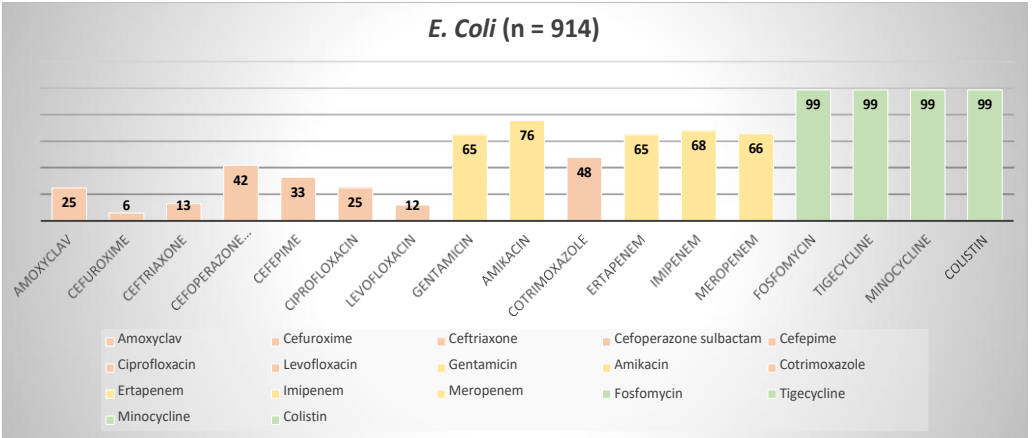
GROUP	GRAM NEGATIVE ORGANISM	GRAM POSITIVE ORGANISM
PAN DRUG RESISTANCE (PDR) (organism resistant to all drug classes)	NIL	NIL
EXTENSIVE DRUG RESISTANCE (XDR) (organism resistant to all drug classes except one or two)	Carbapenem Resistant <i>A. baumani</i> , Carbapenem Resistant <i>K. Peumonia</i>	NIL
DIFFICULT TO TREAT (DTR) (organism resistant to all 1 st line drugs beta lactams, carbepenems and fluoroquinolones)	Carbapenem Resistant <i>A. baumani</i> , Carbapenem Resistant <i>K. Peumonia</i>	NIL
MULTI-DRUG RESISTANCE (MDR) (organism resistant to at least one agent in 3 or more drug classes)	<i>E.Coli</i> , <i>P. Aeruginosa</i>	MRSA, VRE
CEPHALOSPORIN RESISTANT ENTROBACTEREACAE	<i>A. baumani</i> , <i>K.Peumonia</i> , <i>E.Coli</i> , <i>P. Aeruginosa</i>	NIL

HOSPITAL ANTIBIOGRAM (2024-25 YEAR)

Figure 1- Percentage Susceptibility of *E. Coli*



Percentage Susceptibility (*E. coli*)

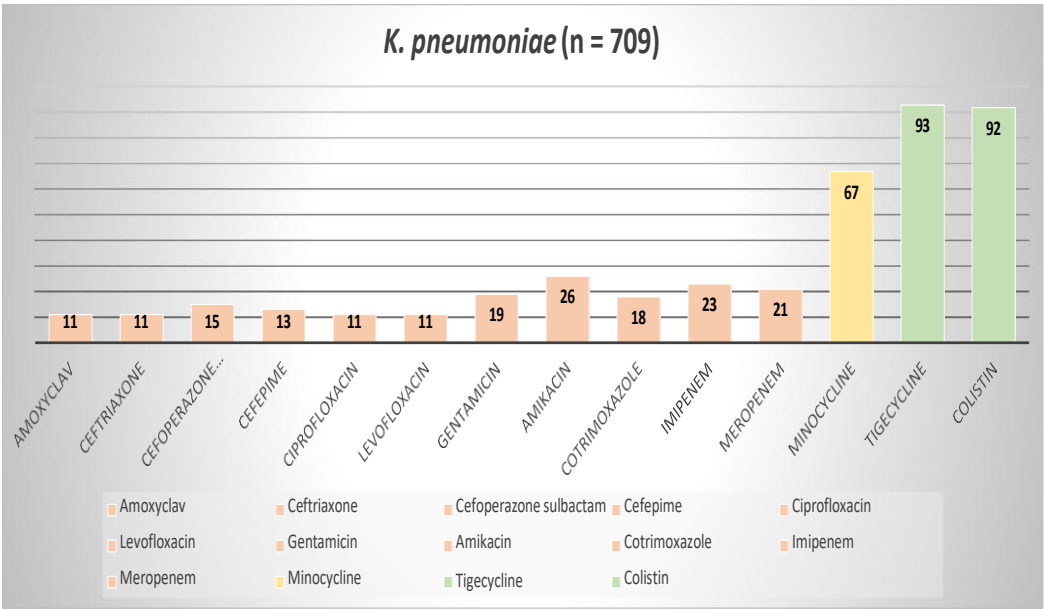


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Figure 2- Percentage Susceptibility of *K. Pneumoniae*



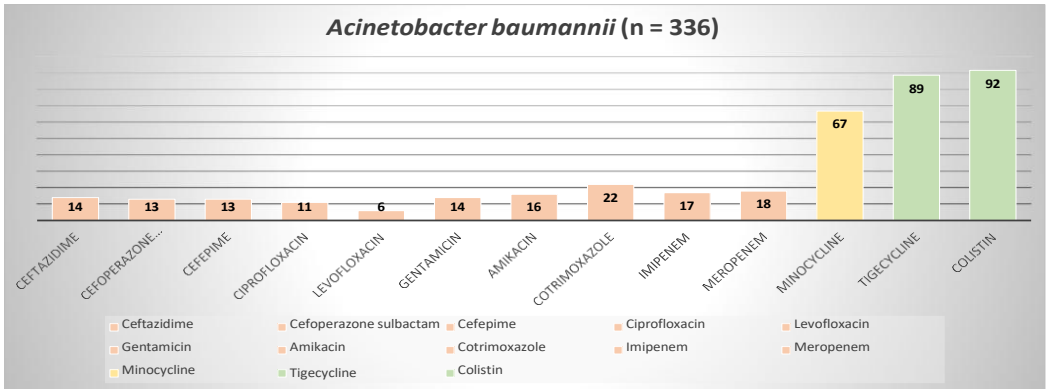
Percentage Susceptibility (*K. Pneumoniae*)



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Figure 3- Percentage Susceptibility of A. baumannii

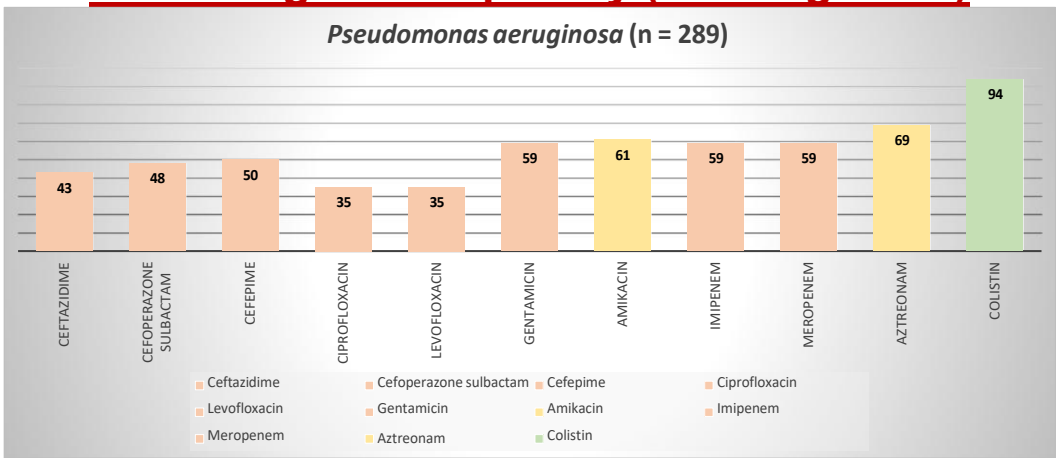
Percentage Susceptibility (A. baumannii)



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Figure 4- Percentage Susceptibility of P.aeruginosa

Percentage Susceptibility (P. aeruginosa)

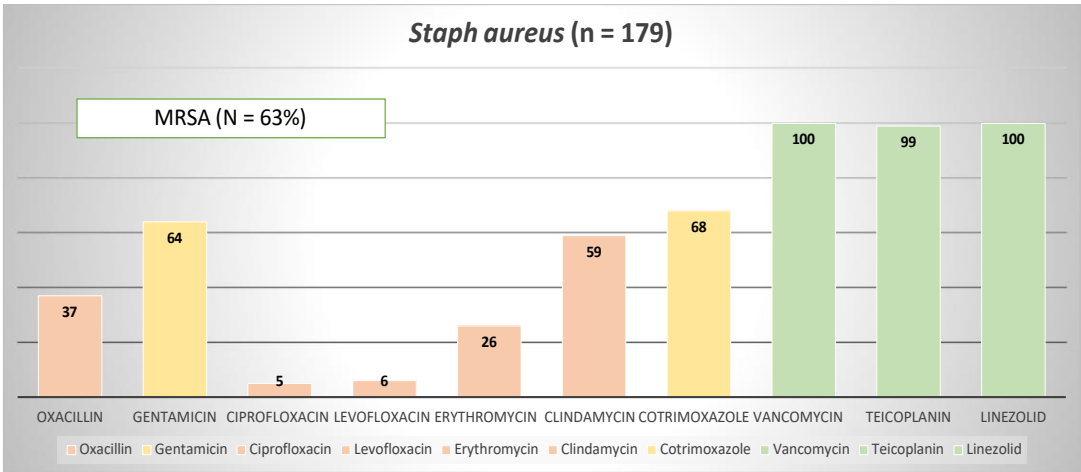


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Figure 5- Percentage Susceptibility of Staphylococcus Aureus



Percentage Susceptibility (*S. aureus*)

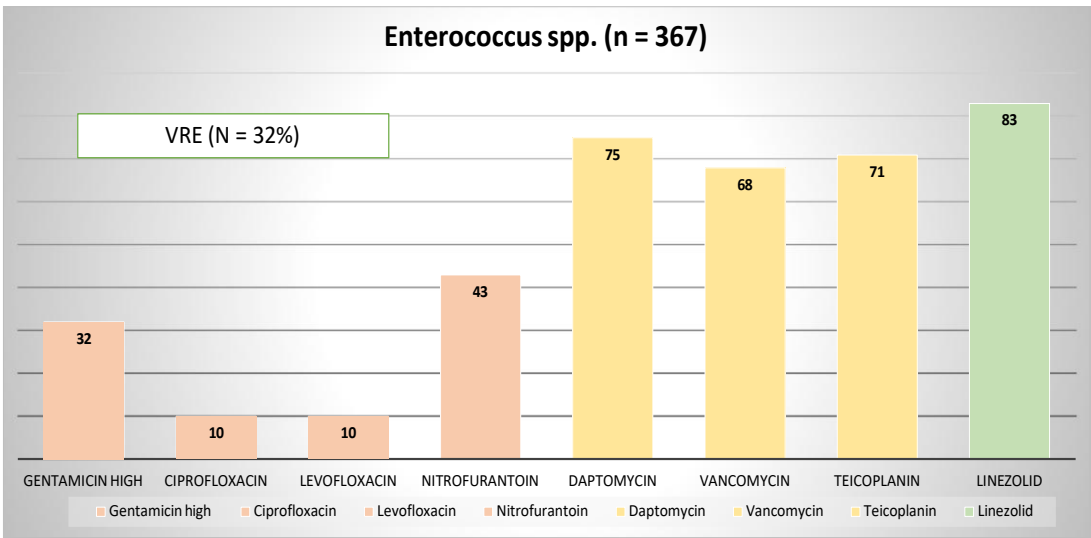


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Figure 6- Percentage Susceptibility of Enterococcus species



Percentage Susceptibility (*Enterococcus spp.*)



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This pattern of escalating resistance in gram negative and gram-positive organism to first line agents in WHO AWaRe class Access and Watch group antimicrobial drugs necessitates increased use of Reserve antimicrobials and the importance of Antimicrobial Stewardship Program (AMSP) in hospital to prevent the therapeutic options across all AWaRe categories.⁷

Our hospital Antimicrobial Stewardship Committee has adopted the National Medical Commission National Action Plan on Antimicrobial Resistance (NMC-NAP -AMR 2024) Formulary restriction of antimicrobials.⁸ Taking into consideration the WHO Reserve group of antimicrobials list -2023⁹ and drugs approved by Central drug standard control organization (CDSCO) & available in India the committee has approved the following list of restricted/reserve antimicrobials administered by intravenous (IV) route – Ceftazidime Avibactam, Ceftazidime Avibactam+ Aztreonam, Colistin, Polymyxin B, Minocycline, Tigecycline, Fosfomycin, Vancomycin, Daptomycin, Linezolid.

METHODOLOGY

Study design and Setting

A prospective observational single center study was conducted at Joint Commission international (JCI) accredited India first academic medical center Mahatma Gandhi Medical College & Hospital, Jaipur, Rajasthan.

Study duration

This study was conducted from April 2025 to September 2025 (6 months).

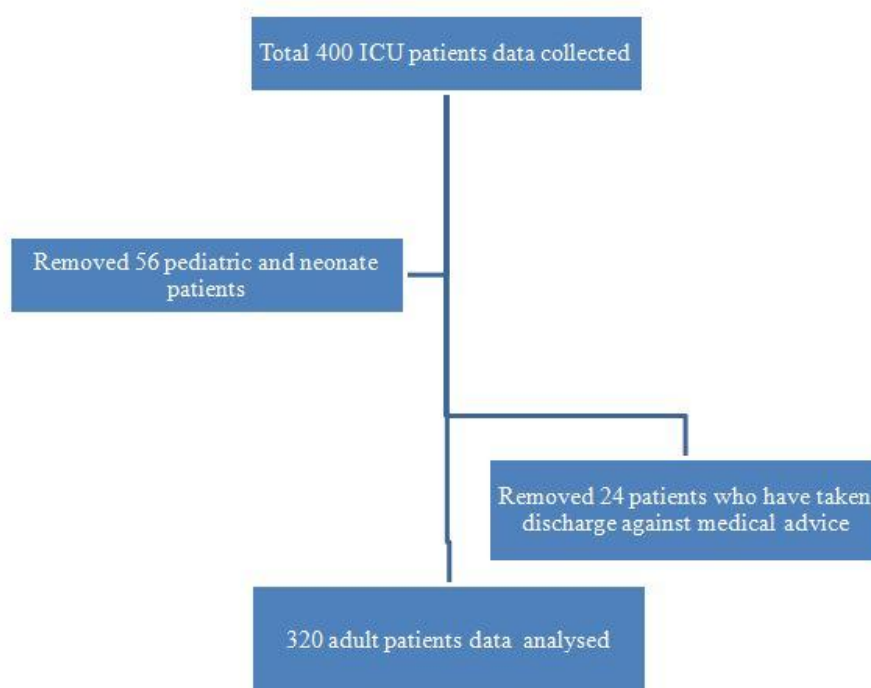
Sampling and sample size

Last year hospital data revealed that about 200 ICU patients received restricted antimicrobials in one month. Therefore in 6-month study duration, expected total patients to be observed were 1200 (Population).

Using Rao soft sample size calculator with 5% margin of error and 95% confidence interval for population of 1200, the recommended sample size comes out to be 292 ICU patients.

Hence, our sample size of 400 ICU patients was far above the recommended sample size of 292 patients. On screening of 400 ICU patients, 56 pediatric & neonate patients and 24 patients discharged against medical advice were removed from the study. Finally, 320 adult patient data was analyzed. (Figure 7)

Figure 7- Screening flowchart of ICU patients



Inclusion and Exclusion criteria:

All adult patient admitted in the ICU of the hospital who themselves or their relatives were willing to give informed consent were included in the study while pediatric and neonate patients admitted in ICU and patients who underwent discharge on request against medical advice were excluded from the study.

Data collection Tools and Techniques

Data was collected and analyzed for 320 adult ICU patients of different medical/surgical specialties by the Restricted Antimicrobial Usage Form.

Antimicrobial Stewardship approach (A,B,C,D) generally followed in our hospital ICUs is as per Figure 8.

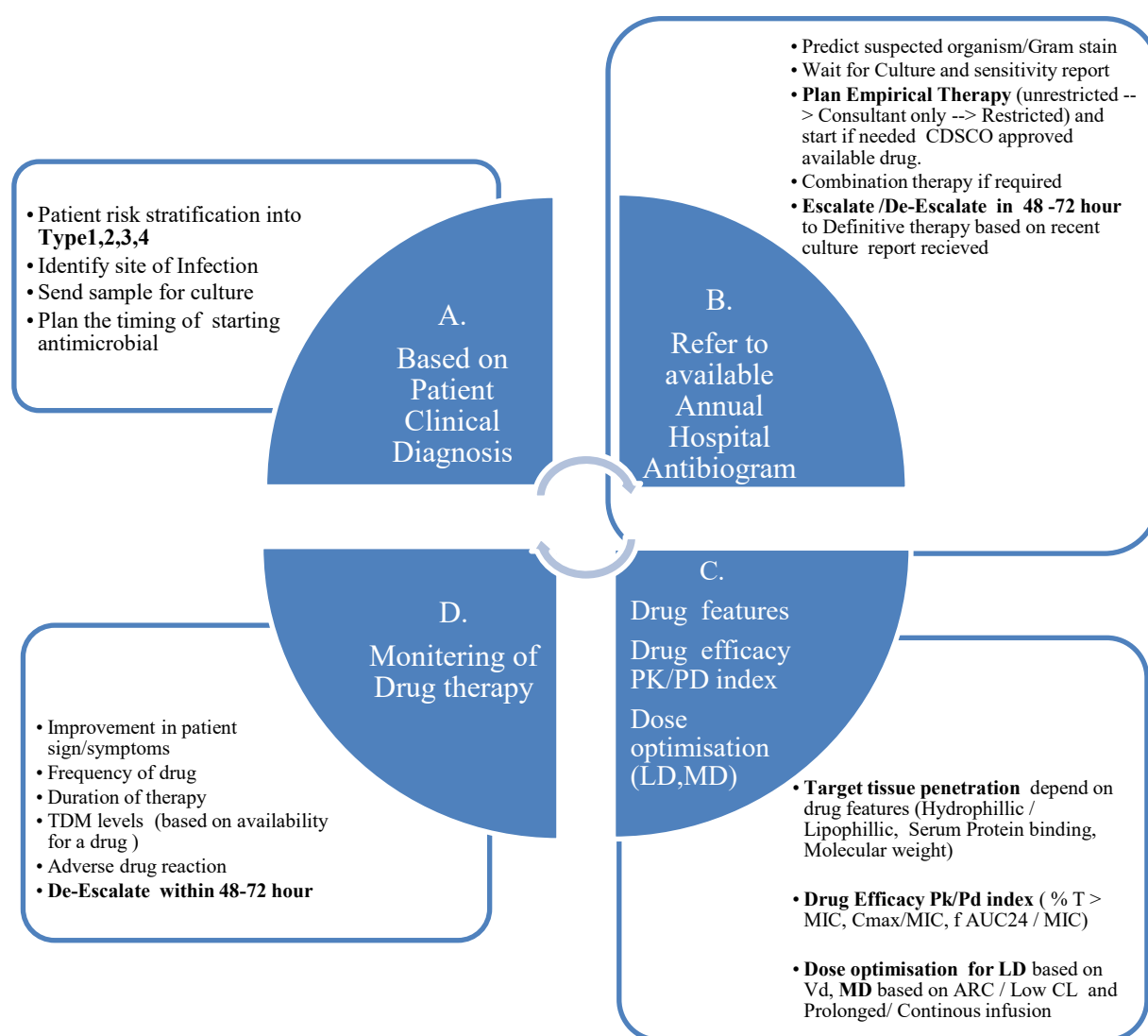


Figure 8- Antimicrobial stewardship approach in ICU (A, B, C, D)

(LD: Loading Dose, Vd: Volume of distribution, MD: Maintenance dose, CL: Clearance, ARC: Augmented renal clearance, TDM: Therapeutic drug monitoring).

Patients admitted to the ICU were categorized as per Patient Risk Stratification into Type 1, Type 2, Type 3 and Type 4 based on their history, clinical examination and diagnosis by the treating doctor. (Table -5) ^{10, 11, 12}

Table 5-Patient risk stratification

Patient type 1 (Community acquired infection)	Patient type 2 (Health care associated/hospital acquired infection)	Patient type 3 (Health care associated /hospital acquired infection)	Patient type 4 (Health care associated /hospital acquired infection)
No contact with health care system (within last 90 days)	Contact with health care system (recent hospital admission, nursing home visit, dialysis)	Long hospitalization >5 days and/or invasive procedures	Type 3 patient with fever despite antibiotic therapy (>5days) with no obvious source / after appropriate source control
No prior antibiotic treatment (within last 90 days)	Recent antibiotic therapy	Recent and multiple antibiotic therapies	Severe sepsis/septic shock PLUS
No procedures done (within last 90 days)	Minimum procedures done (iv cannula, central line, intubation, etc.)	Patient old (>65 yr) with multiple co-morbidities	Has 1 or more than 1 of the following factors. (but not limited to) for invasive fungal infections:
Patient young with no or few co-morbidities (Non-ESBL/MSSA)	Elderly patients (>65 yr) with few co-morbidities (more prone for MRSA/ ESBL organisms)	Major invasive procedures done (Laparotomy etc.)	TPN, Hemodialysis, immunodeficiency of variable origin, Major Abdominal surgery, Multi-focal candida colonization, Diabetes
		Structural lung disease, AIDS, Neutropenia other severe immunodeficiency (Prone for ESBL/MRSA as well as carbapenemase producing organisms) (Inherently resistant organisms like <i>Pseudomonas</i> , <i>Acinetobacter</i>)	Risk of Bacterial infections with pan/ Extensive-drug resistant organism
			High Risk of Invasive fungal infections

ESBL, Extended-spectrum beta-lactamase, MSSA, methicillin sensitive *Staphylococcus aureus*; MRSA, methicillin resistant *Staphylococcus aureus*; AIDS, acquired immune deficiency syndrome

Restricted antimicrobial was given “empirically” if prescribed before the culture report was available and as “definitively” if prescribed after that. For each empirical prescription, we asked prescribing doctor to justify their decision by categorizing the patient into Type 1,2,3,4 according to their severity of illness at time of admission and mention the risk factors on case-to-case basis which compelled them to use restricted antimicrobials empirically.

Empirical prescriptions with restricted antimicrobials were considered as appropriate if the patient was in Type 3 (high risk) or Type 4 (very high risk) category with documented clinical reasons, understanding the prevalence of XDR, DTR, MDR ESKAPE organisms in the current hospital antibiogram and if appropriate dose optimization with loading and maintenance dose delivered by prolonged/ continuous infusion has been done as per the ICMR treatment guidelines 2022.¹³

Clinical Pharmacist used to ensure that the Restricted Antimicrobial Usage Form was completely filled by the treating doctor and approved by the antimicrobial stewardship committee team members of the hospital on daily basis. Restricted antimicrobial usage data so generated was discussed in antimicrobial stewardship committee meetings held on monthly basis.

Statistical analysis:

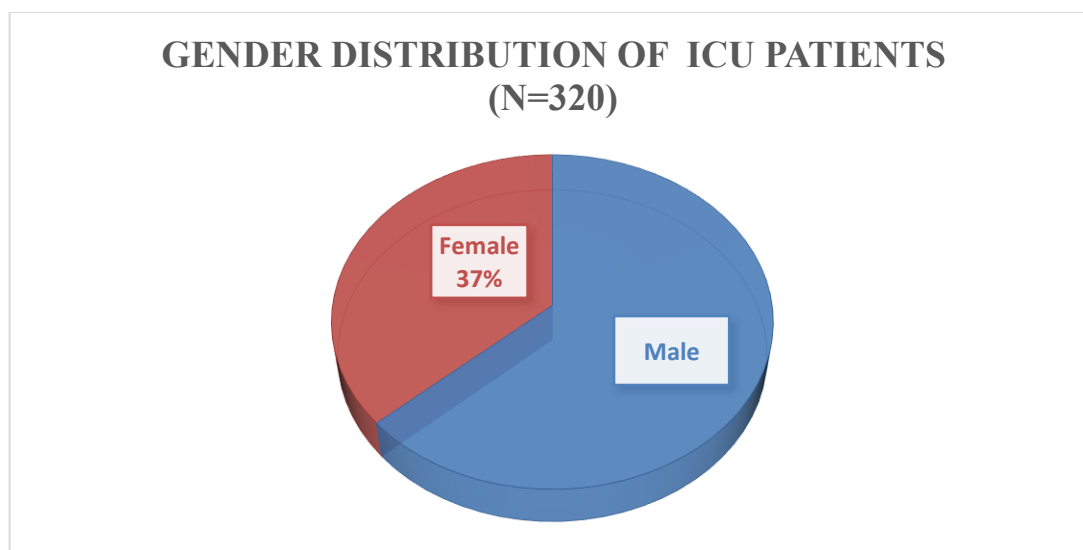
Nominal/categorical variables were expressed as percentage (%).

Ethical Considerations

This study was approved by the hospital ethics committee and was registered in Clinical Trial Registry of India (CTRI) vide registration number **CTRI /2023 /05 /052739**.

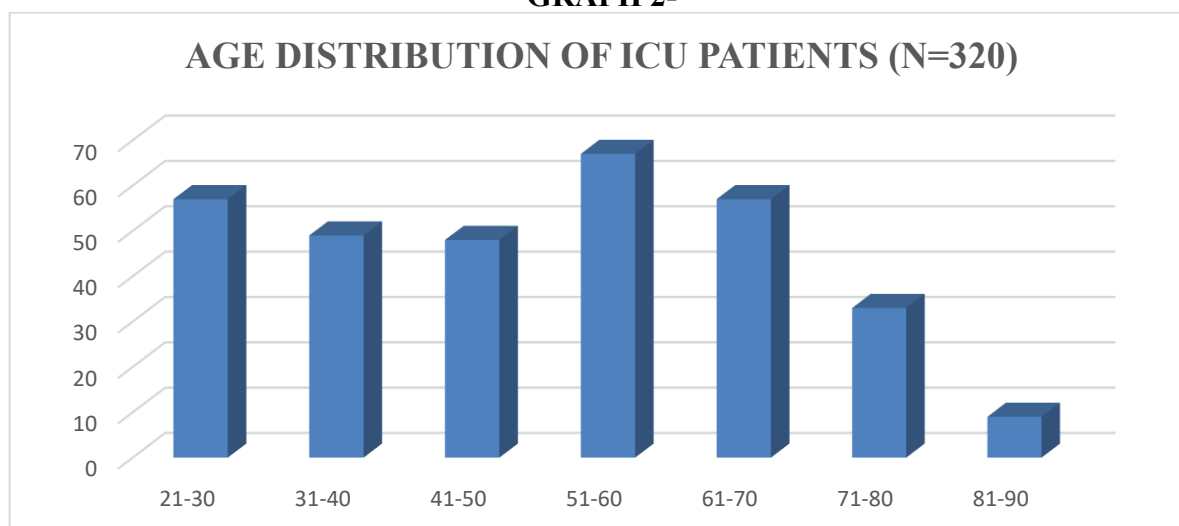
RESULTS:

GRAPH 1-



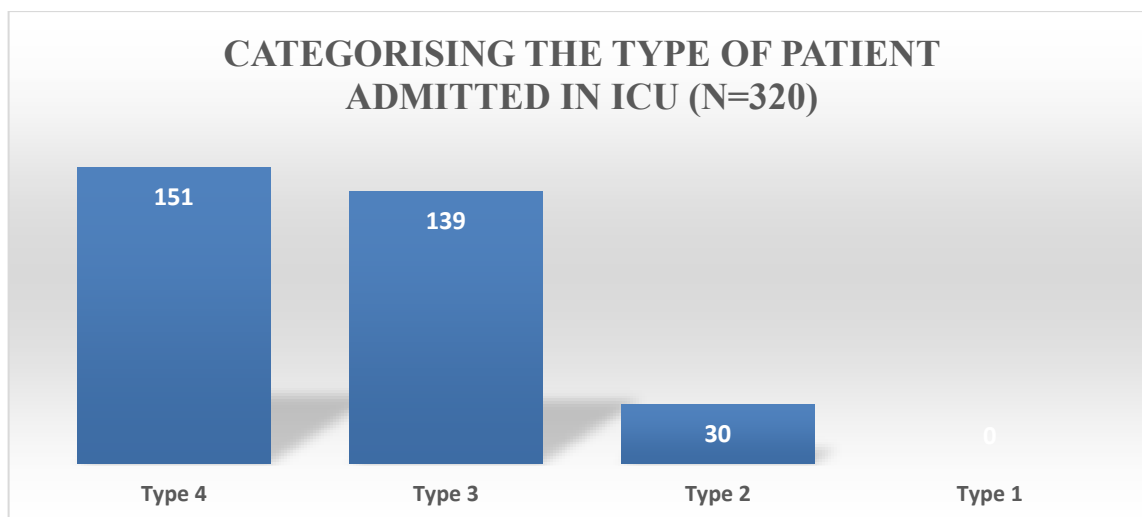
In the study maximum number of patients admitted in ICU were male (63 %) as compared to female (37%)

GRAPH 2-

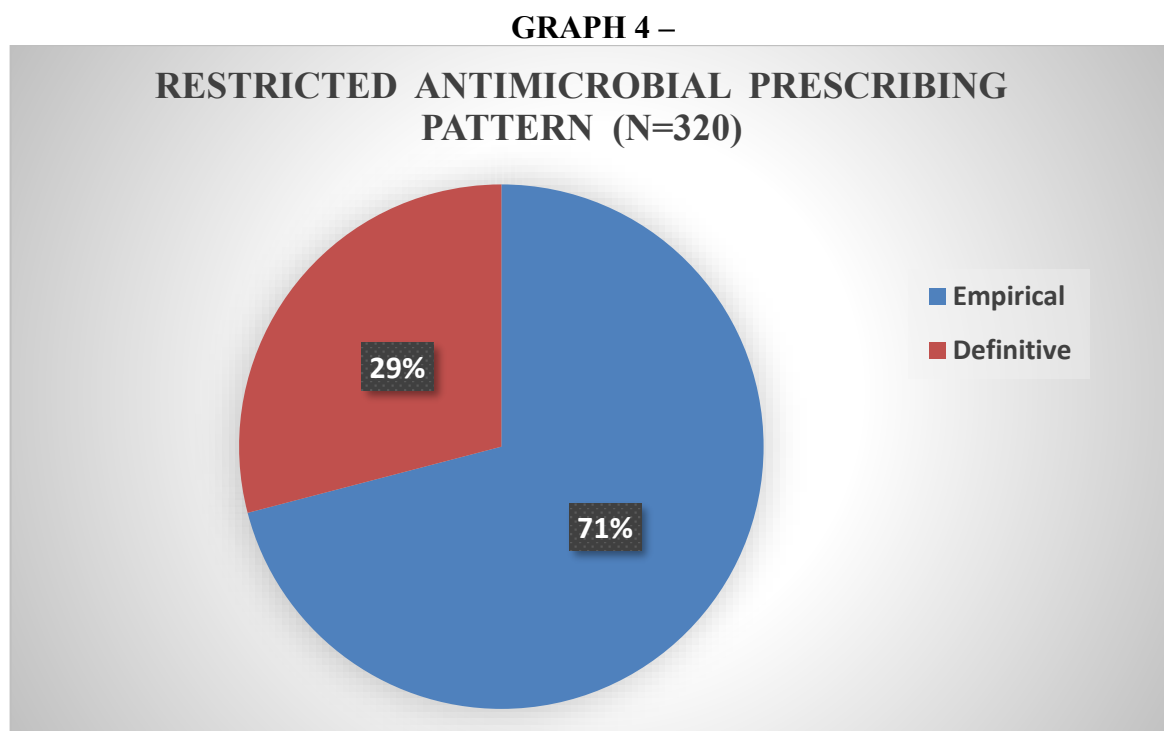


In the study maximum number of patients admitted in ICU belong to 51-60 year of age group followed by 61-70 year of age group.

GRAPH 3-

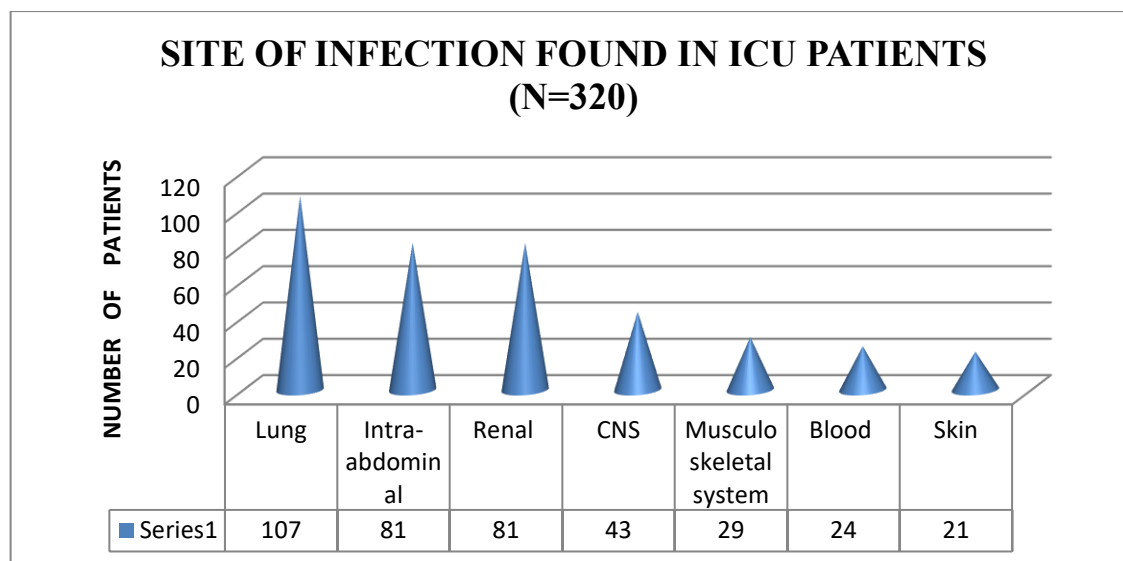


Out of 320 patients admitted in ICU, Type 4 category (very high risk) were 151 patients (47%), Type 3 category (high risk) were 139 patients (44%) while Type 2 category (moderate risk) were only 30 patients (9%). There was no patient in Type 1 category.



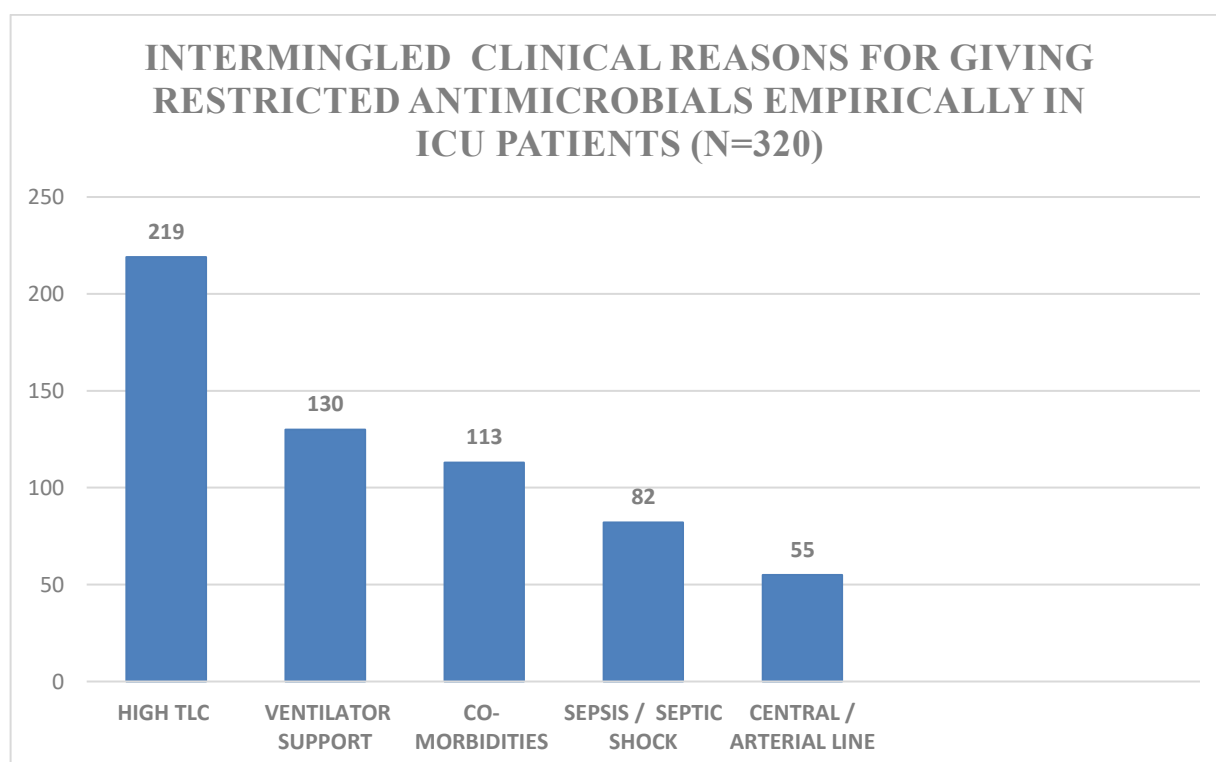
Empirically restricted antimicrobials were given in 71 % patients and Definitive restricted antimicrobials were given in 29% patients.

GRAPH 5-



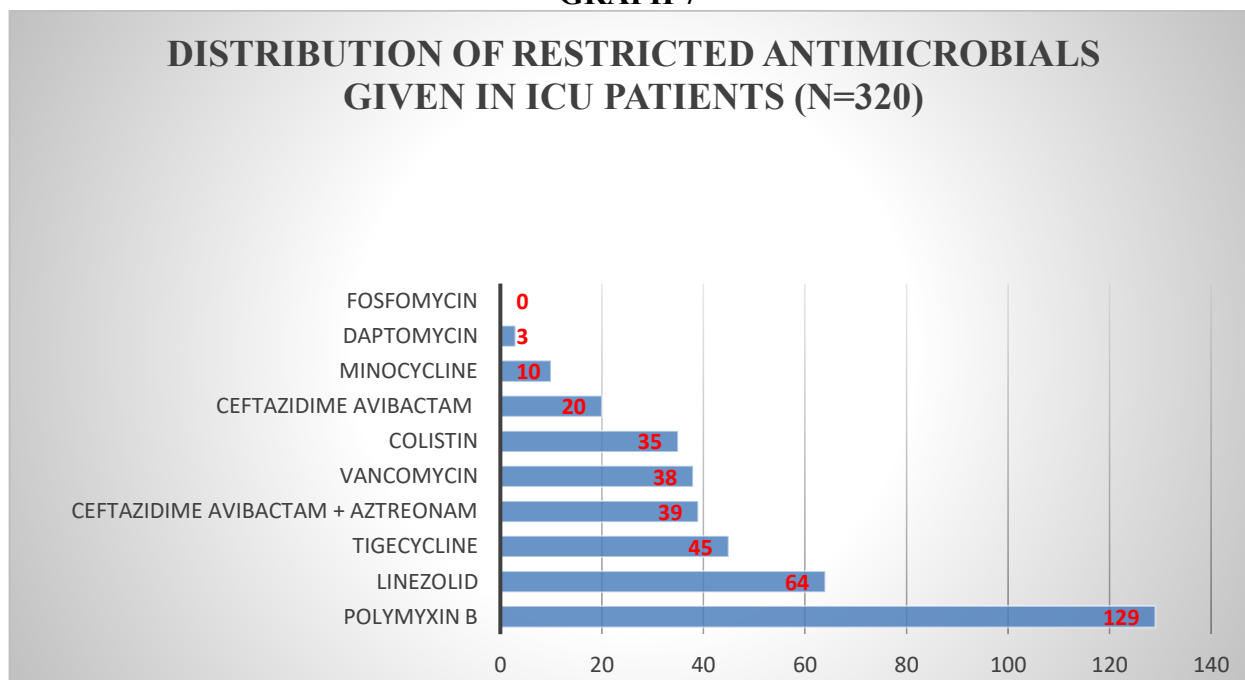
The most common site of infection was lung seen in 107 patients (34%) followed by intra-abdominal infections seen in 81 patients (25%) and renal infections seen in 81 patients (25%) then central nervous system infections (CNS) seen in 43 patients (14%), musculoskeletal system infections in 29 patients (9%), blood infections in 24 patients (8%) and skin infections in 21 patients (7%).

GRAPH 6-



The top five intermingled clinical reasons for giving empirical restricted antimicrobials were high Total Leucocyte Count (TLC) in 219 patients (68%), ventilator support in 130 patients (41%), comorbidities (diabetes, hypertension, asthma, cancer, kidney failure, liver failure) in 113 patients (35%), sepsis/septic shock seen in 82 patients (26%) and central/arterial line insertion done in 55 patients (17%). In most of the patients we found that there was mix of all these above reasons for starting the restricted antimicrobials empirically.

GRAPH 7-



Out of 320 patients Polymyxin B was given to 129 patients (40 %), Linezolid to 64 patients (20%), Tigecycline to 45 patients (14%), Ceftazidime Avibactam + Aztreonam to 39 patients (12%), Vancomycin to 38 patients (12%), Colistin to 35 patients (11%), Ceftazidime Avibactam to 20 patients (6%), Minocycline to 10 patients (3%), Daptomycin to 3 patients (1%) and Fosfomycin to none.

DISCUSSION

In our study maximum number of patients admitted in ICU were male (63%) and belongs to 51-60 year of age group followed by 61-70 year of age group. **(Graph 1, 2)**

Out of 320 patients admitted in ICU, Type 4 category (very high risk) were 47%, Type 3 category (high risk) were 44% while Type 2 category (moderate risk) were only 9 %. Altogether 91 % of the patients were either of Type 3 or Type 4 categories. **(Graph 3)**

Empirically restricted antimicrobials were given in 71 % patients as maximum of them belong to type 3 and type 4 category as mentioned above. Definitively restricted antimicrobials were given to 29% patients. **(Graph 4)**

Michael Samarkos et al ¹⁴ found that 67.2% of all prescriptions for restricted antimicrobials were empirical. Worldwide reported rates range from 50.6% in Romania, 60% in France, 80.90% in Thailand, and 96% in Oman. The isolation of pathogens resistant to the prescribed restricted antimicrobials suggests that in a setting with widespread antimicrobial resistance, it could be difficult to reduce the empirical use of restricted antimicrobials without risking inadequate treatment.

So, overall reduction of the rate of empirical prescriptions in our hospital can be possible but the major obstacle is the presence of XDR, DTR, MDR bugs. AMSP team monitors that Type 1 and Type 2 patients admitted in ICU should strictly not be prescribed restricted antimicrobials upfront unless justified as the patients are in stable condition.

Ines Pauwels et al ¹⁵ found that empirical prescribing of Reserve antibiotics ranged from 34.3% in high-income countries to 41.4% in upper-middle income and 53.0% in lower-middle-income countries. In lower-middle-income countries lack of diagnostic capacity is a challenge.

In our study the most common site of infection was lung (34%) followed by intra-abdominal infections (25%) and renal infections (25%) then central nervous system infections (14%), musculoskeletal system infections (9%), blood infections (8%) and skin infections (7%). **(Graph 5)**

Ines Pauwels et al ¹⁵ study found that reserve antibiotics were mainly used to treat pneumonia (26.2%), skin and soft tissue infections (12.9%) and intra-abdominal infections (10.5%). The site of infection can be variable across different hospitals depending on the medical/surgical specialties available there.

We found that the top five intermingling clinical reasons for giving empirical restricted antimicrobials in Type 2, 3 and 4 patients were high Total Leukocyte Count (68%), ventilator support (41%), comorbidities (diabetes, hypertension, asthma, cancer, kidney failure, liver failure) (35%), sepsis/septic shock (26%) and central/arterial line insertion (17%). In most of the patients we found that there was mix of all these above reasons for starting the restricted antimicrobials empirically to achieve control on patient progressive illness well in time and reduce the morbidity /mortality rate. **(Graph 6)**

Amongst the 320 patients, restricted antimicrobials IV administered- Polymyxin B was given maximum to 129 patients (40 %), Linezolid to 64 patients (20%), Tigecycline to 45 patients (14%), Ceftazidime Avibactam + Aztreonam to 39 patients (12%), Vancomycin to 38 patients (12%), Colistin to 35 patients (11%), Ceftazidime Avibactam to 20 patients (6%), Minocycline to 10 patients (3%), Daptomycin to 3 patients (1%) and Fosfomycin to none. **(Graph 7)**

Ines Pauwels et al ¹⁵ analyses of the 2118 Reserve prescriptions in the dataset showed that linezolid was the most commonly used Reserve antibiotic worldwide (29.9% of all Reserve prescriptions; 19.1% in East and South Asia to 62.1% in Northern Africa). In Northern America, daptomycin represented up to 30.1% of all Reserve prescriptions. Overall, colistin accounted for 27.0% of Reserve use (8.7% in Northern America to 50.5% in West and Central Asia).

This will vary from hospital to hospital according to the patient clinical diagnosis.

Antimicrobial stewardship approach in ICU (A, B, C, D) Figure 8 -

A.) Factors affecting the choice of Empirical antimicrobial therapy in ICU patients:

In our hospital factors determining the empirical therapy in ICU patients depends on past history of antimicrobial exposure, clinical severity of disease, age, co-morbidities, allergy status, immune status, site of infection and suspected MDR/DTR/XDR organism based on current hospital antibiogram.

Patient risk stratification was done into Type 1,2,3,4 to ensure judicious use of limited restricted antimicrobials.

Vu Quoc Dat et al ¹⁶ remarks that in their study the majority of initial diagnosis of infection were clinically made, partly related to the lack of rapid diagnostics whilst the empirical antibiotic prescribing decisions were influenced by doctors' experiences and by level of hospitals. It makes the interpretation of empirical antibiotic choice difficult and must be related to the current burden of antibiotic resistant pathogens in community and in a particular ICU.

Pharmacokinetic/Pharmacodynamic changes in critically ill patients' pathophysiology

Empirical decision making – depends on pharmacokinetic/pharmacodynamic (PK/PD) considerations typical of critically ill patients (e.g. acute kidney injury and organ failure, hypo albuminemia, continuous renal replacement therapies, vasoplegia and capillary leak syndrome, altered volume body compartments and third fluid space accumulation) in setting of major surgery, trauma, burns and sepsis. ^{18,22}

The penetration of antimicrobial drugs into tissues ensures the achievement of clinical recovery from infections and, possibly, the eradication of infective foci.¹⁹

Importance of knowing the site of infection

M. Ippolito and A. Cortegiani¹⁸ suggest that effective empirical antimicrobial therapy should be first guided by accurate identification of the most probable site of infection. This is based on clinical presentation and diagnostic information. The identification of the source allows for reasoning on the most commonly involved pathogens, appropriate microbiological sampling, and the eventual need for source control procedures. Moreover, the infection site influences the choice of antimicrobial even before microbiological results, because of the tissue penetration characteristics of different drugs. The tissue availability of each drug varies based on both the drug and the tissue characteristics. Central nervous system and the lungs have poor while bloodstream and the urinary tract have good drug penetration .¹⁸

Timing of giving restricted antimicrobials empirically

The usual clinical response /recovery signs to antimicrobials come after the drug has been given for multiple doses over 24 to 48 hours period, the time very crucial in deciding the prognosis of critical ill patients and the patients will not be benefited if given suboptimal treatment leading to increased morbidity and mortality.

Marin H.Kollef ¹⁷ found that from the day of start of treatment with inappropriate antimicrobial the risk of mortality for each day is very high as compared to the risk of resistance emergence. The antimicrobial dose should be administered quickly within 1 hour in case of septic shock and within 4-5 hour in case of suspected sepsis.

Timely administration of appropriate antibiotic therapy is the cornerstone of the management of serious ICU infections. C- reactive protein and Procalcitonin biomarkers were commonly used for sepsis prediction.²⁰

Such time constraint situations influence the rate of empirical use of restricted antimicrobials and make it high (71%) in our hospital because if by chance you happen to prescribe a less effective antimicrobial therapy empirically then you may be losing time in saving a life.

B.) Prevalence of resistant microorganism in hospital antibiogram, challenge of rapid bug identification and Plan for Empirical therapy

The spectrum of microorganisms involved in community acquired infections depends on local epidemiology and type of infection (e.g. community-acquired pneumonia, meningitis). In case of hospital- or ICU-acquired infections, patients have risk factors for MDR ESKAPE pathogens.¹⁸

A simple quick test of 'Gram stain' was done of fresh sample of infectious site to provide more targeted antimicrobial therapy.

Indeed, the long turnaround time of standard microbiological cultures 48 to 72 h and in vivo antimicrobial susceptibility testing patterns, although pivotal for selecting targeted treatment, hamper their usefulness in making decisions about empirical treatment.¹⁸

So, rapid bug identification tests are urgently needed to reduce the rate of empirical use of restricted antimicrobials.

Plan empirical therapy from NMC -NAP-AMR 2024 drug Formulary Restriction groups (Unrestricted, Consultant only, Restricted) and start if needed CDSCO approved available drug.

Give Combination therapy if required. Escalate /De-Escalate in 48 -72 hour to definitive therapy based on recent culture report received.

C.) Drug features affecting drug efficacy and dose optimization

Target tissue penetration based on antimicrobial determinants

The antibacterial efficacy of antimicrobial depends on the reach to site of infection, bactericidal / bacteriostatic nature and effective antibiotic concentration. Pathogens are typically considered sensitive to an antibiotic when serum concentrations reach at least four times the MIC following the standard dose with exception to protein bound drug and specific infection site (cerebrospinal fluid, prostate ,abscess) environment factors (acidity, oxygen levels) and emergence of resistant strains and temporal dynamics (sterilization levels change overtime) of antimicrobial concentration.²¹

Antimicrobial with favorable characters like low molecular weight, lipophilicity and low degree of protein binding facilitate tissue and cellular penetration, with easier availability of the antimicrobial at the infection site.¹⁸

Beta-Lactams are exceptions; they are hydrophilic agents for which it is possible to achieve high distribution to interstitial compartments, owing to their wide and favorable therapeutic window, allowing high doses to be used. This results in higher tissue concentrations (e.g. respiratory system, abdomen, bone and skin) especially in patients with altered volume of distribution (e.g. those with sepsis). Another important determinant is the presence of inflammation, which may increase tissue distribution of antimicrobials because of leaky tissue/blood barriers, the opening of intercellular tight junctions and oedema formation. An example is the increased penetration of β -lactams into the cerebrospinal fluid (CSF) in meningitis. Although, their penetration in the CSF in the absence of meningeal inflammation is generally poor.¹⁸

While PK/PD index values generally remain consistent across infection sites, pneumonia presents an exception due to variations in epithelial lining fluid (ELF) penetration. For example, vancomycin demonstrates better efficacy in models focusing on non-pneumonia infections due to its limited penetration into ELF.²¹

Furthermore, the presence of resistant clones and the need to prevent their diffusion are mandatory prerequisites to prescribe effective doses. These factors justify the use of antimicrobials in regimens that may be considered off-label for the dose (for example, tigecycline), the route, and modalities of administration (i.e., continuous infusions of linezolid).

Moreover, doubling the dose of tigecycline (loading dose 200mg and maintenance dose 100mg q12h) may increase the probability of cure rates, especially in patients with a high body mass index. A similar strategy has been identified for linezolid because an IV bolus of 0.6 g followed by a continuous infusion of 1.2 g/day was associated with an ELF/plasma ratio of 1X.^{19,24}

The knowledge of tissue penetration of antibacterials in ICU patients may guide the choice of the most effective chemotherapy, according to bacterial strain sensitivity and tissue/plasma penetration ratio.¹⁹ Table -6

Antimicrobial efficacy against microbes based on PK/PD indicators

In vitro is different from in-vivo conditions (such as the presence of immune system components, tissue-specific factors, and varying biochemical environments) contributing to the sustained antibacterial activity observed.

Mohammad Sina Alikhani²¹ suggests that PK/PD principles guide clinicians in selecting the most appropriate antibiotics and dosing strategies tailored to individual patient needs. PK/PD indicators also help developing new drug dosage formulations to the specific needs of various infections, such as targeting intracellular bacteria, overcoming biofilm-associated infections, or penetrating difficult-to-reach tissues.

The three main PK/PD indicators used to predict antimicrobial effects are: the duration (% of time between consecutive administration of an antibiotic) in which the drug concentration exceeds the MIC (%T> MIC), the maximum drug concentration to MIC ratio (C max / MIC), and the 24-hour ratio of the area under the free drug concentration-time curve to MIC (f AUC₂₄ /MIC).

%T > MIC

β -lactam antibiotics show varying %T>MIC values depending on the type of antibiotic, with cephalosporins (≥ 50 -70%) having a greater value than penicillins (≥ 50 %), and penicillins having a greater value than carbapenems (≥ 40 %). This hierarchy is attributed to their differing sterilizing abilities. Furthermore, the protein binding rate significantly impacts PK/PD index values, with differences observed even within the same antibiotic class.^{21, 26}

PK/PD index values may also vary depending on bacterial strain and host immune status. For instance, the %T>MIC requirement is lower in staphylococci compared to Gram-negative rods or streptococci.²¹

The optimal PK/PD target for guiding β -lactam dosing remains unclear. In critically ill patients, 100% of time where the free concentration is above the MIC (100% fT > MIC) is often suggested as a therapeutic target for β -lactams.^{22, 23}

The closer the %T > MIC parameter is to 100% the greater the likelihood of antimicrobial efficacy in immunosuppressed patients and in the case of Gram-negative infections. It is easy to deduce that the lower the MIC value of an antibiotic, the easier it is to achieve the required parameter with a standard dosage. In the case of higher MIC values, it may be necessary to reduce the dosing range, e.g., from every 8 h to every 6 h or every 4 h or to use continuous or prolonged infusions depending on the summary of product characteristics or to choose another antibiotic for which the PK/PD index will be achieved. Many authors believe that this parameter should be presented in a more detailed form, i.e., fT > 4 x MIC, due to the fact that the concentration of the antibiotic should be 4–5 times the MIC to be therapeutic and in addition, only the concentration of the free fraction of the antibiotic is relevant (unbound to plasma proteins (f) for the therapy to be effective.²⁶ More aggressive β -lactam targets (i.e., 4–5 × MIC) have also been considered to minimize the occurrence of microbiological failure due to difficult to treat infections and/or resistance.²²

C_{max} / MIC

This comprises concentration-dependent antimicrobials with a long post antibiotic effect (PAE), such as aminoglycosides, fluoroquinolones and daptomycin.

These antimicrobials exert a faster and more extensive sterilization effect at higher concentration so administering high dose helps to maximize their effectiveness (ex. Daptomycin).²¹

This parameter is characteristic of antimicrobial whose efficacy depends on maximum concentration (C_{max}) which is many times greater than the MIC (8-10 times). Lower MIC values are more likely to meet the efficacy condition for these antibiotics while reducing the risk of toxic concentrations.²⁶

In a recent Italian study, a steady-state concentration/MIC ratio of ≤ 5 was identified as an independent predictor of microbiological failure in critically ill patients with Gram-negative bacillary infections.²²

f AUC₂₄ / MIC

f AUC₂₄ represents the total exposure of the body to unbound drug over 24 hour and is calculated from the graph of drug concentration in the blood stream versus time. f AUC₂₄/MIC parameter maximizes the amount of antimicrobial exposure (for time and concentration both).

This comprises time-dependent antimicrobials with a long PAE. Although high concentrations of these antibiotics in the body do not increase their sterilizing power, they do have the unique ability to suppress bacterial regrowth for an extended period of time. Therefore, increasing the dose of antibiotics to increase the AUC/MIC ratio is critical to maximize their efficacy.²¹

For Vancomycin (AUC/MIC > 400, f AUC/MIC > 200), Tigecycline (skin-AUC/MIC ≥ 17.9 , intra -abdominal AUC/MIC ≥ 6.69 , hospital acquired pneumonia-AUC/MIC ≥ 4.5), Polymyxins (AUC/MIC > 50, f AUC/MIC > 25).²⁶ Table -6.

Dose optimization

It refers to the dose, dose administration rate, dosing interval that ensure optimal antimicrobial exposure for a given susceptibility of a pathogen at the site of infection to maximize bacterial killing.²⁷

Optimal antibiotic usage involves avoidance of under dosing, while preventing adverse effects associated with overdosing. An initial large loading dose is required to “fill” the higher than usual volume of distribution in severe sepsis—roughly 1.5 to 2 times the standard dose. Then dosing should occur according to drug clearance. For beta-lactams, the best effect is related to time above minimum inhibitory concentration (MIC) of the target pathogen; high daily doses for prolonged duration are best administered by using continuous/extended infusions.^{18,20} Table-6

Even with appropriate antibiotic therapy, it is necessary to use the correct dose, often higher than usual in septic patients, who can have augmented renal clearance of antibiotics, along with alterations in volume of distribution, cardiac output and penetration to the site of infection.²⁰

Dosing antibiotics in special populations such as the elderly, obese individuals, and patients with comorbidities presents unique challenges and limitations due to their altered PK /PD. This is particularly important for drugs like aminoglycosides and vancomycin, where renal function must be closely observed to avoid toxicity.²¹

Obese patients require dosing adjustments based on actual or lean body weight to ensure effective tissue penetration, especially for lipophilic antibiotics such as daptomycin and vancomycin. Similarly, patients with renal or hepatic impairments need customized dosing strategies to prevent drug accumulation and toxicity.²¹

Loading Dose (LD) according to changes in Volume of distribution (Vd)

Sepsis and administration of fluids, inotropes and vasopressors increase the Vd of antimicrobials. Hydrophilic drugs (particularly β -lactams, amino- glycosides, and vancomycin) which have a low Vd are more susceptible to the impact of these pathophysiological changes. Factors such as the presence of pleural effusion, ascites, and surgical drains and large volume crystalloid administration may further expand the Vd of these drugs and alter the infection site concentration of antibiotic.^{17, 22}

Hypoalbuminemia is commonly found in critically ill patients (burn injuries), and baseline serum albumin concentrations fall below 25 g/L in over 40% of ICU patients. Hypoalbuminemia may therefore lead to an increase in the fraction of unbound drug in the blood; this fraction is freely distributed into tissues, further extending the Vd of these drugs.²²

The empirical standard dosing regimens lead to subtherapeutic concentrations of different classes of antibiotics. As the Vd of antibiotics is often increased, higher loading doses are needed for hydrophilic antimicrobials (e.g., β -lactams, vancomycin, aminoglycosides, and colistin) to achieve similar and adequate therapeutic concentrations. New optimal β -lactam loading doses have been suggested (8 g in 3 h for piperacillin, 4 g in 3 h for ceftazidime and cefepime, and 2 g in 0.5 h for meropenem) based on population PK analysis and Monte Carlo simulations.²²

Similarly, higher than recommended loading doses have been proposed for vancomycin, aminoglycosides, and colistin; this approach has been supported by findings from clinical validation studies, which have shown improvements in PK/PD target attainment for all three of these antibiotics. Notably, the loading dose should not be altered in patients with renal impairment or those receiving Renal Replacement Therapy.^{18, 22}

Maintenance Dose (MD) according to changes in drug clearance (CL)

Augmented renal clearance (ARC)

ARC is defined as a creatinine clearance (CrCl) greater than 130 mL/min/1.73 m² in males and greater than 120 mL/min/1.73 m² in females. ARC has been linked with subtherapeutic β -lactam and glycopeptide concentrations.¹⁷ Augmented renal clearance (ARC) is a multifactorial condition that affects approximately 25% of ICU patients.¹⁹

Hyperdynamic states resulting from fluid resuscitation and vasopressor administration may lead to increased blood flow in major organs such as the kidney, and thereby increase renal elimination.²²

Risk factors for the development of ARC include young age, sepsis, trauma, surgery or neurosurgery, febrile neutropenia, and burn injuries. Hydrophilic drugs that are primarily cleared via the kidney may exhibit substantial changes in CL in the presence of ARC. It is therefore essential to evaluate the measured CrCl on a daily basis to better identify ARC in patients receiving hydrophilic antibiotics (e.g., β -lactams, vancomycin, or aminoglycosides).²² In this context, Claire Roger²² found that most patients who developed ARC in the

cohort presented with an episode within the first week of admission; in addition, the condition developed within 3 days in half of the cases. The duration of ARC varied widely, with a median and maximum time frame of 5 days and more than 1 month, respectively.

The most common strategy used for altered PK parameters in critically ill patients and achieve greater time above the MIC has been prolonged or continuous infusions of time-dependent antimicrobials, including β -lactams, carbapenems, and vancomycin.

Claire Roger ²² reviewed studies that evaluated the continuous administration of β -lactam antibiotics have demonstrated improved outcomes including a higher rate of PK/PD target achievement, higher clinical remission rates, and superior microbiological eradication. In this context, observational studies have shown that continuous infusions of linezolid achieved the PK/PD targets (AUC₂₄/MIC >80 and %T > MIC >85%) in patients with ARC, those who were obese, and those with elevated MICs (2–4 mg/L). Continuous infusion of linezolid was also found to be associated with improved alveolar diffusion and better clinical outcomes, in terms of clinical improvement and mortality.

Decreased Renal Clearance

Notably, altered renal elimination may also lead to varying degrees of renal impairment. More than 50% of patients hospitalized in ICUs suffer from acute kidney injury and 20%–25% of affected individual requires renal replacement therapy (RRT) during the first week.²²

Dose reduction on the basis of creatinine clearance should not be applied routinely in the setting of an ICU, as full antimicrobial dose should be provided to patients with septic shock for probable clinical benefit at least for the first 24–48 h in case of transient Acute Kidney Injury. In addition, increased dosage may be needed in those undergoing renal replacement therapy.¹⁸

D.) Monitoring of Antimicrobial Therapy

Doctors monitor the sign/symptoms of patient recovery, duration of drug therapy and any adverse drug reaction every day.

De-escalation is essentially done within 48–72 hour once the situation is under control and patient is out of risk to prevent unnecessary drug exposure thereby minimizing adverse drug reactions and resistance development. Therapeutic Drug Monitoring (TDM) facility for restricted antimicrobials is currently not available at our hospital.

Table -6-Restricted antimicrobial PK/PD indicators in general population and alterations in critical illness and drug tissue/plasma ratios ^{13,18,20,22,23,24,26,27,32}									
S. n o	DRUGS COVERING GRAM NEGATIVE ORGANISM	PK variable	PK in general population (healthy)	Alterations in critically ill patients	PD KILL FEATURE / Drug Efficacy Optimal PK/PD index	Dosing scheme objectives	Standard Dose	Tissue Penetration (tissue/plasma ratio)	Adverse drug reaction
	HYDROPHILIC								

Analysis Of Appropriateness Of Reserve/Restricted Antimicrobials Usage In The Adult Icu Patients Of Different Departments Of The Hospital As A Part Of Antimicrobial Stewardship Program- A Prospective Observational Study.

1	CEFTAZIDIME – AVIBACTAM (IV) (10% protein bound)	Volume of distribution	Low	Increased (3rd space)	Time-dependent % T > MIC	Maximize duration of exposure-prolonged infusions	2.5 g (2 g/0.5 g) q8h plus Aztreonam 2g IV q8h (infusion over 3 h)	LUNG BRONCHIAL SECRETION (0.76 X) ELF (0.21-0.44X) ABDOMEN-Peritoneum (0.35-0.56 X) CNS (0.24X)	Diarrhea, nausea, Vomiting
2	CEFTAZIDIME – AVIBACTAM (IV) (10% protein bound) + AZTREONAM (IV) (70% protein bound)	Clearance	Mainly renal	Renal function dependent: Increased (ARC) or Decreased (AKI, ARF, CRF)					
3	COLISTIN (PolyE) (IV) (50-60 % protein bound)	Penetration	Extracellular (Poor cell penetration)	Decreased interstitial penetration	fAUC24/MIC >25	Maximize amount of exposure	Loading dose: 9 MIU (infusion 30 min to 1 h) Maintenance dose: 4.5 MIU q12h after 12 h	SKIN (0.2-0.3) SOFT TISSUE / MUSCLE (0.2-0.25) BONE (<0.2) PERITONEAL FLUID (0.1-0.25) ELF (VARIABLE0.1 -0.25) CNS (<0.1X)	More Nephrotoxic
4	POLYMYXIN B (IV) (80-95% protein bound)						Loading dose: 2.5 mg/kg (1-h infusion) Maintenance dose: 1.5 mg/kg q12h (1-h infusion) after 12h	LUNG (2.8-2.96) SKIN (1.46-1.53) HEART (0.98-1.05)	Less Nephrotoxic
5	FOSFOMYCIN (IV) (< 5% protein bound)	Volume of distribution Clearance Penetration	Moderate Mainly renal (unchanged drug) Extracellular largely	Renal function dependent: Increased (ARC) or Decreased (AKI, ARF, CRF)	fAUC/MIC > 40-80	Maximize amount of exposure	6–8 g q8h PROLONGED AND CONTINUOUS INFUSION	SUBCUTANEOUS ADIPOSE TISSUE (0.76X) MUSCLE ISF (0.71X) SKIN (0.62-0.7X) LUNG (0.53X) BONE (0.43X) CSF (0.18X) BRONCHIAL SECRETION (0.13X)	Hypernatremia Hypokalemia
	LIPOPHILIC								
6	TIGECYCLINE (IV) (70-90 % protein bound)	Volume of distribution Clearance	High Mainly hepatic	Unchanged Hepatic function dependent (unchanged, decreased	Concentration-dependent with time dependence fAUC24/MIC >17.9 (skin)	Maximize the amount of antibiotic exposure	Loading dose 100–200 mg, Maintenance dose: 50–100 mg q12h	BILE(>600X) GB(>34X) SKIN STRUCTURE (>18) ELF (1.7X)	Nausea, Vomiting and Diarrhea

		Penetration	Intracellular (Good cell penetration) & extracellular	or increased) Unchanged interstitial penetration	>6.96 (abdomen) >4.5 (pneumonia)			BONE (0.41–2X) SYNOVIAL FLUID (0.6–0.9X) CNS (0.5X) CSF (0.2X)	
7	MINOCYCLINE (IV) (70-76 % protein bound)				Concentration-dependent with time dependence $fAUC_{24}/MIC = 12$	Maximize the amount of antibiotic exposure	LD -200 MG MD-100 - 200 MG q12h	LUNG (3.8X), LIVER, GB, BILE, PROSTATE, GENITOURINARY(>1X), CSF (poor)	GI symptoms (nausea, vomiting, diarrhea, flatulence), vestibular disturbance, reversible hyperpigmentation

S. No	DRUGS COVERING GRAM POSITIVE ORGANISM	PK variable	PK in general population (healthy)	Alterations in critically ill patients	PD KILL FEATURE / Optimal PK/PD index	Dosing scheme objectives	Standard Dose	Tissue Penetration (tissue/plasma ratio)	Adverse drug reaction
	HYDROPHILIC								
8	VANCOMYCIN (IV) (50% protein bound)	Volume of distribution	Low	Increased (3 rd space) Renal function dependent: Increased (ARC) or Decreased (AKI, ARF, CRF)	Concentration-dependent with time dependence <i>fAUC₂₄/MIC = 200</i>	Maximize the amount of antibiotic exposure	15mg/kg q8h (max. 2 gm)	ISF (0.37X) BONE (0.4-0.57X) LUNG (0.4X) ELF (0.2X)	Nephrotoxic
9	LINEZOLID (IV) (31% protein bound)	Clearance Penetration	Mainly renal Extracellular (Poor cell penetration)	Decreased interstitial penetration	Time-dependent %T > MIC	Maximize duration of exposure-prolonged infusions	0.6 g q12h	MUSCLE (1X) ISF (1X) SUBCUTANEOUS (0.9X) ELF (0.97X) Skin (0.75X) CSF (0.5-0.9X) Bone (0.3-0.7X)	Diarrhea, Decrease WBC count and platelet count
10	DAPTOMYCIN (IV) (90% protein bound)				Concentration-dependent killing <i>fAUC₂₄/MIC = 60-100 for MRSA</i>	Maximize the amount of antibiotic exposure	4-10 mg/kg	BONE (1.2 X) ADIPOSE TISSUE (1.1X) SOFT TISSUE ISF (0.7-0.9X) CSF (.05X)	Insomnia, headache, dizziness

Restricted antimicrobials (IV) used to treat gram negative organism were Polymyxin B, Tigecycline, Ceftazidime avibactam+ Aztreonam, Colistin, Ceftazidime avibactam, Minocycline, and Fosfomycin. As per the hospital antibiogram we are currently dealing with XDR/DTR (Carbapenem resistant *A.baumannii* and *K. Pneumonia*), MDR (*E.coli*, *P.aeruginosa*, MRSA, VRE) and Cephalosporin resistant enterobacteriaceae (*A. baumannii*, *K. Pneumonia*, *E.coli*, *P.aeruginosa*).

According to our hospital antibiogram MDR *E. coli*, XDR Carbapenem resistant *K. Pneumonia*, XDR Carbapenem resistant *A.baumannii* have good susceptibility to Colistin, Tigecycline and Minocycline drugs while MDR *E. coli* has good susceptibility to Fosfomycin also and MDR *P.aeruginosa* has good susceptibility to colistin alone.

In our study we found that Polymyxin B was used maximum as the patients were of high-risk category of Type 3 and Type 4 mostly. It is active drug administered directly. It has less renal clearance so lower urinary concentration. It was used to treat blood stream infections caused by MDR (*E. coli*, *P.aeruginosa*), Carbapenem resistant *A.baumannii* (CRAB) and *K. Pneumonia*. It was preferred over colistin because it has better pharmacokinetic characters and is less nephrotoxic. It was used in combination with Tigecycline and aminoglycoside to which organism has demonstrated susceptible MIC. It is also co-prescribed with high dose carbapenem (if MIC < 8-16 mg/L). Polymyxin B was given in Loading dose of 2.5 mg/kg (1 hour infusion) and maintenance dose of 1.5 mg/kg q12h (1 hour infusion) after 12 hour. No dose adjustment was required for it.^{13,31} Tissue/plasma penetration ratio for lung, skin and heart are given in Table -6.³²

Tigecycline was used to treat intraabdominal infections and skin & soft tissue infections caused by MDR *E. coli* and DTR Carbapenem resistant *A.baumannii* and *K. Pneumonia*. It has been given in combination with colistin or polymyxin B due to its synergistic effects in high-risk patients with carbapenem resistant enterobacteriaceae blood stream infection and Ventilator acquired pneumonia (VAP) / Hospital acquired pneumonia (HAP) CRAB infections in high loading dose of 200 mg followed by maintenance dose of 100mg twice daily which reduces mortality as compared to standard dose. No dose adjustments are required.^{13,24}

Tigecycline have concentration-dependent killing, and the AUC/MIC parameter predicts their efficacy. It causes higher gastrointestinal adverse events (nausea, vomiting and diarrhea) with high dose therapy compared to standard dose.^{19,24}

In Indian scenario, almost all the NDM-producing *E. coli* (>95%) and dual NDM/ OXA-48-like-producing *K. pneumoniae* isolates (at least 60%) are completely resistant to ceftazidime / avibactam. This suggests that ceftazidime/avibactam is a reasonable alternative to standard therapy only for the treatment of infections caused exclusively by OXA-48-like-producing Enterobacteriales.²

Ceftazidime Avibactam was used to treat complicated intra-abdominal infection (cIAI), complicated urinary tract infection (cUTI), HAP/VAP due to MDR gram negative organism (ESBL & Carbapenemase). It was given in recommended dosage of 2/0.5g every 8h by intravenous infusion over 3 hours. Dose adjustment to impaired renal function was done.

The broad spectrum covering along with ESBL producing Enterobacteriaceae and significant proportions of *P. aeruginosa*, makes ceftazidime avibactam a strong component of empiric regimens in patients with risk factors for MDR infections.²⁴ It has good tissue penetration for Bronchial secretions (0.76X) and Abdomen peritoneum (0.35-0.56X) determined by tissue plasma ratio value (X).²³

Combining aztreonam with ceftazidime/avibactam (over 3hour infusion) was used to treat MBL- expressing Enterobacteriales infections with NDM strains commonly seen in India causing cUTI, cIAI, HAP/VAP.^{13,24} There is currently no practical and widely accepted susceptibility testing method available to assess the efficacy of the aztreonam-ceftazidime-avibactam combination in routine diagnosis.¹³

Colistin was used to treat bacteraemia and VAP caused by MDR ((E. coli, P.aeruginosa) and XDR carbapenem resistant K. Pneumonia and A. Baumanii. It was given in Loading dose: 9 MIU (infusion 30min to 1 h) and Maintenance dose: 4.5 MIU q12h after 12 h. The daily maintenance dose was adjusted according to patient creatinine clearance. High CrCL of >80 mL/min decreases the ability to achieving the appropriate steady state colistin levels attributed to a higher amount of colistin cleared by the kidneys, probably causing the necessity of combinations or higher dosing.²⁴

Regarding carbapenem resistant E.coli, carbapenem resistant K.pneumonia, CRAB the combination of colistin with meropenem (if MIC is ≤ 8 mg/L) have resulted significantly in reduction of mortality particularly in patients with septic shock and high mortality score.²⁴

Colistin will continue to be considered as a fundamental companion drug for the treatment of carbapenem-resistant Enterobacteriaceae (particularly in areas where MBL predominate), for the treatment of CRPA (in many cases being the only in vitro active drug) as well as CRAB.²⁴

Minocycline is a wide spectrum antimicrobial used to treat XDR CRAB as a combination therapy with Polymyxins B.

It is metabolized by liver with 76% protein binding and excretion half life of 15 to 23 hours. No need for renal or hepatic dose adjustments. Easy conversion between IV to Oral formulation has increased its clinical use.^{28, 29} The 200-mg i.v. q12h minocycline dosing regimen currently employed was given in clinical practice.¹³

Fosfomycin (IV) was not prescribed in any of the patient as it was regarded as salvage treatment for breakthrough infections in patients already having anti XDR treatment. It is best used in cUTI. It covers the XDR and PDR carbapenem resistant E.coli and K.Pneumonia infections, especially in the presence of colistin resistance or production of metallo- β -lactamases. It has poor protein binding < 5% and half life of 2-3 hours. Doses upto 16-24 g/day have been used in MDR infections. It has in vitro and in vivo evidence of synergy with carbapenems. Monitoring the risk of sodium overload in patient with heart failure and hypokalemia is required.^{13,30}

Restricted antimicrobials (IV) used to treat gram positive organism were Vancomycin, Daptomycin and Linezolid.

Empirical cover for MRSA should be considered if sterility is compromised during insertion of central lines, in MRSA colonizers, in patients with a history of MRSA infections, dialysis patients, carbapenem resistant blood stream infection-related shock, IV drug abuse, and in the presence of MRSA risk factors. Vancomycin or teicoplanin are the drugs of first choice for MRSA. Teicoplanin can be an alternative to vancomycin in cases where vancomycin levels monitoring facility is not available or nephrotoxicity is a concern. Daptomycin or Linezolid may be used as an alternative therapy for MRSA.^{13, 25}

Vancomycin was used to treat brain abscess, meningitis and central nervous system infections in the presence of a shunt. Its level monitoring is recommended in critically sick patients, those with renal dysfunction, serious infections, and those on prolonged therapy. As per new recommendations, calculation of AUC/MIC ratio for vancomycin is desirable instead of the traditional trough concentrations. This is because the trough level guided dosing is associated with higher nephrotoxicity as compared to AUC based dosing. The desirable AUC/MIC ratio is 400–600 and fAUC/MIC >200.^{25, 26} TDM facility for vancomycin is currently not available at our hospital. For patient's allergic / refractory to vancomycin therapy, linezolid was used.

Daptomycin was used to treat severe infections of the skin and soft tissues, and bacteremia. The drug demonstrates concentration-dependent killing that is predicted by AUC/MIC values ≥ 600 and fAUC₂₄/MIC 60-100 for MRSA and maximum plasma concentration (C_{max})/MIC ratios > 100. It was given in dose of 4mg/kg IV q24hr. The plasma protein binding of daptomycin accounts for 80–90%.²³ Table-6

Severe infections of the bone and soft tissues were cured by linezolid due to its high penetration regardless of the severity of sepsis. It promptly diffuses into ELF (0.97X) and skin (0.75X). Linezolid does penetrate the cerebrospinal fluid, where it rapidly achieves tissue/plasma ratios equal to 0.5–0.9X regardless of the meningeal inflammation. Linezolid is a paradigmatic example because it is a hydrophilic antimicrobial with a low plasma protein binding (31%). A target AUC/MIC ratio of 80–120 and a T > MIC value 85% are predictive of linezolid efficacy.¹⁹ Table -6

Newer Diagnostic tests

MALDI-TOF, which allows for fast and accurate identification of pathogens (i.e. 10-30 min) from subcultures, with an antibiogram available at ~24 h. Furthermore, rapid microbiological methods can reduce the duration of inappropriate antibiotic treatment by up to 45% (37.9-52.1%) and provide some cost-saving.¹⁸ More recent development has been rapid T2 magnetic resonance techniques (e.g. T2 Bacteria and T2 Resistance assays), able to detect amplified DNA of the six ESKAPE pathogens and different resistance determinants from whole blood specimens. Such rapid microbiological techniques have profoundly changed the diagnostic approach to infections in critical care and provided a paradigm shift from empirical antimicrobial therapy to quasi targeted therapy.¹⁸

SeptiCyte™ LB, (Immun express, Seattle, WA) has been cleared by the FDA in the United States, for discriminating sepsis from non-infectious systemic inflammation.²⁰

Newer antimicrobials.

CDSCO in past few years has approved Enmetazobactam and Plazomicin to treat gram negative organisms while Dalbavancin, Tedizolid and Levonadifloxacin to treat gram positive organisms.³³

LIMITATION OF THE STUDY

In the study we have excluded the pediatric and neonate patients so in future we wish to conduct similar study with this age group.

CONCLUSION

We found that Type 4 (very high risk) and Type 3 (high risk) patients altogether constituted 91% but 71% patients received restricted antimicrobials empirically and in appropriate doses as prescribed by the ICMR 2022 guidelines to cover the Extensive drug resistance (XDR), Difficult to treat (DTR), Multi drug resistance (MDR) organism prevalent in the hospital ICU. The complex very high-risk critical patients were managed well within timelines with limited rapid microbial diagnostic methods with varied PK/PD index parameters of available limited effective restricted antimicrobials influenced by patients' dynamic pathophysiology changes and expected adverse drug reactions based on patient clinical diagnosis. Highest level of wisdom was implied while choosing the empirical antimicrobial against resistant bugs in correct loading and maintenance doses delivered via prolonged /continuous infusions for dose optimization in order to reduce the patient morbidity and mortality.

Recommendations

Newer rapid microbial diagnostic tests and newer effective and safe antimicrobials are need of the hour to shoot down the resistant hospital bugs and improve the health and survival of the critically ill patients. Continuous antimicrobial stewardship team monitoring is required to ensure judicious use of limited restricted antimicrobials.

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Conflict of interest

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