REVIEW ARTICLE

Antimicrobial Stewardship Program in Critical Care—Need of the Hour

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Abstract

Maximum antibiotic usage within hospitals occurs in critical care areas. Reasons for this usage are the moribund state of patients, invasive devices, and protocol based necessity for empiric antibiotic initiation in most critical conditions. Although unavoidable, prudent use of antibiotics (empiric and therapeutic) should be tailored based on national or if available, unit-based hospital antibiogram. This forms the footstool of every antibiotic policy formulated at tertiary care hospitals. Strict adherence to antibiotic policy formulated based on hospital antibiogram largely benefits patients and hospital-wide antimicrobial stewardship is ensured. The necessity, benefits, key targets, and usefulness of antimicrobial stewardship program (AMSP) in critical care has been elaborated in this review.

Keywords: Antibiotics, Antimicrobial resistance, Antimicrobial stewardship program, Antimicrobials, Critical care, Infections, Resistance.

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Introduction

Antimicrobial stewardship program (AMSP) has gained its reputation due to various national programs and regulatory guidelines released in the recent past. The reason for a robust AMSP is the evolving antimicrobial resistance (AMR) in community as well as hospital levels. The Government of India has recognized AMR as a high priority area since it directly and indirectly influences putting all layers of the population at risk.[1] Although community level antibiotic usage and abuse is maximal, healthcare providers should focus on antibiotic misuse within the hospital as well. The basis of AMSP in hospitals is formed by background data on type, cost, quantity, and duration of antibiotics being used on patients.[2] The same data need to be reviewed after implementation of an AMSP to evaluate effectiveness of the program. Another major challenge is uniformity in antibiotic use within various units of the hospital which should be based on an antibiotic policy. Antibiotic policy is devised based on unit-wise antibiogram generated by microbiology laboratory on a regular basis. It is therefore important to use a customized antibiotic policy for prescribing antibiotics within hospitals, especially in critical care units where maximum use of antibiotics occurs on a daily basis.

Infection Spectrum in Critical Care Units

One encounters a maximum combination of community-acquired and healthcare-associated infections (HAIs) in critical care areas. Factors attributing to this coexistence are long length of stay, comorbidities and complicated health conditions, invasive procedures and devices, moribund state of patients, etc. It is important to delineate community-acquired and healthcare-acquired infections since the causative agents as well as their susceptibility patterns are distinct. A knowledge on the type of microorganisms anticipated help in choice of empiric antibiotics as well as escalation and de-escalation of antibiotics. Table 1 lists the common organisms associated with various community and HAIs from ICUs based on various studies and national reports.

National as well as organization-based guidelines help clinicians initiate empiric antibiotics based on site and source of infection. Organizational antibiotic policies are ideal in making this choice based on susceptibility pattern of prevalent microorganisms in every institution. However, to ensure uniformity and to encourage stewardship, a national syndrome-based antimicrobial treatment guideline was released initially in 2016 and updated the year after. This guideline was framed by collating susceptibilities of various major institutions across the country. The choice of antibiotic for each infection based on this national guideline is listed in Table 2.

Apart from these guideline-based choices of antibiotics, one can use the institutional antibiotic policy based on the local antibiogram. These guidelines and policies help in reducing the risk of evolution of AMR by restricting use of high-end antibiotics. Another major advantage is the promotion of prudent use of antibiotics by junior level doctors and private practitioners.

AMR in Healthcare

A most recent global report by the World Health Organization (WHO) in April 2019 has highlighted the disastrous AMR crisis across the globe. A projected mortality due to multidrug-resistant infections by 2050 is about 10 million every year, compared to the present statistics of 700,000 deaths per year. The projected facts and figures are alarmingly high and calls for urgent interventions to avert

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Table 1: Types of infections in critical care units

Infections	*Commonly attributed microorganisms*
Community-acquired infections[3]	
Community-acquired pneumonia (CAP)[4]	*Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, Enterobacteriaceae.
Urinary tract infection (UTI)	Enterobacteriaceae, *Enterococcus* species, non-fermenting gram-negative bacilli (NFGNB).
Sepsis/bloodstream infections (BSI)	Enterobacteriaceae, *Staphylococcus aureus*, coagulase-negative *Staphylococcus* (CoNS), NFGNB.
Skin and soft tissue infections (SSTI)	*Staphylococcus aureus*, *Streptococcus* species, Enterobacteriaceae, NFGNB, *Candida*, Zygomycetes.
Gastrointestinal infections	Enterobacteriaceae (coliforms), *Enterococcus* sp., anaerobes, *Candida*, NFGNB.
Community-acquired meningitis	*Streptococcus pneumoniae*, *Listeria monocytogenes*, *H. influenzae*, Meningococcus.
Healthcare-associated infections[3]	
Ventilator-associated Pneumonia (VAP)	*E. coli*, *Klebsiella pneumoniae, Pseudomonas aeruginosa, Acinetobacter baumannii.*
Catheter-associated urinary tract infection (CAUTI)	*Pseudomonas aeruginosa, Acinetobacter* sp., Enterococci, *Candida* species.
Central line-related bloodstream infections (CRBSI)	*Staphylococcus aureus, Staphylococcus epidermidis,* Enterobacteriaceae, NFGNB.
Surgical site infections (SSI)	*Staphylococcus aureus*, CoNS, Enterobacteriaceae, Enterococci, NFGNB.
Antibiotic-associated diarrhea	*Clostridioides difficile* (old name: *Clostridium difficile*. Nomenclature changed in 2016)

Table 2: Guideline-based antibiotic recommendation for common infections in intensive care units[3,5]

Infections	*Guideline-based choice of empiric antibiotics*
Community-acquired infections	
Community-acquired pneumonia (CAP)	Ceftriaxone or piperacillin–tazobactam + azithromycin or doxycycline.
Urinary tract infection (UTI)	Cystitis: Nitrofurantoin, cotrimoxazole, ciprofloxacin.
	Acute pyelonephritis: Piperacillin tazobactam, ertapenem.
	Acute prostatitis: Doxycycline, cotrimoxazole, ciprofloxacin.
Sepsis/bloodstream infections (BSI)	Imipenem–cilastatin or meropenem.
Community-acquired meningitis	Cefotaxime/ceftriaxone + ampicillin
Gastrointestinal infections	Enteric fever: Ceftriaxone.
	Biliary tract infections/bacterial peritonitis/intra-abdominal abscess: Piperacillin–tazobactam or cefoperazone–sulbactam or ertapenem.
Skin and soft tissue infections	Cellulitis/abscesses/carbuncles: Cefazolin.
	Necrotizing fasciitis: Piperacillin–tazobactam or cefoperazone–sulbactam + clindamycin.
Hospital-acquired infections	
Ventilator-associated pneumonia (VAP)	Piperacillin–tazobactam or cefoperazone–sulbactam.
	Add colistin if carbapenem resistance is high.
Catheter-associated urinary tract infection (CAUTI)	Piperacillin–tazobactam or cefoperazone–sulbactam.
Central line-related bloodstream infections (CRBSI)	Piperacillin–tazobactam or cefoperazone–sulbactam + vancomycin.
	Add colistin if carbapenem resistance is high.
Surgical site infections (SSI)	Treat based on culture and sensitivity.
Clostridioides difficile-associated diarrhea (CDAD)	Mild to moderate: Metronidazole.
	Severe: Vancomycin + metronidazole.

global threat due to AMR.[6] Emerging drug resistance among various organisms is increasing. Initial reports on emergence and incidence rate of these pathogens in our country are elicited in Table 3.

Inappropriate as well as illicit use of antimicrobials has resulted in this menace of AMR. An ideal antimicrobial prescription should follow the rule of "right drug at the right dose and right time through the right route for the right duration".[14] Antimicrobial resistance develops once this rule is breached along with poor infection control practices resulting in rise and spread of multidrug-resistant bugs. Another major disadvantage of antimicrobial use is the "collateral damage" to normal microbiota in the body. Our gut is loaded with trillions of normal/harmless microorganisms which get altered with every course of antibiotic given to the patient. These normal microbiota have major beneficial effects by various mechanisms, such as (1) secretion of vitamin K and B_{12}, (2) prevent colonization of pathogens by competing attachment sites or for essential nutrients, (3) production of substances which inhibit or kill non-indigenous species (non-specific fatty acids, peroxides, bacteriocins), (4) low levels of antibodies produced against components of the normal flora are known to cross-react

Table 3: Emerging drug-resistant microorganisms[3]

Drug-resistant organisms	*Year reported*	*Incidence rate in India*
Methicillin-resistant *Staphylococcus aureus* (MRSA)	1961[7]	35.7%
Vancomycin intermediate *Staphylococcus aureus* (VISA)	1996[8]	0.1%
Vancomycin-resistant *Staphylococcus aureus* (VRSA)	2002[9]	Few scattered reports
Vancomycin-resistant enterococci (VRE)	1986[10]	8.6%
Extended-spectrum beta-lactamase (ESBL)	1983[11]	*Escherichia coli*: 83% *Klebsiella pneumoniae*: 80%
Carbapenem-resistant Enterobacteriaceae (CRE)	1980[12]	*Escherichia coli*: 18% *Klebsiella pneumoniae*: 35%
Colistin-resistant gram-negative bacilli	2015[13]	Enterobacteriaceae: 1% *Pseudomonas aeruginosa*: 10% *Acinetobacter baumannii*: 22%

with certain related pathogens, and thereby prevent infection or invasion.[15,16] Considering all these benefits of the normal human microbiota, inappropriate antimicrobial use is deleterious to their existence, thereby indirectly affecting normal functioning of the body, cognition, metabolism, etc. Alteration in gut flora and colonization by drug-resistant pathogens result in their multiplication, thereby becoming the major endogenous source of HAIs in hospitalized and critically ill patients.

Prolonged exposure to certain classes of antibiotics paves the way to the development of *Clostridioides difficile*-associated diarrhea (CDAD) and pseudomembranous colitis.[17] Antibiotics frequently causing CDAD are fluoroquinolones, cephalosporins, clindamycin, and penicillins. *Clostridioides difficile*-associated diarrhea is occasionally caused by prolonged use of macrolides, trimethoprim, and sulfonamides; rarely caused by use of aminoglycosides, tetracyclines, chloramphenicol, metronidazole, and vancomycin.[18] Since majority of the commonly used antibiotics may result in CDAD, judicious use is mandatory in order to prevent emergence and spread of *Clostridioides difficile* within a healthcare facility. Need for contact isolation, stringent antibiotics targeting *C. difficile*, and effective hand hygiene are mandatory to combat recalcitrant toxigenic strains of *C. difficile*. Another noteworthy fact is the resistance of *C. difficile* spores to low- and intermediate-level disinfectants. Therefore, cleaning and disinfection practices should be monitored and carried out effectively.

Precisely, the encounter of ESCAPE (*Enterococcus faecium*, *Staphylococcus aureus*, *Clostridioides difficile*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and Enterobacteriaceae) pathogens is common in healthcare facilities especially in ICUs due to prolonged exposure to antibiotics, colonization with these multidrug resistance (MDR) pathogens, and preexisting comorbid conditions.[19] Once these pathogens have been isolated in ICUs, it becomes pretty difficult to thoroughly eliminate them from the environment. Their environmental niches coupled with poor hand hygiene adherence and many other faulty infection control practices facilitate rapid spread of ESCAPE pathogens within ICUs. These drawbacks have pushed to the extent of emergence of pan drug-resistant gram-negative organisms and multidrug-resistant *Candida auris* in the recent past.

AMSP—Need of the Hour?

Antimicrobial stewardship program in India gained its limelight after the famous "Chennai Declaration" of 2012 by Ghafur et al., which was followed by a 5-year plan introduced in 2015.[20,21] Until then, people's awareness on the burden of AMR was negligible and un-prioritized. The crux of this 2015 "Chennai Declaration" was the introduction of a list of 1-, 2-, and 5-year plans to tackle AMR in India. This was a time bound action plan for targeted achievements on a national level by involving various stakeholders, collaborators, organizations, etc. On an institutional level, AMSP involves a team work of infectious disease by consultants, physicians, surgeons, pharmacists, and microbiologists. There was a major need for AMSP implementation since 30–60% of antibiotics are not properly used for the right patient at the right time at the proper dose and duration for the right indication.[22] Though these data are from the western part of the world, it can be extrapolated to being much higher in India.

The first goal of AMSP is to ensure appropriate prescription of antibiotics. The 30% rule described way back in 2007 portrayed that 30% inpatients at any given time to receive antibiotics and about 30% pharmacy costs are due to antibiotic use.[23] These figures are much higher in India and contribute to worse patient outcome and cost. On the contrary, 10–30% pharmacy costs can be cut down by following AMSP which signifies its impact on our country's economy. In India, Schedule H drugs have been identified and circulated with a list of antibiotics under this category. These drugs cannot be purchased over the counter without a doctor's prescription. Another major initiative by the government was to ban illicit combination of antibiotics manufactured and marketed by pharmaceutical companies. These antibiotics cause more harm than good by promoting AMR. Having said the major impacts of AMSP, the practical aspects and hurdles specifically in critical care areas are analyzed.

Antibiotics used for empiric therapy are broad spectrum having coverage for most pathogens one encounters in ICUs. Use of these broad-spectrum antibiotics with inappropriate de-escalation paves the way to emergence of drug-resistant pathogens in ICUs. Therefore, sending appropriate samples for culture before initiating antibiotics play a pivotal role to help de-escalation. Once susceptibility reports are collected, empiric broad-spectrum antibiotics should be de-escalated.[24,25] If there is no evidence of microbial growth or infection, antibiotics should be stopped immediately. Unnecessary use of broad-spectrum antibiotics wipes out the normal intestinal flora and selects resistant organisms to multiply in the gut. This is known as selective antibiotic pressure. Once a patient gets colonized with these drug-resistant bugs, more likely infections with multidrug-resistant organisms are anticipated in these patients. To avoid unnecessary exposure to broad-spectrum antibiotics which lay the foundation to emergence of drug-resistant bugs, antibiotics should be withdrawn when there are no signs of infection.[26] Overt use of antibiotics always cause more harm to the patient than good. The very importance of critical care consultants as antimicrobial stewards comes into play at situations where unnecessary antibiotics should be stopped or de-escalated.

To help clinicians choose the appropriate antibiotics at the right time, national antibiotic prescribing guidelines should be followed. Critical care consultants and other practitioners should be made aware of the latest update in these guidelines made based on emerging resistance. National guidelines are user-friendly and more applicable to Indian scenario compared to western guidelines framed based on AMR patterns of the west. Of course another major drawback of antimicrobial treatment guidelines from the west is that India is a hot bed of AMR and our AMR rates are higher. As one step further, one should be aware of antibiotic policies of their respective hospitals and follow it religiously with the help of infectious disease by consultant or the clinical microbiologist. Active interaction, case discussions, and interdepartmental meets are mandatory to promote judicious use of antibiotics as well as make clinicians understand any new emerging resistance patterns in their units.

Role of Microbiology Laboratory in Critical Care AMSP

One major drawback among antibiotic prescribing clinicians is their inability to distinguish colonization with actual infection. The golden rule "never treat colonizers" is strongly not adhered in ICUs, especially in patients with invasive devices which are mostly colonized with microorganisms. This is where the clinical judgment of clinicians comes into play. Colonization of invasive devices leads to biofilm formation wherein a group of microorganisms bind together and serve as a niche for transmitting AMR genes.[26] Culture of various specimens should not be performed without a definite sign of infection. A lot of interaction before sending specimens as well as releasing any report is therefore mandated. In case culture reports are doubtful, the major role of any microbiology laboratory is to avoid reporting colonizers where treatment has no role.[27] Microbiology labs must strictly and judiciously report only true pathogens taking into account the normal flora encountered with each specimen tested in the laboratory. Quantitative cultures are useful in distinguishing colonization from infection. Specimens collected from respiratory tract, urinary tract, and central line tips are examples of specimens which should be subjected to quantitative culture.[28] Treatment is not warranted if colony counts are insignificant in these specimens.

Another major key to aid AMSP is the selective reporting of antibiotics by the microbiologist. Antimicrobial susceptibility testing and reporting should follow only the Clinical and Laboratory Standards Institute (CLSI) guidelines.[29] Microbiology laboratories should restrain from reporting high-end antibiotics if low-end antibiotics are susceptible. Few examples include avoiding carbapenem reporting for gram-negatives sensitive to cephalosporins, beta-lactam–beta-lactamase inhibitor combinations, fluoroquinolones, etc., avoiding vancomycin, teicoplanin, and linezolid reporting for methicillin susceptible *Staphylococcus aureus*, and avoiding daptomycin reporting for glycopeptide susceptible Enterococci isolates.[30] Another major role of microbiology laboratories is to mention the intrinsic resistance of bacteria to various antibiotics. This helps in appropriate choice of antibiotics by clinicians. Intrinsic resistance plays a pivotal role while selecting empiric antibiotics since the pathogens exhibiting intrinsic resistance will not be targeted if these antibiotics are used. The intrinsic resistances of most bacteria are elicited in Table 4.

A significant boon to the AMSP will be effective use of the local antibiogram for prescribing antibiotics. Antibiogram is a summary of susceptibility patterns of microorganisms isolated in specific locations over a period of time. The CLSI has laid down specific guidelines for preparing an antibiogram, such as:[32,33] (1) Data analysis should be performed annually, once in 6 months or more frequently if the isolates are more, (2) Susceptibilities of at least 30 isolates should be analyzed, (3) Susceptibility should be expressed in percentage, (4) Only the first isolate from a patient should be included irrespective of type of specimen, (5) Colonizers should be excluded, (6) Screening cultures should be excluded [e.g., Methicillin-resistant *Staphylococcus aureus* (MRSA) screening, carbapenemase screening], (7) Antibiogram should be stratified as outpatient, inpatient, and ICU isolates, and (8) Antibiotics that are routinely tested should be included in the antibiogram.[34] Stratification of antibiotic susceptibility data for ICUs is very useful in helping clinicians decide empiric antimicrobial therapy since susceptibility patterns are distinct in ICUs.

WHONET is a free software developed by the WHO for computing details of all isolates with their antibiotic data to derive susceptibilities, resistance trends, etc. It can be customized according to the user needs to include details of specimen type, location, patient identifiers, and common resistance phenotypes. Another major advantage of using this software is the ability to link the software with the hospital's intranet using a software called "BacLink".[35] With the availability of the WHONET software one can customize the antibiograms department/unit-wise, specimen-wise, location-wise, etc. All these updates have progressed the role of microbiological data in implementing and practicing the AMSP. Laboratories even on small scale should move forward to utilize these softwares and databases to bring about an effective change in antibiotic prescribing practices as well as antimicrobial stewardship.

Antibiotics in the Pipeline—Implications and Drawbacks

Whenever a new antibiotic is developed, the most important consideration is to target critical priority pathogens. Reason for this prioritization is the unavailability of antibiotics to treat infections with these bugs due to high rate of resistance. The terms multidrug resistant, extensively drug resistant, and pan drug resistant are important while describing these critical priority pathogens.[36]
MDR: Resistance to three or more antimicrobial classes.
Extensive drug resistance/extreme drug resistance (XDR): Resistance to most tested antimicrobial classes.

Pan drug resistance (PDR): Resistance to all antimicrobial agents.

Top three critical priority bugs according to the 2017 WHO report are carbapenem-resistant *Acinetobacter baumannii*, carbapenem-resistant *Pseudomonas aeruginosa*, and carbapenem-resistant/third-generation cephalosporin-resistant (ESBL) Enterobacteriaceae.[37]

Antibiotics licensed by the Food and Drug Administration (FDA) in the recent past, their indications, and target pathogens are explained in Table 5.

Apart from these antibiotics, few drugs are in phase 1 and phase 2 trials. The availability of these new antibiotics in India as well as the cost is of questionable value. Cost and availability are the major drawbacks of any newly licensed antimicrobial agent. These agents might be effective since they target critical priority pathogens which are frequently encountered in critical care units. However, the ability of these new antibiotics to withstand resistance over time would be a wait and watch phenomenon. Since the available antibiotic reserve is depleted due to misuse and over use, newer

Table 4: Intrinsic resistance of microorganisms to antimicrobial agents[31]

Intrinsic resistance in bacteria and yeast like fungi	
Microorganisms	*Antibiotics/antifungals intrinsically resistant to*
Citrobacter freundii	Ampicillin, amoxicillin–clavulanate, first- and second-generation cephalosporins, cephamycins, and cefuroxime.
Citrobacter diversus	Ampicillin, piperacillin, ticarcillin.
Enterobacter species	Ampicillin, amoxicillin–clavulanate, first- and second-generation cephalosporins, cephamycins, and cefuroxime.
Klebsiella pneumoniae	Ampicillin, ticarcillin.
Morganella morganii	Ampicillin, amoxicillin–clavulanate, first- and second-generation cephalosporins, tigecycline, nitrofurantoin, polymyxin B, and colistin.
Proteus mirabilis	Tetracyclines, tigecycline, nitrofurantoin, polymyxin B, and colistin.
Proteus vulgaris	Ampicillin, first- and second-generation cephalosporins, tetracyclines, tigecycline, nitrofurantoin, polymyxin B, and colistin.
Providencia species	Ampicillin, amoxicillin-clavulanate, first-generation cephalosporins, tetracyclines, tigecycline, nitrofurantoin, polymyxin B, and colistin.
Serratia marcescens	Ampicillin, amoxicillin-clavulanate, first- and second-generation cephalosporins, cephamycins, nitrofurantoin, polymyxin B, and colistin.
Acinetobacter baumannii	Ampicillin, amoxicillin, amoxicillin–clavulanate, aztreonam, ertapenem, trimethoprim, chloramphenicol, fosfomycin.
Pseudomonas aeruginosa	Ampicillin, amoxicillin, amoxicillin–clavulanate, cefotaxime, ceftriaxone, ertapenem, tetracyclines/ tigecycline, trimethoprim, trimethoprim sulfamethoxazole, chloramphenicol.
Burkholderia cepacia	Ampicillin, amoxicillin–clavulanate, cefotaxime, ceftriaxone, cefepime, aztreonam, imipenem, ertapenem, colistin, aminoglycosides, fosfomycin, piperacillin, ticarcillin, piperacillin–tazobactam, trimethoprim.
Stenotrophomonas maltophilia	Ampicillin, amoxicillin–clavulanate, cefotaxime, ceftriaxone, aztreonam, imipenem, meropenem, ertapenem, aminoglycosides, fosfomycin, piperacillin, ticarcillin, piperacillin–tazobactam, trimethoprim.
Salmonella and *Shigella*	Aminoglycosides, first- and second-generation cephalosporins, and cephamycins.
Enterococcus species	Cephalosporins, low-level aminoglycosides, clindamycin, trimethoprim, trimethoprim–sulfamethoxazole, fusidic acid.
Candida krusei and *C. glabrata*	Fluconazole, flucytosine.
C. lusitaniae	Amphotericin B.
C. guilliermondii	Amphotericin B, flucytosine.
C. albicans serotype B	Flucytosine.

antimicrobial agents should be used with caution ideally being prescribed by only clinicians with expertise.

Use of Point-of-Care Tests (POCTS) for Regulating AMSP

"Diagnostic stewardship" forms the base of antibiotic reporting which further affects antibiotic prescription, escalation, de-escalation, etc. The components of diagnostic stewardship are (1) Collection of culture specimens prior to the initiation of antibiotics, (2) Appropriate choice of diagnostic tests for early diagnosis, (3) Avoiding unnecessary sampling for cultures, (4) Critically analyzing culture reports for need to start antibiotics, and (5) Understanding the role of biomarkers for prudent use of antibiotics. Diagnostic stewardship and antimicrobial stewardship therefore go hand in hand. There are limited point-of-care tests available for infectious syndromes therefore using them based on the availability depends on one's clinical judgment. Few common and newer point-of-care devices are described here under.

Procalcitonin (PCT)[43]

Procalcitonin (PCT) is a precursor of calcitonin which elevates in response to bacterial infections. It starts to rise by 4 hours and reaches a peak by 8–24 hours after. Normal value of PCT is <0.5 ng/mL, a level >2 ng/mL suggests high risk of systemic infection and progression to sepsis, whereas a value >10 ng/mL signifies severe sepsis and septic shock. Procalcitonin is more likely to denote gram-negative infection. Procalcitonin plays a remarkable role in monitoring treatment prognosis and as an indicator to de-escalate antibiotics.[44]

Lactate

Lactate is the end product of anaerobic metabolism, the presence of which signifies tissue hypoxia/shock. Serum lactate levels below 1 mg/dL are considered normal. Higher value signifies poor prognosis. Lactate is used as a marker for prognosis in patients with sepsis.[45]

Interleukin 6

Interleukin 6 (IL6), a proinflammatory cytokine is the earliest measurable marker of sepsis which elevates within 2 hours. This is a useful marker to aid in starting empiric antibiotics in patients with suspected sepsis. Interleukin 6 also enhances the production of C reactive protein by the liver. The use IL6 in conjunct with other markers helps in distinguishing bacterial infections from other inflammatory conditions. Once non-infectious etiologies are eliminated, unnecessary use of antibiotics is avoided.[46]

Table 5: Antibiotics recently approved and in developmental phase[38–42]

Newer antimicrobial and class	*Indication*	*Spectrum of action*
Ceftobiprole (cephalosporin)	Community- and hospital-acquired pneumonia	MRSA
Dalbavancin (lipoglycopeptide)	Acute bacterial skin and skin structure infections, community-acquired bacterial pneumonia	Enterococci (VRE), MRSA, VISA, VRSA
Oritavancin (glycopeptide)	Acute bacterial skin and skin structure infections caused by gram-positive bacteria, including MRSA	*Staphylococcus aureus*, MRSA, enterococci, and streptococci
Tedizolid (oxazolidinone)	Acute bacterial skin and skin structure infections, hospital-acquired bacterial pneumonia	Linezolid-resistant staphylococci, enterococci
Ceftolozane + tazobactam (novel cephalosporin + beta-lactamase inhibitor)	Complicated UTIs and intra-abdominal infections, kidney infections, and hospital-acquired bacterial pneumonia	ESBL, *Pseudomonas aeruginosa*
Levofloxacin inhaled aeroquin (fluoroquinolone)	Chronic pulmonary infections in adult patients with cystic fibrosis	*Pseudomonas aeruginosa*
Ceftazidime + avibactam (novel cephalosporin + beta-lactamase inhibitor)	Complicated UTIs and intra-abdominal infections	ESBL, KPCs, *Pseudomonas aeruginosa*
Imipenem — relebactam	Complicated UTIs and intra-abdominal infections, hospital-acquired bacterial pneumonia	ESBL, KPCs, *Pseudomonas aeruginosa*
Meropenem—vaborbactam	Complicated UTIs and intra-abdominal infections, pyelonephritis	ESBL, KPCs, same as meropenem for *Pseudomonas aeruginosa*
Aztreonam—avibactam	Complicated UTIs and intra-abdominal infections, hospital-acquired bacterial pneumonia, bacteremia	ESBL, KPCs, MBL, *Pseudomonas aeruginosa*
Cefiderocol	Complicated UTIs	ESBL, KPCs, MBL, *Pseudomonas aeruginosa*, *A. baumannii*
Phase 3		
Meropenem + novel boronic beta-lactamase inhibitor (carbavance)	Complicated UTIs and intra-abdominal infections, kidney infections, and hospital-acquired bacterial pneumonia, febrile neutropenia, bacteremia	CRE
Delafloxacin (fluoroquinolone)	Acute bacterial skin and skin structure infections, community and hospital-acquired bacterial pneumonia, uncomplicated gonorrhea, complicated UTIs, and intra-abdominal infections	*Pseudomonas aeruginosa* and other gram-negative bacilli
Eravacycline (tetracycline)	Complicated UTIs and intra-abdominal infections, hospital-acquired bacterial pneumonia	ESBL, KPCs, MBL, *A. baumannii*
Plazomicin (aminoglycoside)	Complicated UTIs and intra-abdominal infections, hospital-acquired bacterial pneumonia, hospital-acquired bloodstream infections	ESBL, KPCs, MBL, *Pseudomonas aeruginosa*, *A. baumannii*
Solithromycin (macrolide)	Community-acquired bacterial pneumonia, uncomplicated urogenital gonorrhea, urethritis	Common respiratory gram-positive and fastidious gram-negative pathogens

KPC, *Klebsiella pneumoniae* carbapenemase; MBL, Metallo-beta-lactamase

Immature Platelet Fraction[47]

Immature platelet fraction is a simple to perform analyte which signifies presence of bacterial infection in blood. The value is higher in patients with sepsis therefore making it important for use in critically ill patients. It can be performed as part of complete blood count in automated analyzers. It can therefore be used easily as a marker for escalation and de-escalation of antibiotics.

Presepsin

Presepsin is a pathogen recognition molecule which is present on the surface of inflammatory cells. It is another useful marker of sepsis which can be used in emergency rooms before initiating antibiotics on patients.[48] Presepsin has proved to be a sensitive marker to distinguish bacterial and non-bacterial infections. This would bring about an evolutionary change in use of broad-

spectrum antimicrobials which are more deleterious to evolution of drug-resistant bacteria in the gut. It can be used as a marker for diagnosis as well as follow-up, thereby increasing its value in tailoring antibiotic therapy.[49]

Molecular Techniques

The demand of every clinician is to significantly reduce the turnaround time of diagnostic tests. Microbiological diagnosis has tremendously leaped up in this regard due to the introduction of nucleic acid amplification assays, such as polymerase chain reaction (PCR)-based tests. A common example is the Gene Xpert RIF which has revolutionized the field of diagnostic microbiology. Many other compact systems and hybridization assays are readily available to detect the infectious pathogens directly from clinical specimens without prior processing. These molecular diagnostic tests help in detecting viruses, fungi, bacteria, and parasites, thereby cutting short exposure time to antibiotics in patients with non-bacterial infections. In the recent past, simple cartridge-based multiplex assays to detect multiple number of pathogens in one go within an hour is trending.[50]

Point-of-care devices have revolutionized modern medicine and play a pivotal role in AMSPs across the country. The use of these devices in small sectors as well as in a community level should be encouraged to aid prudent use of antibiotics.

The Way Forward for AMSP in Critical Care

Certain steps to be followed for AMSP implementation and practice in critical care are elicited as follows:[2,3,20,21]

- Avoid using high-end antibiotics by choosing appropriate guideline-based empiric antibiotics.
- Involve an expert opinion team (consultant, ID physician, clinical microbiologist) for suggestions before using high-end antibiotics.[51]
- Antibiotic cycling should be practiced to restore the usefulness of frequently used antibiotics by reducing antibiotic pressure due to over use.[52]
- Procure an exclusive ICU-specific antibiogram, specimen wise if need be to help prescribe antibiotics in ICUs.
- De-escalate antibiotics as soon as culture reports are available. If culture report is negative, all antibiotics should be stopped.
- Making judicious use of point-of-care devices for de-escalation of antibiotics.
- Laboratories should procure and use automated identification and susceptibility systems to reduce turnaround time.
- Using molecular tests for early diagnosis leads to short duration of antibiotic therapy.
- Development of a mobile application for smart phones containing information on antibiotic spectrum of action, antibiogram, and antibiotic policy of the hospital to help junior doctors and consultants to effectively prescribe antibiotics.
- Stringent infection control practices, such as cohort/barrier nursing, hand hygiene, contact isolation for MDR pathogens will help reducing cross transmission of infection between patients in ICUs.
- Screening high-risk patients and screening for colonization before procedures for drug-resistant pathogens, such as MRSA and CRE, can help in anticipating infections with these bugs if the colonized patients develop infection.
- Motivating nurses and allied health staff in ICUs as stewards to monitor infection control practices and hand hygiene compliance.
- Most importantly, continuous on the job training and education to reiterate infection control practices will ensure effective control in spread of multidrug-resistant bugs.

Conclusion

Antibiotics are magic bullets but can have devastating effects if used inappropriately. As the old saying goes "Practice makes a man perfect", antimicrobial stewardship is every individual's responsibility which can be mastered to perfection by putting into practice on a daily basis. Antimicrobial stewardship program directly as well as indirectly influences patient outcome, mortality from HAIs, hospital revenue, economy, productivity, etc. Antimicrobial resistance has already affected millions of lives with added impact on future of healthcare leaving behind a very limited list of antibiotics to choose from. Conserving this limited antibiotic reserve by itself is the next huge task. Using new antibiotics should also be guided by guidelines and used prudently.

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