IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Optimizing Antibiotic Combination Therapy In Critically Ill ICU Patients: A Comprehensive Review

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Abstract:-

The administration of antibiotics is a crucial component of treating severe infections in critically ill patients within the ICU. Combination therapy is frequently employed in clinical practice to enhance the likelihood of effectively eradicating the infection and to mitigate the development of antibiotic resistance. Commonly utilized antibiotic combinations encompass carbapenem + tazobactam, cefotaxime + vancomycin, and meropenem + colistin. Combination therapy finds applications in a diverse range of infections, including sepsis, pneumonia, urinary tract infections (UTIs), skin and soft tissue infections, intra-abdominal infections, and central line-associated bloodstream infections. Nevertheless, it is imperative to acknowledge that combination therapy carries inherent risks, and the selection of antibiotics should be undertaken in close consultation with healthcare professionals.

The practice of combination antibiotic therapy is prevalent in the Indian subcontinent. It's worth noting that combination therapy has its drawbacks, and its unwarranted utilization can exacerbate the already critical issue of antibiotic resistance, which has global implications. The pervasive emergence of multidrug-resistant (MDR) bacterial pathogens presents a formidable challenge of worldwide significance. MDR infections present formidable treatment challenges and are frequently associated with high mortality rates. While it's not uncommon to employ multiple antibiotics to combat such infections, it's important to recognize that scientific evidence does not consistently advocate the use of combination therapy in most cases.

Highlight keywords : Antibiotic, Empirical therapy , Intensive Care Unit (ICU) , Combination therapy , Empirical therapy , Sepsis

Introduction

Antibiotics play a pivotal role in the care of critically ill patients in the Intensive Care Unit (ICU), where timely and appropriate antibiotic therapy can be a life-saving intervention. The prescription of antibiotics in ICU patients is a multifaceted and evolving aspect of medical practice(1,2). It demands a delicate equilibrium between addressing the underlying infection and mitigating the risks associated with antibiotic resistance, adverse effects, and healthcare-associated infections. In this introduction, we offer an overview of the critical factors and considerations that influence the prescription patterns of antibiotics in the ICU, particularly focusing on combination therapy(3–5).

Critically ill patients in the ICU face a heightened susceptibility to infections due to various factors, including invasive procedures, multiple comorbidities, and compromised immune systems(5–7). Consequently, antibiotics are commonly prescribed in the ICU, both for therapeutic and prophylactic purposes. The choice of antibiotics prescribed in ICU patients varies according to the suspected type of infection, the patient's underlying medical conditions, and the local antibiogram. Nevertheless, certain fundamental principles guide this practice(8).

In many cases, antibiotics are initiated empirically in ICU patients, indicating that they are administered before culture results become available. This approach is adopted because early initiation of antibiotics has demonstrated substantial benefits for patients with sepsis. The selection of empirical antibiotics is predicated on the likely site(s) of infection and the most probable pathogens involved. For example, a patient with suspected pneumonia would typically receive a broad-spectrum antibiotic that encompasses both Gram-positive and Gram-negative bacteria, such as a cephalosporin or carbapenem. Combination therapy means using two or more antibiotics with different ways of fighting infections. This is often done to make sure we can effectively treat tough infections and lower the chances of bacteria becoming resistant to the drugs(7,9).

We use combination therapy in severe cases like sepsis or pneumonia when there could be different types of bacteria involved or when there's a high risk of resistance. It's common in the ICU for patients with severe infections or those at risk of drug-resistant bugs.Combination therapy helps by covering a wider range of bacteria, making the treatment stronger, and decreasing the risk of resistance. Some common combos include tazobactam + carbapenem, cefotaxime + vancomycin, and meropenem + colistin(10,11).

It's used for various infections in ICU patients to make sure they get the best care.Sepsis and shock

- Pneumonia
- Urinary tract infections
- Skin and soft tissue infections
- Intra-abdominal infections(8).

Combination therapy, while effective, isn't without its potential downsides. It can raise the chances of adverse effects, including drug interactions and the development of antimicrobial resistance(7,9). However, in critically ill patients dealing with severe infections, the advantages of combination therapy often surpass these risks(12,13).

Empirical combination therapy of antibiotics for Sepsis

Sepsis is a major global healthcare challenge and a significant problem for healthcare practitioners worldwide. It has emerged as a leading cause of death, and its incidence continues to rise, resulting in a substantial burden in terms of increased sickness and mortality, prolonged hospital stays, and an elevated risk of antimicrobial resistance(14).

Combination antibiotic therapy is commonly used to treat severe Gram-negative infections but is a subject of debate and controversy. There are potential benefits to using combinations rather than monotherapy, such as a broader range of antibacterial coverage, potential synergistic effects, and a reduced risk of resistance emerging during treatment(15,16). In the absence of well-established treatment options, combinations are increasingly utilized to enhance the antibacterial impact of available drugs, particularly when dealing with multidrug-resistant strains. However, it's essential to be cautious about overusing combinations, as it can lead to higher risks of toxicity, superinfections, the selection of resistant strains, and increased healthcare costs(17,18).

The purpose of this review is to present and discuss the current knowledge regarding combination therapy for severe infections caused by Gram-negative bacteria(11,19). It also aims to explore the potential of using antibiotic combinations and in vitro studies to address the increasing threat posed by multidrug-resistant Pseudomonas spp., Acinetobacter spp., and Enterobacteriaceae.

When it comes to sepsis, combination therapy involves the use of multiple antibiotics to target a wide spectrum of possible pathogens. The choice of specific antibiotics in the combination can vary based on factors like the suspected source of infection, local patterns of antibiotic resistance, and patient-specific factors such as allergies and renal function. Empiric therapy is initiated before identifying the exact pathogen causing sepsis. The primary objective is to provide broad-spectrum coverage against a diverse range of potential pathogens(20,21).

Common empiric antibiotic combinations may include the following classes of antibiotics:

a. Beta-lactam/Beta-lactamase Inhibitor Combinations:

Example: Piperacillin/Tazobactam (e.g., Tazocin)

The mechanism of action for beta-lactam antibiotics works by blocking the synthesis of bacterial cell walls. Additionally, beta-lactamase inhibitors serve to shield beta-lactam antibiotics from degradation caused by beta-lactamase enzymes produced by certain bacteria. This dual action allows these antibiotics to be effective against a broad range of bacteria, including both gram-negative and, to a certain extent, gram-positive species(17,22,23).

b. Cephalosporins:

Example: Cefepime

Mechanism of action: Cephalosporins are beta-lactam antibiotics that are effective against a broad range of bacteria, including gram-negative organisms(18).

c. Glycopeptides or Lipoglycopeptides:

Example: Vancomycin or Teicoplanin

- After obtaining culture results, it's essential to customize antibiotic therapy according to the identified pathogens and their susceptibility profiles. This approach guarantees precise and efficient treatment.
- Additional Antibiotics Based on Susceptibility:
  In response to culture and sensitivity results, adjustments may be made to the treatment plan, including the addition of more antibiotics or alterations to the existing ones. The selection of antibiotics should be based on the susceptibility of the identified pathogens, as indicated by references(22,24).
- Duration of Therapy:
  The duration of antibiotic therapy for sepsis is not fixed and depends on several factors, including the source of infection, the type of microorganism causing it, the patient's clinical progress, and the presence of any complications. Generally, antibiotics are given for a minimum of 7-10 days, although in specific situations, an extended course may be necessary.
- Monitoring and Dose Adjustment:

Patients with sepsis require close monitoring, including vital signs, laboratory parameters, and clinical response to treatment(22,24).

Dose adjustments may be necessary based on renal function and other patient-specific factors

- De-escalation:

Once culture results become available, and if the patient's condition is stable and improving, a crucial step is to de-escalate therapy. This involves narrowing down the antibiotic coverage to the most effective and specific options to reduce the risk of antibiotic resistance and minimize side effects(25–27).

Collaboration with infectious disease specialists and adherence to local guidelines and hospital protocols for sepsis management are imperative. The selection of antibiotics should always be made in consultation with healthcare professionals, considering the most recent local antibiotic resistance patterns and patient-specific factors(27).

It's important to note that the information provided here is based on knowledge available up to September 2021, and treatment guidelines may have evolved since that time(28).

Empirical combination therapy of antibiotics for Septic shock

Septic shock is a life-threatening condition that arises when sepsis, the body's response to infection, results in critically low blood pressure and cellular metabolism irregularities. Sepsis-3 defines septic shock as a subset of sepsis with severe circulatory, cellular, and metabolic abnormalities associated with higher mortality risk compared to sepsis alone. Clinically, patients with septic shock require vasopressors to maintain a mean arterial

pressure of 65 mm Hg or higher and exhibit serum lactate levels exceeding 2 mmol/L (>18 mg/dL) without hypovolemia. This combination is linked to hospital mortality rates exceeding 40%(29).

In an ICU (Intensive Care Unit) setting, initiating empirical combination antibiotic therapy for shock is a critical and time-sensitive intervention. The selection of antibiotics and combinations should be broad-spectrum to address a wide array of potential pathogens causing the infection leading to septic shock. Below is an elaboration on the approach to empirical combination therapy(30,31).

• Assessment and Stabilization: It's vital to ensure the patient's airway, breathing, and circulation are stable. Immediate resuscitation measures, including the administration of fluids and vasopressors, should be initiated as required to manage shock effectively(31).

• Blood Cultures: Prior to commencing antibiotic treatment, whenever possible, obtain blood cultures from two distinct sites. This is a critical step in identifying the causative pathogens and determining their susceptibility patterns.

• Empirical Antibiotic Therapy: Opt for a combination of antibiotics that has the capacity to address a wide spectrum of bacteria, encompassing both gram-negative and gram-positive species, along with anaerobes. This broad-spectrum coverage is of utmost importance until culture results become available.

Common empirical antibiotic combinations for septic shock in ICU patients may include:

a. Piperacillin/Tazobactam (Tazocin): This combination provides coverage against a broad spectrum of gram-negative and some gram-positive bacteria, along with certain anaerobes(5,31).

b. Cefepime: Effective against a wide range of gram-negative bacteria.

c. Vancomycin: Effective against gram-positive bacteria, including MRSA.

Additional antibiotics may be considered based on the patient's clinical presentation and risk factors. For instance, if the patient has a history of recent healthcare-associated infections, it may be advisable to add empirical coverage for multidrug-resistant organisms(32,33).

- Tailoring Therapy: Once culture results become available (typically within 48-72 hours), antibiotic therapy should be adjusted based on the identified pathogens and their susceptibility profiles(33).

- Duration of Therapy: The duration of antibiotic treatment depends on the source of infection, the causative microorganism, the patient's clinical response, and any complications. Typically, antibiotics are administered for a minimum of 7-10 days, with the possibility of extension as needed(27).

- Monitoring and Dose Adjustment: Continuous monitoring of the patient's clinical condition, vital signs, and laboratory parameters is essential. Adjust antibiotic doses as necessary, taking into account renal function and other patient-specific factors(34).

- De-escalation: If culture results specify a particular pathogen, and the patient is stable, it may be prudent to narrow down antibiotic coverage to precisely target the identified pathogen(32).

- Source Control: Identifying and addressing potential sources of infection is crucial. This may involve surgical interventions, drainage of abscesses, removal of infected devices (such as catheters), or other necessary procedures(34).

- Multidisciplinary Team Collaboration: Effectively managing sepsis and septic shock in the ICU requires collaboration among ICU physicians, infectious disease specialists, and pharmacists to optimize antibiotic therapy and improve patient outcomes(32,34).

Epidemiology therapy of Adult-population Sepsis with antibiotic

Pharmacoepidemiological studies play a crucial role in enhancing the appropriateness and safety of antibiotic therapy for ICU patients with sepsis and shock. By delving into antibiotic utilization patterns, adverse event risk factors, and the efficacy of various antibiotic regimens, healthcare providers can make more informed decisions when treating these patients. Below are specific examples of how pharmacoepidemiological studies have contributed to the improvement of antibiotic therapy in ICU patients with sepsis and shock(13,35).

- Study on Broad-Spectrum Antibiotics: A comprehensive investigation involving over 50,000 ICU patients unveiled that the use of broad-spectrum antibiotics was linked to a heightened risk of adverse drug events (ADEs), including conditions such as Clostridioides difficile infection. This critical discovery prompted the establishment of guidelines advocating the preference for narrower-spectrum antibiotics whenever feasible in ICU patients with sepsis and shock.
- Study on Antibiotic Duration: Another extensive study, encompassing over 100,000 ICU patients, demonstrated that the duration of antibiotic therapy could safely be reduced to a 7-day course in many patients with sepsis and shock. This insight was instrumental in shaping guidelines that endorse shorter antibiotic treatment courses for sepsis and shock in a significant portion of patients(13).Pharmacoepidemiology is a valuable tool for enhancing the appropriate use and safety of antibiotic therapy in ICU patients with sepsis and shock. It involves studying antibiotic utilization patterns, risk factors for adverse drug events (ADEs), and the effectiveness of various antibiotic regimens. This research helps clinicians make well-informed decisions regarding the treatment of these patients(13,36).Sepsis is a significant global health issue and stands as one of the primary causes of illness and death on a global scale, ranking second in worldwide mortality. However, data on sepsis can vary depending on the data source, such as community-based or hospital-based data, and the methods of data collection, which include sources like medical records, discharge diagnoses, or direct observations(13).

To gain a comprehensive understanding of sepsis, prospective, long-term studies involving diverse cases are essential to ensure that findings apply to a broad range of people. It' sworn ting that most of the available sepsis data originates from Western countries, while information from India is comparatively limited(13,37).

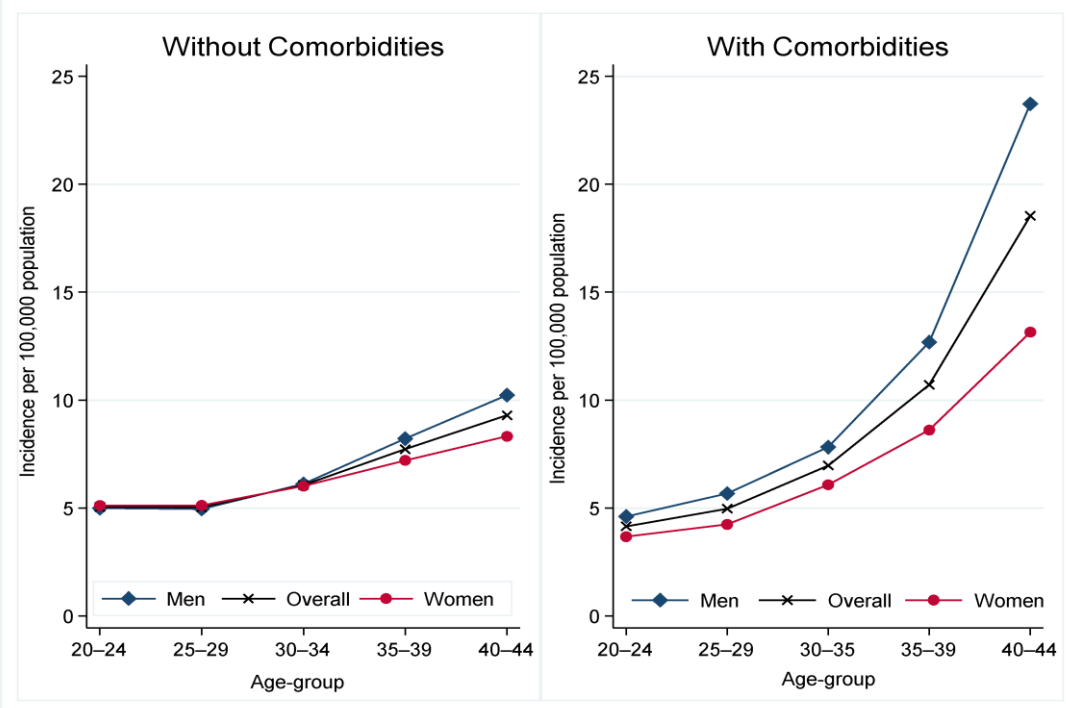

Figure 1:-: Incidence of sepsis according to the presence or absence of comorbidities, and age(38).

The available data often focuses on infections in a broader sense, whether they occur in the community or within hospital settings. What's been lacking is a detailed examination of sepsis, which pertains to how our bodies react to infections(20,37). In India, studies and surveys predominantly center on aspects such as identifying the pathogens responsible for infections, their response to antibiotics, and patient outcomes. There hasn't been as much emphasis on comprehensively understanding sepsis itself(37,38).

To bridge this gap, we sought to gain a deeper understanding of severe sepsis, which refers to infections that have progressed to a very critical stage. Our aim was to determine its prevalence, underlying causes, and the clinical outcomes of patients with severe sepsis in India. This approach allows us to develop a more comprehensive understanding of sepsis in the Indian context and leverage this knowledge to enhance healthcare for individuals affected by sepsis.

• Combination Therapy Of Antibiotics In The ICU Limitations And Challenges

1.Development of Resistance:

Development of Resistance: One of the significant drawbacks of combination antibiotic therapy is the potential for antibiotic resistance development. Using multiple antibiotics concurrently may exert selective pressure on bacteria, which can result in the emergence of resistance to one or both antibiotics. This can foster the growth of multidrug-resistant (MDR) bacteria, subsequently reducing the effectiveness of future treatments(4,13).

2.Increased Risk of Adverse Effects:

Combining multiple antibiotics can heighten the likelihood of adverse effects and drug interactions. Each antibiotic may carry its unique set of side effects, and when employed concurrently, these effects can be amplified, potentially jeopardizing the patient's well-being(38,39).

3.Complex Dosage and Administration:

Overseeing the dosages and administration schedules of multiple antibiotics can present challenges. It demands vigilant monitoring to guarantee that each drug is administered at the appropriate time and dose. Errors in dosing can result in treatment inefficacy or even toxicity(38).

4.Higher Healthcare Costs:

Combination therapy can incur higher costs compared to using a single antibiotic. However, the escalated expenses may not always be warranted, especially when a single effective antibiotic can deliver sufficient treatment(40,41).

5. limited Evidence for Synergy:

While combination therapy is frequently employed with the expectation of achieving a synergistic effect, the scientific evidence supporting such synergy can sometimes be inadequate. In numerous instances, there may be a lack of clear scientific data endorsing the use of particular antibiotic combinations, resulting in uncertainty regarding their effectiveness(19,40).

6.Potential for Overuse:

In certain situations, combination therapy might be prescribed without a distinct clinical justification, leading to the overuse of antibiotics. This overuse can exacerbate the issue of antibiotic resistance, in addition to causing unnecessary healthcare expenses and side effects.

7.Selection of Appropriate Combinations:

Selecting the appropriate combination of antibiotics can pose a challenge. It necessitates a comprehensive understanding of the involved pathogens, their susceptibility to antibiotics, and the patient's clinical condition. Inappropriate combinations may fail to offer any added benefits(38).

8.Complexity of Drug Regimens:

Combination therapy can introduce complex drug regimens, which can make it more challenging for patients to adhere to their treatment plans. This complexity can lead to suboptimal outcomes if patients do not follow their medication schedules as prescribed(42).

9.Limited Availability of Effective Options:

In certain situations, the availability of effective antibiotics for particular infections may be limited, particularly when dealing with multidrug-resistant or extensively drug-resistant pathogens. This limitation can constrain the selection of antibiotics for combination therapy(42).

10.Potential for Allergic Reactions:

Combining multiple antibiotics heightens the risk of allergic reactions. Some patients may be allergic to one or more of the antibiotics used, which can result in severe adverse events(37,42).

Current concepts in combination antibiotic therapy of multi drug resistance for critically ill ICU Patient

One significant obstacle in addressing Antimicrobial Resistance (AMR) is the accurate assessment of the actual impact of resistance, particularly in regions where surveillance is lacking, and data are scarce. While numerous studies have estimated the implications of AMR on infection rates, mortality, hospitalization duration, and healthcare expenditures for specific pathogen-drug combinations in particular locations, as far as our knowledge goes, there are no comprehensive estimates that encompass all regions(43,44). Combination antibiotic therapy is commonly employed in critically ill patients with multidrug-resistant (MDR) infections. However, it's essential to acknowledge that the supporting evidence for this practice is limited, and there is a potential for increased toxicity and the emergence of resistance. The decision to employ combination antibiotic therapy in critically ill patients with Multidrug-Resistant (MDR) infections should be approached on an individual basis, taking into consideration the following factors:

a) The severity of the infection,

b) The suspected pathogen and its susceptibility to antimicrobials,

c) The patient's underlying comorbidities, and

d) The risk of adverse events(44,45)

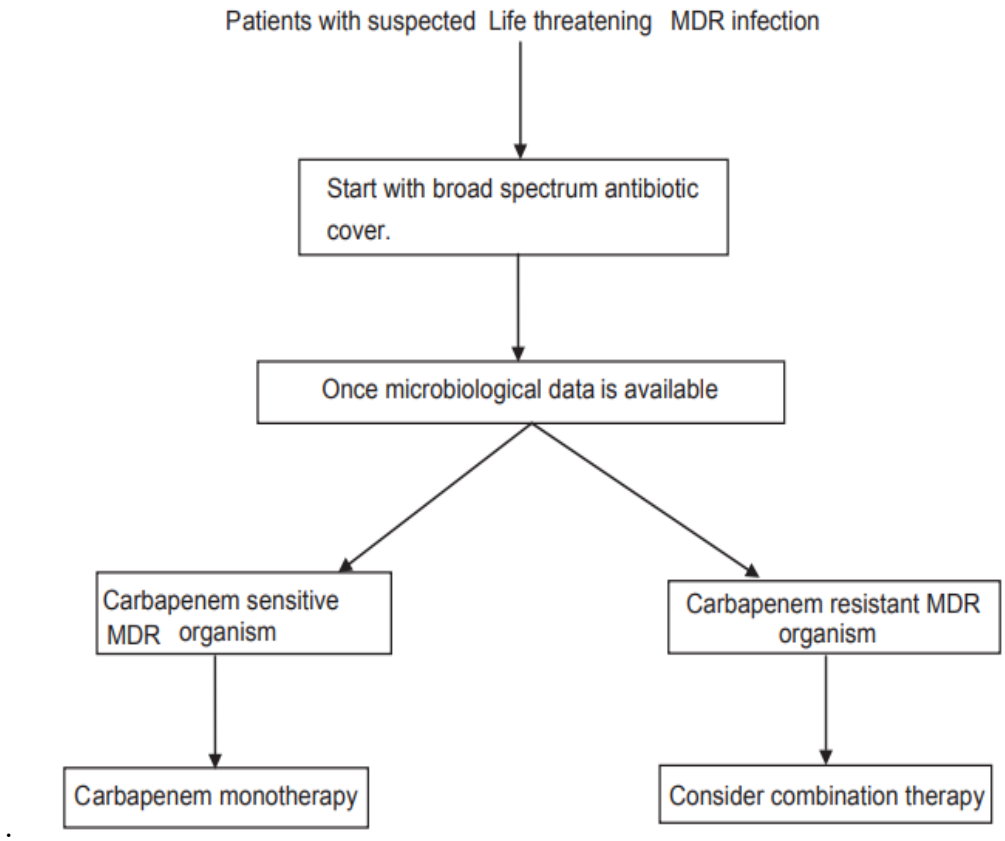

Figure 2:-choosing antibiotic therapy for life threatening infection with MDR pathogen(26).

When opting for combination antibiotic therapy, it is crucial to select agents with distinct mechanisms of action to mitigate the risk of resistance development. Additionally, close monitoring of the patient for any adverse events is imperative, and de-escalation of therapy should be initiated as soon as deemed appropriate. Here are some instances of combination antibiotic regimens that have been utilized to manage MDR infections in critically ill patients.For carbapenem-resistant Enterobacteriaceae (CRE):

  - Meropenem/vaborbactam
  - Imipenem/relebactam
  - Cefiderocol
- For Acinetobacter baumannii:
  - Ceftazidime/avibactam
  - Colistin/tigecycline
  - Colistin/rifampin
- For Pseudomonas aeruginosa:
  - Ceftazidime/avibactam
  - Ceftolozane/tazobactam
  - Piperacillin/tazobactam + amikacin

It's crucial to recognize that the provided examples are merely a subset, and the most suitable combination antibiotic regimen for an individual patient will be contingent on the unique circumstances.

Concept of Combination Therapy: Combination therapy entails the simultaneous use of two or more antibiotics to combat an infection. This approach is frequently employed in critically ill patients grappling with severe infections, like sepsis or pneumonia. The primary objectives of combination therapy are to enhance the effectiveness of treatment and diminish the likelihood of antibiotic resistance development(44,45).

Antibiotic Stewardship Program

Antimicrobial stewardship is defined as the practice of selecting the most appropriate antimicrobial treatment concerning its type, dosage, and duration to achieve the best clinical outcome in infection treatment or prevention. This should be accomplished while minimizing toxicity to the patient and reducing the potential for subsequent resistance(28,44).

Monitoring can be conducted at various levels, including unit, facility, or region. Antimicrobial Stewardship Programs (ASPs) typically utilize diverse data sources, such as electronic health records, laboratory records, and administrative data, to keep track of antibiotic usage and resistance trends. These monitoring data are valuable for recognizing opportunities to enhance antibiotic usage(46–48). For instance, when an ASP observes high rates of antibiotic use for a particular infection type in a specific unit, they can formulate interventions to reduce antibiotic consumption in that unit.

Furthermore, ASPs can employ monitoring data to assess the efficacy of their interventions. For example, if an ASP introduces new antibiotic prescribing guidelines, they can analyze data to determine whether these guidelines lead to reduced antibiotic usage and improved patient outcomes(48).

ASPs have several essential goals:

1. Ensure Appropriate Antimicrobial Use: ASPs aim to collaborate with healthcare professionals to ensure that each patient receives the most suitable antimicrobial treatment, with the correct dose and duration(46,47).
2. Prevent Overuse, Misuse, and Abuse: Another goal is to prevent the overuse, misuse, and abuse of antimicrobial drugs, promoting their judicious and effective use.
3. Minimize Resistance Development: ASPs are dedicated to minimizing the development of antimicrobial resistance, a crucial aspect in combating the emergence of resistant strains of bacteria(48).

Clinical and Microbiological Outcomes of Stewardship Interventions:

Interventions geared toward reducing antibiotic prescriptions have demonstrated positive outcomes. They have been associated with reductions in Clostridium difficile infections as well as decreased colonization and infection rates with aminoglycoside- or cephalosporin-resistant Gram-Negative pathogens, Methicillin-Resistant Staphylococcus Aureus (MRSA), and vancomycin-resistant enterococci. These outcomes underscore the effectiveness of stewardship interventions in improving patient safety and reducing the spread of resistant bacterial strains(6,48,49).

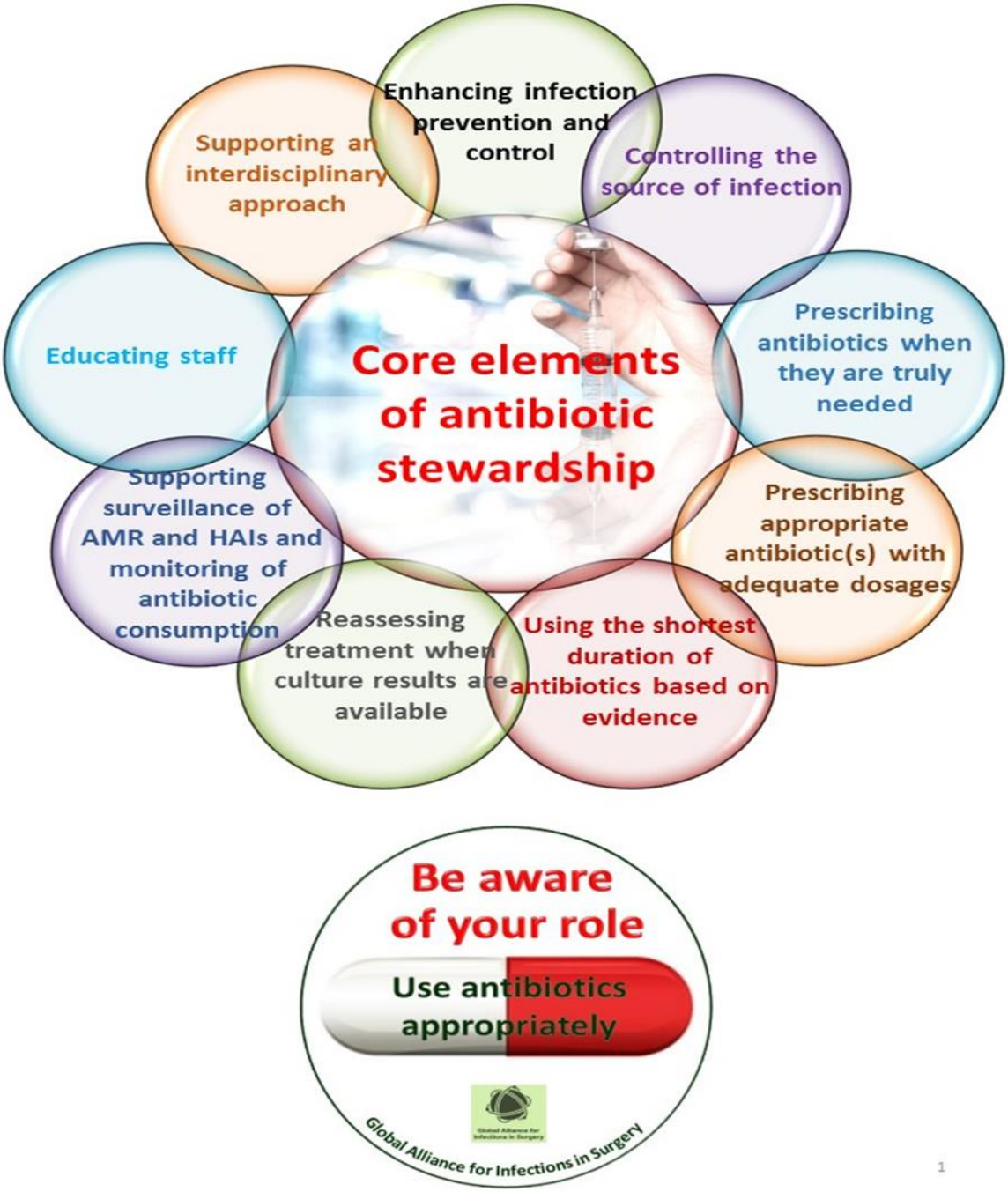

Figure 3:Core element of antibiotic stewardship(5).

Antimicrobial Stewardship Programs (ASPs) employ various monitoring methods to keep a check on antibiotic use and resistance:

1. Antibiotic Use Rates:ASPs can track antibiotic usage rates across different units, facilities, or regions. This data is valuable for identifying units or facilities with high rates of antibiotic use, which might indicate inappropriate antibiotic usage(47).
2. Adherence to Prescribing Guidelines: Monitoring the adherence to antibiotic prescribing guidelines involves reviewing patient records or utilizing electronic health record data. This data aids in identifying areas where healthcare providers may benefit from additional education or support to adhere to prescribing guidelines.
3. Antimicrobial Resistance Rates: ASPs can monitor the rates of antimicrobial resistance by collecting data from the microbiology laboratory. This data helps identify emerging trends in resistance and enables the development of strategies to curtail the spread of resistant pathogens(5,26).

4. Clinical Outcomes: Clinical outcomes, including metrics such as length of hospital stay and mortality, can be monitored by ASPs to assess the impact of antibiotic usage on patient outcomes. This information identifies areas where antibiotic use may be contributing to adverse outcomes.
5. The misuse and overuse of antimicrobial agents pose significant threats, and the rise in antibiotic resistance among hospital-acquired pathogens is predominantly driven by increased antibiotic usage in healthcare settings. Consequently, Antibiotic Stewardship Programs (ASPs) have gained prominence. Antimicrobial stewardship (AMS) encompasses a coordinated set of actions aimed at promoting the responsible and judicious use of antimicrobials(6,8).
6. ASPs are instrumental in optimizing the use of antimicrobial agents, leading to improved patient outcomes, reduced antimicrobial resistance (AMR) and healthcare-associated infections, and cost savings in healthcare. These stewardship programs effectively reduce unnecessary antimicrobial consumption and related expenses(5,10).

Methodology

Data collection: Collect data on antibiotic prescriptions from ICU patients, including the following information:

- Type of infection
- Empirical antibiotic therapy (if any)
- Definitive antibiotic therapy (once culture results are available)(6,50).

Data analysis: Analyse the data to identify trends in antibiotic prescribing, such as:

- The most commonly prescribed antibiotics
- The most common combinations of antibiotics used
- The duration of antibiotic therapy
- Antibiotic Stewardship Program
- The appropriateness of antibiotic prescribing (e.g., adherence to guidelines, de-escalation of therapy).

Guideline Comparison: Evaluate antibiotic prescribing against evidence-based guidelines, such as those provided by organizations like the Infectious Diseases Society of America (IDSA).

Identify Improvement Areas: Recognize opportunities for enhancing antibiotic prescribing, including minimizing the use of broad-spectrum antibiotics, increasing the adoption of narrow-spectrum antibiotics, and promptly de-escalating therapy when appropriate(8).

Conclusion:

Combination therapy in critically ill patients offers several advantages, including broader pathogen coverage, potential synergistic effects, and reduced antibiotic resistance risk. Addressing inappropriate antibiotic-prescribing patterns in ICUs requires improved guidelines, physician and patient education, annual vaccination, and stewardship programs. Regular antimicrobial stewardship interventions in healthcare facilities are recommended to minimize inappropriate antibiotic prescribing and enhance stewardship efforts, thus preventing antibiotic resistance. Enhanced prescription auditing is essential to counter the emerging threat of antibiotic resistance. The decision to use combination therapy in critically ill patients should be based on a case-by-case assessment, considering factors like infection severity, suspected pathogens, comorbidities, and the risk of adverse events. When employing combination therapy, choosing agents with different mechanisms of action is crucial to mitigate resistance risk. Furthermore, close patient monitoring is vital for early detection of adverse events, and de-escalation of therapy should be pursued when appropriate.

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