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A systematic review on de-escalation of antibiotics uses in surgical patients in clinical sepsis

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Abstract

Antimicrobial resistance is a feature of the current topography of clinical sepsis, and in the future, fewer and fewer new antibiotics, especially those from novel classes1, will be developed to address these problems. Effective antimicrobial treatment is necessary to ensuring good patient outcomes. Increased duration of stay, multidrug-resistant infections, and death can result from improper or inefficient use of antibiotics. Patients in intensive care who are critically sick are at risk for antibiotic failure and secondary infections brought on by improper antibiotic usage, especially those with severe sepsis and septic shock. Providers can speed up the treatment of common intensive care unit (ICU) infections by starting active empiric antibiotic therapy based on local susceptibilities, daily review of infection signs and symptoms, and, where practical, restricting antibiotic therapy. Antimicrobial Resistance (AMR) occurs when bacteria, viruses, fungi and parasites change over time and no longer respond to medicines making infections harder to treat and increasing the risk of disease spread, severe illness and death. As a result of drug resistance, antibiotics and other antimicrobial medicines become ineffective and infections become increasingly difficult or impossible to treat. Early detection of septic patients enables the use of evidence-based therapies, including goal-directed resuscitation, rapid antibiotic administration, and activated protein C. It may be simpler to provide appropriate care for sepsis if this clinical entity is divided into several phases and new delivery structures that span traditional boundaries are implemented. More specialized treatments will be possible with a better understanding of the molecular underpinnings of the illness process.

Key words: Antimicrobial; Antimicrobial Resistance; Multi Drug Resistance; Global Action Plan; Antimicrobial Stewardship Programme; Intensive Care Unit; Center for Disease Control; Septic Shock

1. Introduction

1.1. De-escalation

Antimicrobial resistance is a feature of the current topography of clinical sepsis, and in the future, fewer and fewer new antibiotics, especially those from novel classes, will be developed to address these problems. This possibility has led to a shift in emphasis toward making the greatest use of the current antibiotics to enhance their therapeutic impact and durability. Such activities have been reduced into two interconnected major themes, with the new "hit it hard and hit early treatment paradigm for serious sepsis being enmeshed inside the all-encompassing idea of antimicrobial stewardship.

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Antimicrobial de-escalation is a method that enables effective initial antibiotic therapy to be provided, especially in situations of severe sepsis, while avoiding needless antibiotic usage that would encourage the emergence of resistance. Therefore, this definition covers two essential characteristics. First, based on clinical response, findings of the culture, and susceptibilities of the identified pathogens, it is planned to focus antibiotic coverage more narrowly. Secondly, if no infection is detected, antimicrobial therapy will be discontinued.

Benefits of de-escalation therapy include: • Treatment outcomes that are consistent with the traditional therapy strategy of keeping patients on their initially prescribed antibiotics • A positive impact on the institution's antimicrobial resistance profile has been seen through surveillance at both the micro and macro levels; and • A decrease in antibiotic-related adverse events, such as the incidence of Clostridium difficile infection and/or superinfection with w. influenza (1)

Lack of understanding on how to make judgments to de-escalate is one of the characteristics that fosters clinician uncertainty; this permeates to varied degrees each of the scenarios that the health care professional experiences. However, while the relative contributions of the various components vary depending on the various clinical settings, the treatment approach to each scenario is really comparable. The preceding section discussed how clinical risk evaluations may play a role in the decision-making process. Consideration of the patient's clinical development and the information that is accessible for investigations are the other 2 pertinent characteristics.

In the two typical situations where the patient is either improving or not, Figs. 1 and 2 offer algorithms for de-escalation decision-making at roughly day 3 of therapy, when the microbiological data typically first become available. Each of these is based on the presumptions that the patient has received successful therapy, the right empiric antibiotic selection and dose, and that the infection's source has been located and controlled. The clinical evaluation of the patient includes a thorough physical examination in addition to the usual measurements like blood pressure, temperature, pulse, and oxygen saturation.

At every overall examination, it is crucial to take other non-infectious reasons of the patient's illness into account. Evaluation of inflammatory indicators such white blood cell count, C-reactive protein, and procalcitonin as well as the proper use of imaging modalities are further investigations that can provide insight on the decision-making process. A risk evaluation of the perceived gaps in the spectrum of cover and any anticipated prospective foci of infection is balanced against a value judgment when antibiotic medication is increased in the presence of a deteriorating patient with negative microbiological.

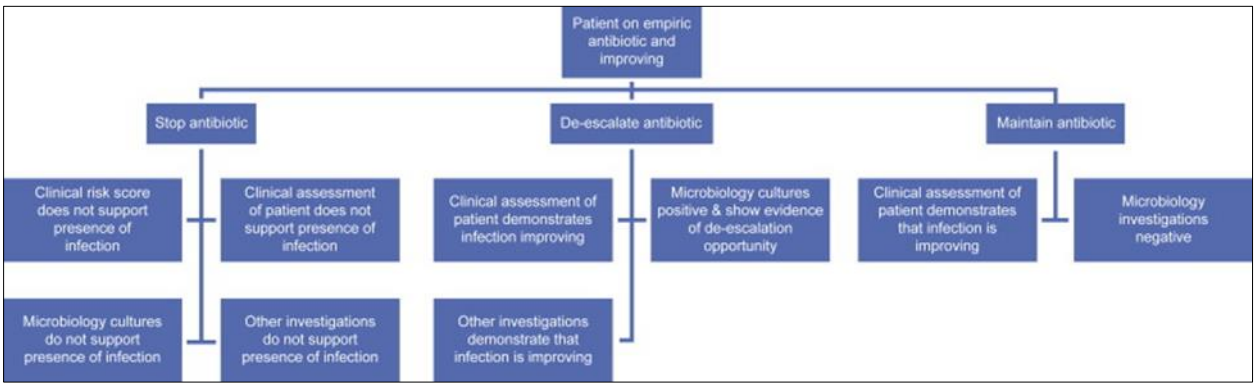

Figure 1 Algorithm for de-escalation decision-making at day 3 in an improving patient

Further de-escalation possibilities must be taken into account after the first day 3 evaluation. The fact that the patient is recovering but that microbiological cultures were negative meant that the initial empiric antibiotics were maintained at day 3 is crucial in this scenario. It will be required to make a decision at a later time on when the therapy can be ended as soon as possible or changed to an oral drug with a narrower scope. This final assessment will be made in light of the clinical response, the most likely cause of sepsis, and any possible infections that need to be considered.(2)

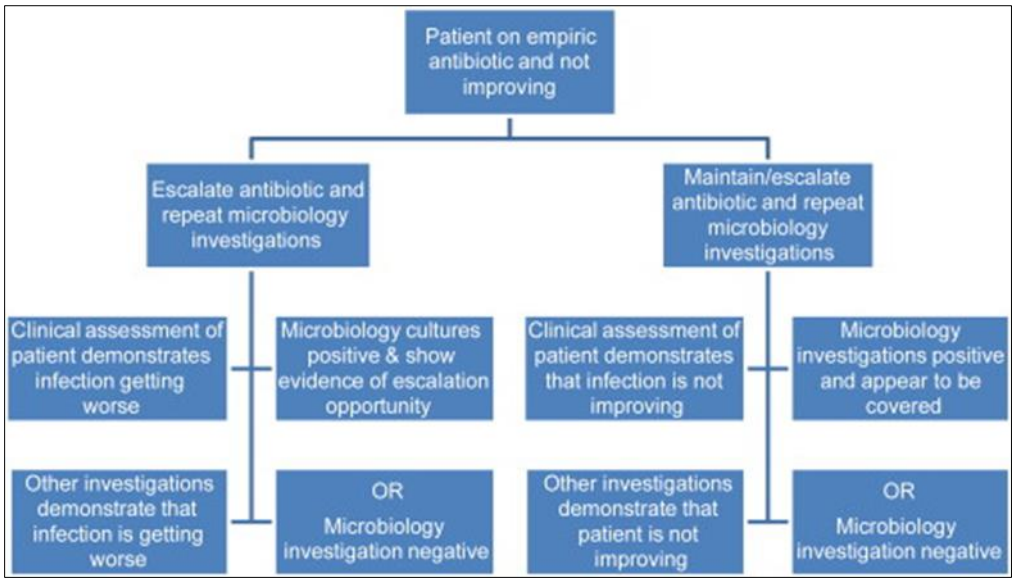

Figure 2 Algorithm for de-escalation decision-making at day 3 in a patient not improving on the empiric antibiotic therapy

1.2. Antimicrobial Stewardship

The efficacy of antimicrobial stewardship initiatives in the ICU has varied. Infectious disease doctors and pharmacists can work together to form stewardship teams that can help evaluate patients and provide suggestions for improving treatment. 2 Different tactics might be used, such as limited formularies, recommendations and therapeutic paths, prospective audit and feedback, and education.

A mix of these activities is frequently what yields the best results. an interdisciplinary approach including specialists in infectious disease, intensive care medicine, pharmacy, and nursing When feasible, trained persons should be used. Guidelines for empiric treatment may be helpful in assisting ICU doctors in selecting an antibiotic. Antibiotic time outs (ATO) have been adopted at several institutions to better assist deescalation and shorten the overall length of antimicrobial therapy.(3,4)

The official procedure of reevaluating antimicrobial therapy 48 to 72 hours after the start of antibiotics is known as a "antibiotic time out," and it is based on a predesigned checklist or notice.Patients obtain shorter periods of medication and have their cost of antibiotics reduced when a proper ATO is put into place. Time outs can be implemented through direct communication, questionnaires distributed in handouts, and electronic prompting. The greatest impact appears to come from face-to-face interactions.

To determine the benefit to patient outcomes and stop adverse occurrences, ATO should be further examined. Reducing the number of days spent on antibiotic therapy and the overall cost of antibiotics is the antimicrobial stewardship initiative that consistently achieves results. More elusive endpoints, such as mortality, length of stay, and reduction in resistance, have yielded conflicting results, according to Campion and Scully, frequently as a result of the short study durations and small patient groups. Accepting ideas and making adjustments in treatment can be difficult. The implementation and maintenance of cultural changes might take time. Interventions in antimicrobial stewardship can help doctors evaluate antibiotic treatment more critically. (5,6,7)

1.3. Clinical sepsis

The pathologic process of infection is brought on by the invasion of typically sterile tissue, fluid, or bodily cavity by germs that are harmful or might become pathogenic The clinical state known as sepsis is characterized by the coexistence of an infection and a systemic inflammatory response. Septic shock is a combination of severe sepsis and a state of acute circulatory failure characterized by persistent arterial hypotension, which is defined as a systolic arterial pressure below 90 mmHg, a mean arterial pressure below 60 mmHg, or a reduction in systolic blood pressure of more than 40 mmHg from baseline, that persists despite adequate volume resuscitation and is unrelated to other conditions. A patient's chance of getting at least one antibiotic now or in the past, as well as any current antimicrobial therapy agent making culture-based infection detection more challenging. The list of sepsis symptoms provided by the 2001 Sepsis

Definitions Conference is a helpful diagnostic aid and should raise suspicion of sepsis when present without any other plausible explanation. None of the symptoms, however, alone can diagnose sepsis. For instance, there are several infectious and non-infectious causes of fever in ICU patients. (8,9)

1.3.1. Some signs of sepsis

- Rashes, fever (sometimes hypothermia)
- Respiratory tachycardia/alkalosis, oedema, and positive fluid balance
- A widespread hematopoietic/inflammatory response
- Higher (sometimes lower) white blood cell count
- Inflammatory markers were elevated (c-reactive protein, procalcitonin, interleukin-6)
- Changes in hemodynamics
- A vascular hypotension
- Unaccounted-for tachycardia
- High svo2, reduced systemic vascular resistance, and increased cardiac output
- Altered skin vascularity
- Reduced urine production
- Unaccounted-for hyperlactataemia and a widened base deficit
- Organ dysfunction symptoms
- Hypoxemia (acute lung damage) (acute lung injury)
- Altered state of mind
- Unaccounted-for change in renal function
- Hyperglycaemia
- Disseminated intravascular coagulation and thrombocytopenia
- Unaccounted-for change in liver function tests (hyperbilirubinaemia)
- An intolerance to food (altered gastrointestinal motility)

Attempts have been made to find a marker of sepsis that could be used to quickly determine or rule out the diagnosis and to follow the course of the disease, similar to how cardiac troponins and creatine kinase are used to diagnose acute myocardial infarction. This is because sepsis is difficult to diagnose and because there is growing awareness of the importance of early resuscitation and therapy on outcomes from severe sepsis. The ideal indicator of infection should be present early in the course of the disease, be easily and quickly measured, be specific enough to distinguish infection from other triggers that may cause a systemic inflammatory response, and be sensitive enough to detect the presence of infection in patients with little to no host response. (10,11,12)

1.4. Management of sepsis

The therapy of the patient with severe sepsis generally consists of four major factors: infection control, individual organ support, basic standard of care, and support for hemodynamics, immunomodulatory treatments, and metabolic and endocrine support. Although the different sections are frequently implemented concurrently in practice, for the sake of clarity, we shall address these four components individually.

1.5. Preventing infection

Two factors are necessary to control infection: removing an infected focus and using the right antimicrobial medication.& Repeated clinical examinations and the available imaging tools must be used to locate any contaminated foci, and where required, they must be removed surgically. When trying to locate a source, it's important to keep in mind the "big five" of sepsis, with the primary focus being on the abdomen, lungs, urine, wounds, and catheters. In the effort to revive the patient with acute sepsis, simple precautions like removing a possibly contaminated catheter shouldn't be overlooked. Proper antibacterial treatment. Prior to beginning antimicrobial medication, all necessary cultures (blood, urine, wound fluid, cerebrospinal fluid, respiratory secretions, ascitic fluid, etc., as needed) should be obtained. Keep in mind, nevertheless, that delaying the commencement of antimicrobial therapy is linked to poorer results. As many as 40% of ICU patients with sepsis lack an isolatable organism, making it challenging to determine the causal microorganism(s) . Based on the suspected source(s) in the patient and local trends of microbial prevalence and antimicrobial resistance, empiric antibiotics should be begun with a spectrum encompassing any potential infectious agents. The selection of an empiric antimicrobial agent is crucial because patients who receive the right antibiotics do better than those who receive antibiotics that are initially ineffective.(13,14)

1.6. Hemodynamic support and stabilization

The fact that hemodynamic resuscitation should begin as soon as feasible is one of its most crucial aspects. Prior to admission to the intensive care unit (ICU), Rivers et al. [17] found that early goal-directed resuscitation (with fluids, transfusions, and vasoactive agents administered in accordance with protocol to achieve a central venous pressure (CVP) of 8-12 mmHg, a mean arterial pressure between 65 and 90 mmHg, and a central venous oxygen saturation of at least 70%) in patients with septic shock was associated with

Basically, there are two main parts to hemodynamic stabilization: giving fluids (including blood) and using vasoactive substances.

- Administration of fluids. Fluid resuscitation can be accomplished with either colloid or crystalloid, or typically a combination of the two, and there is no evidence to recommend one form of fluid over another. The amount of fluid is maybe more significant than the kind. Fluid challenge should be used while doing fluid resuscitation, and fluids by themselves can occasionally be enough to regain hemodynamic stability.
- The type of fluid to administer (such as colloid or crystalloid), the rate of fluid administration (such as 500–1,000 ml over 30 min), the critical end points to be achieved (such as mean arterial pressure >70 mmHg, heart rate 110 beats/min), and the safety limits (such as CVP 15 mmHg) are all things that need to be taken into account when performing a fluid challenge.(15)
- Vasoactive substances. In patients with septic shock, vasopressor medication is frequently required to preserve perfusion and is typically started early, even before hypervolemia has been totally restored. The question of which vasoactive agent is best for patients with severe sepsis and septic shock is still being debated, and since there isn't any reliable data supporting or refuting any particular medication, today's decisions are largely based on personal preference.
- Generally speaking, dopamine and norepinephrine are the first-choice medications, with epinephrine being saved for patients who do not respond to the highest doses of these drugs.(16,17)
- Immune-modulating treatments :only drotrecogin alfa (activated), an immunomodulatory medication, has been shown to enhance outcomes in patients with severe sepsis and a high risk of dying Drotrecogin alfa (activated) is not beneficial in patients with a low risk of mortality or in pediatric patients, according to later trials. The cost and higher risk of bleeding are related with the administration of drotrecogin alfa (activated). The risk/benefit ratio of this medication has divided intensivists since the original Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) trial results, and the topic has sparked a great deal of discussion and contention. Therefore, the most recent Surviving Sepsis Campaign recommendations (18,19,20)
- Support for nutrition: In severely sick patients, nutritional care is crucial. By boosting host response, immunonutrition, which involves supplementing enteral feeds with a variety of immune-stimulating substances such arginine, mRNA, and omega-3 fatty acids, may have positive benefits. The injection of arginine could possibly have poorer effects, as not all clinical research have confirmed this finding [64]. Results are more likely to be improved by supplementing with glutamine. Before making any firm suggestions, further research must be done on the ideal immune-enhanced feed composition for septic patients.(21,22,23)

2. Methodology

2.1. Selection of Antibiotics and Resistance Risk Factors in Critically Ill Patients

To reduce the mortality linked to severe sepsis and septic shock, appropriate empiric treatment is essential. The most prevalent pathogens connected to the known or suspected location of infection, local resistance trends, and any host variables linked to risks of uncommon or resistant infections should all be taken into consideration when selecting an empiric antibiotic prescription.(24,25,26)

It is important to distinguish between empiric therapy and broad-spectrum therapy. Broad-spectrum treatment is described as the use of antibiotics to treat resistant infections such methicillin-resistant Staphylococcus aureus and gram-negative organisms like Pseudomonas spp (MRSA).

Broad-spectrum treatment is not as crucial as antimicrobial treatment that is effective against the most likely infections. Hospitals should decide on preferred empiric treatment plans for particular illnesses, taking into account local, state, and federal regulations as well as regional antimicrobial susceptibilities. It is advised to use an antibiogram made in conjunction with the microbiology lab, updated at least yearly, to report local susceptibilities. Prior to selecting an antibiotic regimen, patient-specific factors should be taken into account. Extended organism coverage may be required

in cases of multiorgan failure, invasive catheters, prior health-care exposure, antibiotic use, and immunosuppression. (27,28).

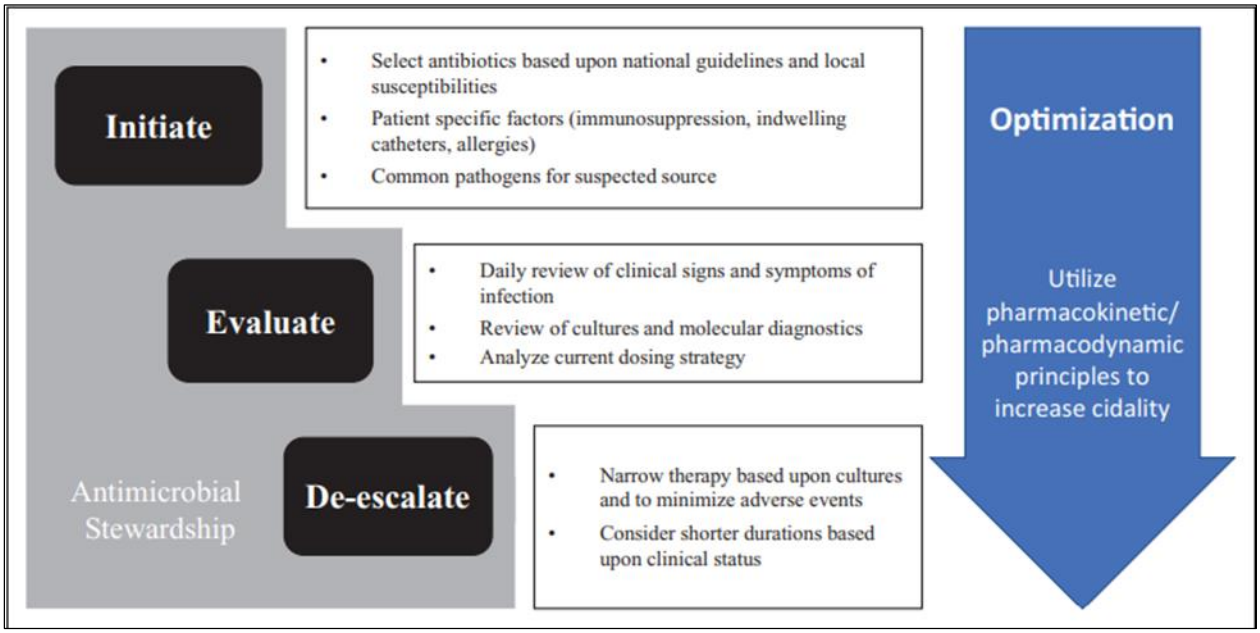

Figure 3 Approach to De-escalate antibiotic use in the intensive care unit (ICU**)**

Sepsis is one of the most frequent causes of ICU admission and is connected to high mortality. 3,8,25 Although implementing a "sepsis bundle" for timely sepsis treatment and prompt administration of antimicrobial therapy has reduced sepsis mortality, it has been found that the selection of an appropriate antibiotic is one of the better indicators of survival. 3,8,13,25,26 If the right pathogens are not covered based on the suspected site of infection, prior antibiotic exposure, and immune-host factors, simply giving broad-spectrum antibiotics is not enough.

The common microbiota of the presumed etiology of sepsis should be the focus of the antimicrobial treatment. Treatment for sepsis with unclear cause must be effective against both gram-positive and gram-negative bacteria. Based on the infection site and the patient's risk factors for resistant gram-negative organisms, such as exposure to healthcare, prior antibiotic use, immunosuppressive therapy, and indwelling catheters, extended gram-negative coverage (e.g., b-lactam/b-lactamase inhibitors with covering pseudomonas, third- and fourth-generation cephalosporins, and carbapenems) should be administered.

Based on the infection location, particular risk factors, previous MRSA infections, and rates of MRSA colonization inside the institution, the necessity for MRSA coverage is assessed.

Inpatient admission histories and earlier cultures can be reviewed to help choose the best empiric treatment.(29,30)

Longer hospital stays or exposure to medical treatment, recent antibiotic usage, and surgical infection are linked to poorer outcomes and nosocomial pathogens for intra-abdominal infections (IAIs). 33 The most typical pathogens, including enteric gramme negatives, should be treated with intra-abdominal empiric medication. Enterobacteraceae resistance patterns should be considered while developing antibiotic regimens. 33 The majority of enterococci and Staphylococcus aureus in intra-abdominal infections are b-lactam sensitive, therefore multi-drug resistance treatment like vancomycin or linezolid may not be required. Treatment regimens should cover gram-positive organisms. The majority of intra-abdominal infections are polymicrobial, and source management is necessary for the best results. 36 Antibiotic therapy might not be necessary in certain situations, such as severe or necrotizing pancreatitis without a known infection or simple diverticulitis. According to recent studies, antibiotic use in these last two cases does not enhance clinical outcomes and should not be routinely practiced. (31,32)

Utilizing antibiotics with diverse modes of action for the empiric treatment of illness will probably become increasingly significant as gram-negative resistance and lower susceptibilities become a bigger problem, especially in areas with increased bacterial resistance. Usually, a b-lactam is used in combination with an aminoglycoside or fluoroquinolone to provide dual gram-negative coverage. When anti-pseudomonal b-lactam medicines show 90% susceptibility for local

isolates, this dual coverage is advised. Comparing b-lactams as monotherapy or with adjunctive fluoroquinolone usage, it has been demonstrated that treatment combining a b-lactam and an aminoglycoside more efficiently provides empiric coverage. To maintain carbapenem action, dual antibiotic treatment is recommended to empiric carbapenem therapy.

2.2. Clinical Assessment Using Lab Diagnostics

Optimal antibiotic therapy and more effective, targeted infection treatment can be facilitated by appropriate culture collection and the use of biomarkers. Molecular diagnostics, procalcitonin, and Gram stain and culture are a few instruments that can bolster the capacity of the clinicians to provide antibiotics. Due to inherent worries about the reproducibility of slide preparation and interpretation, the use of Gram stains in predicting culture findings and guiding therapy is challenging. Due to the Gram stain's limited utility, healthcare personnel have been forced to provide empiric broad-spectrum antibiotic medication for up to 5 days while they wait for the final culture findings using standard procedures.

Despite the limited ability of the Gram stain to forecast pathogenic organisms, providers may find benefit from the Gram stain's negative predictive value. Albert et colleagues assessed the correlation between Gram stain and culture outcomes in endotracheal aspirate and bronchoalveolar lavage in ventilator-associated pneumonia in a multicenter randomized controlled experiment.

In contrast to the absence of gram-negative organisms, which had an 81% negative predictive value in this research, the absence of gram-positive organisms on Gram stain in endotracheal aspirates had a 93% NPV for gram-positive pneumonia.

44 When comparing samples from endotracheal aspirate and bronchoalveolar lavage, there was no difference between the results of the Gram stain and the results of the cultures. Patients treated after trauma who develop ventilator-associated pneumonia have a comparable negative predictive value (Gram-positive NPV: 83%). (33,34)

2.3. Empiric antibiotic

The SSC advises prompt delivery of empiric intravenous antibiotics likely to cover microorganisms responsible for sepsis. It is proposed that a significant amount of is the prompt delivery of antibiotics in a sepsis bundle. In a retrospective research including more than 2000 septic shock patients, Kumar and colleagues27 found that every hour that antibiotics were delayed resulted in a 7.6% reduction in survival. When antibiotics were administered during the first 30 minutes after hypotension, patients had a survival rate of 82.7% compared to 42% if medication was given after 6 hours. Gaieski and colleagues28 conducted a prospective study of 261 patients having EGDT and found that mortality was reduced (19.5% vs 33.2%) when antibiotics were administered within an hour of the patient's arrival at the emergency room.

Table 1 Antimicrobial choices for acute diverticulitis

Severity	Monotherapy	Combination
Low risk	Ampicillin/sulbactam Ticarcillin/clavulanate Cefoxitin Cefotetan Moxifloxacin	Quinolonea 1 metronidazole Cefazolin 1 metronidazole
High risk	Imipenum/cilastatin Meropenum Piperacillin/tazobactam	Aztreonam 1 metronidazole Aminoglycosideb 1 metronidazole Third or fourth generation cephalosporinc 1 metronidazole

Empiric antibiotics that cover enteric gram-negative aerobic and facultative bacilli as well as enteric gram-positive streptococci should be given to patients with IAIs.

Diverticulitis's most often isolated organisms are similar to those seen in other IAis. Escherichia coli and Bacteroides fragilis are the most frequently isolated bacteria, and the majority of patients will have a combination of aerobic and anaerobic bacteria, so antimicrobial treatment should target those germs. Although particular antibiotic regimens are not advised, IAI guidelines have recently been modified. Level 1 data on antibiotic selection is scarce, and expert agreement is frequently used to guide recommendations. But categorising patients as low- or high-risk might aid the practitioner in navigating the rules. Low-risk individuals typically have a few comorbid diseases and a community-

acquired infection when they first visit.On the other hand, high-risk individuals exhibit signs of malnutrition, liver or renal failure, higher APACHE II scores, and infections contracted in a hospital. Both single-agent and combination therapies are indicated for the treatment of complex diverticulitis, with different regimens for low-risk and high-risk patients (Table 1).

The choice of antibiotic will depend on community-specific characteristics such the existence of multidrug-resistant organisms like methicillin-resistant *Staphylococcus aureus*, extended-spectrum b-lactamase-producing Enterobacteriaceae, and pseudomonas. In low-risk individuals, antifungal medication is not advised unless Candida is grown from intra-abdominal cultures. Consideration should be given to the use of antifungals in high-risk individuals on an individual basis. 32 Fluconazole is the preferred antifungal, but therapy with an echinocandin (caspofungin, micafungin, or anidulafungin) is acceptable for patients who have developed resistance to fluconazole or for those who are critically ill. Antimicrobial therapy's ideal duration is still a mystery. Guidelines from the Surgical Infection Society (SIS) and Infectious Diseases Society of America (IDSA)30 advise keeping treatment to 4–7 days unless there is insufficient source control. Patients receiving medication for more than seven days run the risk of toxicities and Clostridium difficile superinfection, with no reduction in treatment failures. Within the first seven days of receiving antibiotics, patients with sufficient source control will display symptoms of infection clearance (afebrile, normal white blood cell counts, and resumement of an oral diet). (35,36,37).

3. Discussion

Antibiotic resistance is a major public health threat worldwide, and the misuse and overuse of antibiotics are contributing factors to this problem. In the context of surgical patients with clinical sepsis, antibiotic de-escalation is a strategy aimed at reducing the duration and spectrum of antibiotic use, while maintaining effective treatment of the infection. A systematic review of the literature on antibiotic de-escalation in surgical patients with clinical sepsis can provide insights into the effectiveness and safety of this strategy. The review can also identify knowledge gaps and guide future research in this area. For high-risk, life-threatening infections, especially those related to clinical sepsis, combination antibiotic treatment enhances survival and clinical response, but it may be harmful for low-risk patients. severe sepsis paradigm and antimicrobial stewardship programmes both place a strong emphasis on de-escalation. The information provided shows that the idea is therapeutically useful. However, the noted gaps in the current data are considerable and grave. These deficiencies include the need to determine the precise effect of de-escalation on the emergence of antibiotic resistance, its true cost-effectiveness profile, and, despite the fact that it has now been amply demonstrated that there are no negative effects for patients, whether it actually improves clinical outcomes.

4. Conclusion

To guarantee the best results for patients in the ICU with clinical sepsis, the treatment of infection through appropriate antibiotic choice, molecular diagnosis, length of therapy, and optimal dose is of the highest significance. Patients with severe sepsis and septic shock require empiric antibiotic therapy to guarantee action against the most likely bacteria while avoiding excessively broad antimicrobial therapy. Coverage with two antibiotics with different modes of action may be required if antipseudomonal b-lactam resistance to local gram-negative bacteria is less than 10% in order to improve empiric antibiotic therapy. When compared to treating with active drugs at the beginning of the antibiotic therapy, escalation is associated with inferior results. The beginning of the regimen. Following the selection of an empiric antibiotic regimen, it is important to continuously assess the clinical condition of the patients and study the test findings to determine whether any adjustments to the antibiotic regimen are required. This is anticipated to result in better treatment results when new molecular techniques for identification and antibiotic susceptibility become more generally accessible. The pressure on antibiotics that can result in resistance is reduced by using the shortest effective course of antibiotic therapy. This also reduces the chance of side effects and can allow the microbiome to be preserved and recovered. The prudent use of our antibiotic regimens may be able to prevent the rise of antibiotic resistance, which jeopardizes our capacity to treat patients.

Compliance with ethical standards

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Disclosure of conflict of interest

I declare that there is no conflict of interest.

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