Reinaldo Salomão[1], Décio Diament[1], Otelo Rigatto[1], Brenda Gomes[1], Eliezer Silva[2], Noêmia Barbosa Carvalho[3], Flavia Ribeiro Machado[4]

Guidelines for the treatment of severe sepsis and septic shock: management of the infectious agent, source control and antimicrobial treatment

Diretrizes para tratamento da sepse grave/choque séptico: abordagem do agente infeccioso - controle do foco infeccioso e tratamento antimicrobiano

1. Sociedade Brasileira de Infectologia – SBI – Brazil.
2. Associação de Medicina Intensiva Brasileira– AMIB – Brazil.
3. Associação Médica Brasileira – AMB – Brazil.
4. Instituto Latino Americano de Sepse – ILAS – Brazil.

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Corresponding author:
Flávia Ribeiro Machado
R. Napoleão de Barros 75 – 5º andar
Zip Code: 04024-900- São Paulo (SP), Brazil.
Phone: +55 (11) 5576-4069
E-mail: fmachado.dcir@epm.br

ABSTRACT

Sepsis is a common and lethal condition that carries a substantial financial burden. In addition, it is the main cause of death in intensive care units. Early diagnosis and treatment of patients has been clearly shown to improve prognosis. Therefore, early diagnosis of the infecting agent, control of the primary infection site and the use of appropriate antibiotic therapy are fundamental to improving outcomes. This guideline reviews the available evidence in the literature concerning infection control and therapy strategies.

INTRODUCTION

The increased mortality observed in severe sepsis and septic shock is clearly related to inappropriate management of the infectious agent. Therapeutic strategies, including antimicrobial therapy, may be substantially different based on the primary site of infection. Source control is a prerequisite for the host's defense mechanisms and the success of antibiotic therapy. Several papers have shown that inappropriate choice of the initial antibiotic regimen may lead to significantly increased mortality rates in septic patients.

Given the evidence available in the medical literature, this article will highlight the main factors related to source control and the main guidelines related to the choice of therapeutic agents.

OBJECTIVES

• To identify the best strategies for identifying infectious agents and to establish appropriate sample collecting techniques;
• To evaluate the effectiveness and safety of infection site management in patients with severe sepsis and septic shock, such as removing catheters, early surgical resection and pleural effusion drainage;
• To review antimicrobial therapy recommendations for septic patients, with respect to indication, early administration, dose tailoring, time of use, role of combined antibiotic therapy and de-escalation.

Description of the evidence collecting method

The Cochrane Library and PubMed databases were searched using the following key words: severe sepsis or septic shock AND culture or hemoculture or uroculture or urine culture or blood culture; severe sepsis or septic shock AND source of infection or focus of infection or surgical

or infection AND control or treatment or therapy or removed; severe sepsis or septic shock AND surgery or operative surgical procedure or operative procedures or surgical procedure or drainage or debridement or necrosectomy or definitive therapy AND early or late or delayed; severe sepsis or septic shock AND pleural effusion or pleural effusions or drainage or drainages or drain; severe sepsis or septic shock AND anti-bacterial or antibacterial or anti-mycobacterial or bactericidal or antibiotics or bactericidal or bactericides or antibacterial AND early or precocious or late or delayed; severe sepsis or septic shock AND monotherapy or broad-spectrum antibiotics or extended-spectrum or empirical therapy or empirical therapies AND anti-bacterial or antibacterial or bactericidal or antimycobacterial or antibiotics or antimicrobial or bactericidal or bactericides; severe sepsis or septic shock AND tailoring or adaptation or adapting or adjustments or adjustment AND dose or dosing or dosage and anti-bacterial or antibacterial or anti-mycobacterial or bactericidal or antibiotics or antibiotic or bactericides; severe sepsis or septic shock AND anti-bacterial or antibacterial or anti-mycobacterial or bactericidal or antibiotics or antibiotic AND maximum tolerated doses or dose escalation or dose-response; severe sepsis or septic shock AND antibacterial or anti-mycobacterial or bactericidal or antibiotics or antibiotic or bactericides or anti-bacterial AND broad-spectrum antibiotics or extended-spectrum or empirical antimicrobial therapy or appropriate antibiotic or escalation therapy or de-escalation or de-escalation or deescalate or adequacy of antimicrobial; severe sepsis or septic shock AND combined or combination or monotherapy or associated or isolated AND anti-bacterial or antibacterial or anti-mycobacterial or bactericidal or antibiotics or antibiotic or bactericides; severe sepsis or septic shock AND anti-bacterial or antibacterial or anti-mycobacterial or bactericidal or antibiotics or antibiotic AND timing or time or treatment course or shortening or short-course or long-course or long term or short term or day or days; severe sepsis or septic shock AND oxacillin-resistant *Staphylococcus aureus* or MRSA or methicillin-resistant *Staphylococcus aureus* AND broad-spectrum antibiotics or extended-spectrum or empirical antimicrobial therapy; sepsis or severe sepsis or septic shock or septicemia AND antifungal agents or agents, antifungal or fungicides, therapeutic or therapeutic fungicides AND broad-spectrum antibiotics or extended-spectrum or empirical antifungal therapy. A total of 61 references were selected.

Quality of evidence and recommendation

A: More consistent experimental or observational trials

B: Less consistent experimental or observational trials

C: Case reports (non-controlled trials)

D: Expert statement lacking critical evaluation, based on consensus, physiology studies or animal models.

1. Is obtaining a new culture for newly diagnosed severe sepsis or septic shock effective in patients already under antibiotic therapy when compared with those who do not obtain a new culture?

The effectiveness of obtaining new culture(s) in severe sepsis or septic shock patients already under antibiotic therapy remains uncertain due to the lack of controlled trials showing differences in prognosis. It is essential that cultures, including blood cultures, are obtained prior to starting antibiotic therapy, as it is indispensable for confirming the infectious agent (**B**),[1] as blood sample sterilization takes place immediately after the initial antibiotic dose (**D**).[2] Another relevant care to be highlighted is in regard to preventing culture contamination. Early blood cultures for the identification of the infective source help configure possible therapeutic strategies (**B**).[3,4]

Recommendation

• Due to the increased morbidity and mortality in patients with severe sepsis and septic shock, blood culture is recommended for all patients with suspected severe sepsis or septic shock, regardless of the infectious source, prior to the initiation of empirical antibiotic therapy. For patients already under antibiotic therapy, cultures should be obtained considering the above mentioned limitations (e.g., the possibility of false-negative results due to previous antibiotic use). Positive cultures may result from the persistence of resistant agents or superinfection.

2. Is it effective and safe to control the site of infection in patients with severe sepsis or septic shock?

Although controlling the infection site frequently means surgery, removal of catheters, prostheses, tubes and foreign bodies is also done to eradicate sites of infection. When signs of infection are detected, initial specific anatomical diagnosis is necessary to decide if an emergent approach to the source is warranted.

The measures used to control possible infection sites should be included in the management plan for all patients with severe sepsis, depending on the source of infection, as illustrated in chart 1. When peripancreatic

necrosis is the suspected source of infection, a surgical approach is recommended, but only after the necrosis is clearly delimited (**A**).[5]

Chart 1 – Recommended source control techniques

Source control techniques	Examples
Drainage	• Intra-abdominal abscess • Chest empyema • Septic arthritis
Surgery	• Pyelonephritis, cholangitis • Infected pancreatic necrosis • Intestinal infarction • Mediastinitis
Removal of access/ device	• Infected vascular catheter • Urinary catheter • Infected intrauterine contraceptive device
Definitive control	• Sigmoid resection for diverticulitis • Cholecystectomy for gangrenous cholecystitis • Amputation for *clostridium* necrosis of the muscle

Adapted from Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Intensive Care Med. 2008;34(1):17-60.[2]

After it is confirmed that source control is required, effective interventions that minimize harm to the patient are recommended. If the vascular access is the suspected source, it should be removed at once, and the patient should be provided with another access site (**D**).[2]

Both the risks and the benefits of any approach should be weighed during the determination of the most appropriate source control method. Several experts have report on the difficulty of conducting controlled clinical trials able to clarify the controversies on this subject. In cases of diffuse peritonitis due to perforated ulcer or clostridial muscle necrosis, source control is indispensable (**D**).[6]

Recommendation

• Source control is recommended in patients with sepsis. The risks and benefits should be weighed in the process of deciding on the best recommended method. These methods include drainage, surgical cleansing, resection or simple removal of accesses or devices. Source control when either the source is an invasive device or a foreign body should occur as soon as possible. For the surgical procedures mentioned in chart 1, an immediate approach is recommended, except for cases of suspected peripancreatic necrosis, where the surgical procedure should be conducted only after the area of necrosis is accurately delimited.

3. In patients with severe sepsis or septic shock, is early surgical removal of the infective source effective and safe when compared with not removing it or removing it later on in the patient's disease course?

The need to control the site of infection is obvious when the site has already been identified. When a surgical approach for managing the infection site is considered, it is not clear what the appropriate timing should be for conducting the procedure. Therefore, source eradication should weigh the risks of the procedure with the patient's clinical status. Of the measures used for source control, abscess drainage, necrotic tissue debridement, removal of infected access and definitive microbial contamination control measures are the most common (**D**).[2]

Necrotizing infections of soft tissues usually require the surgical debridement of devitalized tissues after hemodynamic stabilization is achieved. According to retrospective studies conducted on necrotizing fasciitis, the surgery should be early and aggressive. However, with respect to pancreatitis, a randomized clinical trial favors late debridement (**A**).[5] Better clinical outcomes were achieved when the surgery was postponed for at least 14 days and resulted in a reduction in complications and mortality rates.

For post-surgery intra-abdominal abscess control, percutaneous drainage is recommended over open surgery, as it is less invasive and less expensive, as shown in a retrospective trial (**B**).[7] In this study, no differences in mortality rate were shown when percutaneous and open surgery techniques were compared with regard to the postoperative period for patients with intra-abdominal abscesses, and the procedures were considered to be equivalent to each other.

Determining the optimal time for intervention and removal of the infective focus is difficult and is a decision that should be made with the patient's clinical condition in mind. Clinical trials comparing early and late surgical procedures for each clinical condition are necessary.

Recommendation

• Removal of the site of infection in septic patients should be done early, and the choice of approach (i.e., debridement, drainage or definite control) should be based on the best effectiveness/safety profile. Necrohemorrhagic pancreatitis is an exception, as better results were shown when the surgery was postponed until the area of necrosis was clearly delimited.

4. Is pleural effusion drainage effective and safe in patients with severe sepsis and septic shock when compared with not draining?

The most recent studies on pleural effusion and sepsis occurred in the 1970s and 1980s, and the study designs included only case series and narrative reviews.

In the absence of consistent data concerning whether or not to drain pleural effusions in patients with severe sepsis or septic shock, some guidelines have suggested that effusions above 10 mm should be punctured, and the material should be analyzed, e.g., with Gram staining, leukocyte counts, pH, and protein levels. Intending to synthesize the available therapeutic approaches to the treatment of parapneumonic pleural effusions, experts from the American College of Chest Physicians decided to provide evidence-based guidelines. Therefore, in addition to the establishment of variables that could be predictive of unfavorable outcomes in patients who were not drained early, the experts determined that drainage should be based on a combination of these variables, as shown in chart 2 (**D**).[8]

Chart 2 – Therapeutic approach to parapneumonic pleural effusion

• Pleural effusion < 10 mm is considered small and is not related to complications – do not drain;
• Moderate pleural effusion > 10 mm and < ½ hemithorax, negative Gram staining and culture and pH ≥ 7.2 – do not drain;
• Large pleural effusion, loculated and thick > ½ hemithorax or positive Gram staining/ culture or pH < 7.2 – drain;
• Empyema – drain.

Adapted from Colice GL,Curtis A, Deslauriers J, Heffner J, Light R, Littenberg B, et al. Medical and surgical treatment of parapneumonic effusions: an evidence-based guideline. Chest. 2000;118(4):1158-71.[8]

Recommendation

• Pleural effusion drainage in patients with severe sepsis and septic shock should comply with the clinical criteria for parapneumonic pleural effusion.

5. Are early antibiotics effective and safe when compared with late antibiotics in patients with severe sepsis or septic shock?

As with resuscitation therapy, antibiotic therapy should be started as soon as the septic shock or severe sepsis is identified. Although international guidelines recommend starting antibiotics early, to date, no clinical trial has compared early versus late antimicrobial therapy in septic patients. Therefore, expert opinions from lower evidence level studies should be considered. In a retrospective evaluation of a 2,731 septic patient cohort, the authors found that the survival of septic shock patients was reduced for each hour delay before starting antibiotics. Within the first 6 hours after the patient became hypotensive, there was a 7.6% decrease in survival rates for each hour before effective antibiotic therapy was started (**B**).[9]

An increased mortality rate associated with delayed intervention in these patients attracted the attention of worldwide experts in emergency care and culminated in suggestions and guidelines concerning the planning of antimicrobial therapy, with previous supplement preparation aimed to reduce delays. Another benefit of this finding occurred in regard to planning clinical trials. Of the ongoing trials, one systematic review protocol was currently available in *The Cochrane Library*; it was aimed at evaluating outcomes in early versus late antibiotics regimens in the emergency room among severe sepsis patients, which can render easier decision making on the optimized antimicrobial therapy time (**D**).[10]

Recommendation

• Appropriate and early antimicrobial therapy should be given as soon as severe sepsis or septic shock is diagnosed.

6. Is broad range empirical therapy effective and safe when compared with the absence of this criterion in severe sepsis patients?

Antibiotics are indispensable in the treatment of septic patients (**B**)[9](**D**).[11,12] This therapy remains crucial for these patients' prognosis, as mortality rates were increased in patients receiving inappropriate antibiotic therapy (**B**).[13,14] Clinical practitioners and researchers are even more concerned with the antibiotic choice (**B**).[9] Attempting to cover many potentially responsible organisms, many experts recommend using broad-spectrum therapies (**A**)[15](**B**)[16](**D**).[17] This approach aims to prevent late therapy and inappropriate antibiotics use (**B**).[18,19]

In comparison with monotherapy, antimicrobial associations increase the likelihood of finding susceptible organisms after cultures are available. For this reason, the following criteria should be considered: the underlying disease, the pathogens' susceptibility (e.g., hospital or community), medical history including intolerance to drugs and previous infections. However, it should be considered that one single drug, such as carbapenems, can provide broad-spectrum therapy. In both cases, de-escalation should be considered after identification of the infective agent (**B**)[20](**D**).[21]

Recommendation

• Broad-spectrum empirical therapy should be used for severe sepsis or septic shock patients, aiming to offer the patient the best early antibiotic therapy. When choosing a broad-spectrum therapy, the following criteria should be considered: the primary infective source, the agent's susceptibility according to acquisition (either hospital or community), previous infections and recent antimicrobials use.

7. Are renal dosages of antimicrobials effective and safe when compared to the use of non-renal dosages in severe sepsis or septic shock patients?

The need to control antimicrobial dosages in patients with renal dysfunction is supported primarily by the increased incidence of renal and/or liver failure in severe sepsis or septic shock patients following aggressive volume resuscitation.

The evidence corroborating the positive association between use of antimicrobials and damage to renal function is supported by a controlled and randomized trial that compared two aminoglycoside administration strategies: once daily versus twice daily. In this study, no patient in the group receiving once daily aminoglycosides exhibited renal toxicity, while 15% of patients in the twice daily dosed group exhibited renal toxicity (**A**).[22] The aminoglycoside dosing strategy chosen and the concomitant use of vancomycin were variables associated with increased renal impairment. In addition, other trials have compared the various degrees to which antimicrobials are associated with nephrotoxicity. For example, one study showed that there was increased renal toxicity with gentamycin when compared to amikacin in patients with normal renal function (**B**).[23]

In a randomized clinical trial (cluster), strategies to improve the quality of antibiotic use in lower respiratory tract infections were evaluated (**A**).[24] It was shown that, during the implementation of the guidelines, renal dosing of medication was increased from 79.4% to 95.1% in hospital interventions (OR: 7.32; 95%CI: 2.09-25.7; p=0.02).

To date, no clinical trial has assessed the effectiveness of tailoring antibiotic drug doses according in severe sepsis or septic shock patients.

Given the lack of appropriate studies, some experts recommend giving the complete dose of each antimicrobial and frequently checking serum levels of the drug in critical patients to identify which dose is more effective and poses less of a risk of renal toxicity.

Pharmacokinetic follow-up and dose adjustments are apparently the most effective methods by which to reduce antimicrobial toxicity, primarily in oncology and intensive care unit (ICU) patients (**B**).[25]

Effective antibiotic therapy is crucial in severe infections. Appropriate serum levels are required to achieve effectiveness and concomitantly prevent toxic drug concentrations.

Following the drugs' concentrations may not be feasible in many hospital settings. Thus, the use of blood urea nitrogen and creatinine as possible markers for antimicrobial dose adjustments is a common strategy.

In a review exclusively for databases, the pharmacokinetics and pharmacodynamics of different antibiotic classes were evaluated in studies of critically ill patients (**D**).[26] The authors highlight the characteristics of the antibiotics' microbicidal actions (dependence on concentration, time and concentration/time) and the pharmacokinetic changes in the critically ill patient (changes in distribution volume, protein binding and drug clearance). It is in the setting of these pharmacokinetic and pharmacodynamics variables that a therapeutic regimen should be tailored. The use of renal function measurements can be one of the criteria for tailoring the dose of drugs higher potential to damage the kidneys. In this case, 8, 12 or 24 hour clearance should be used, avoiding the use of formulas for estimating renal function. However, drugs that carry high risk of being nephrotoxic are frequently recommended in their therapeutic ranges.

Given the wide spectra of varying antibiotic classes and the clinical diversity of critically ill patients, in tables 1 and 2, we suggest variables that should be considered in addition to renal function for the individualization of antibiotic therapy.

Recommendation

• The therapeutic regimen should be individualized, with the pharmacodynamics changes seen in critically ill patients taken into account. The use of renal function assessments can be one of the criteria for tailoring the dosage of drugs that is more likely to cause renal dysfunction. In this case, the use of 8, 12 or 24 hour clearance is preferred, and the use of formulas for estimating renal function should be avoided. However, serum levels of some drugs, such as glycopeptides and aminoglycosides, should be used for dosing purposes to improve therapeutic appropriateness while also decreasing the risk of renal damage.

Table 1 – Pharmacokinetics of different antibiotics (hydrophilic and lipophilic) and likely changes in critically ill patients

Antibiotic class	Distribution volume (L/Kg)	Vd increased with fluid changes?	Maximal concentration changes with fluid changes?	Plasma T 1/2 (h)	Protein binding	Changed clearance in critically ill patients?	Therapeutic monitoring required?
Aminoglycosides	0.2 – 0.3 (consistent with extracellular fluid)	Yes	Yes	2 – 3	Low	Variable according to renal function	Yes, to assure appropriate Cmax and clearance
Beta-lactams	Variable, but consistent with extracellular fluid	Yes	Yes	20.5 – 2 except for ceftriaxone 6 - 9 h	Low, except for ceftriaxone and oxacillin	Variable according to renal function (some exceptions)	No
Carbapenems	Variable, but consistent with extracellular fluid	Yes	Yes	1 except for ertapenem 4 h	Low, except for ertapenem	Variable according to renal function	No
Glycopeptides	0.2 – 1.6 Consistent with extracellular fluid	Yes	Yes	4 – 6 vancomycin 80 – 160 teicoplanin	30 a 55% vancomycin 90% teicoplanin	Variable according to renal function; teicoplanin clearance increased with hypoalbuminemia	Yes to assure plasma Cmin > 15 mg/ml
Tigecycline	7 – 10	Unlikely	Unlikely	37 – 66	73 to 79%	May be reduced with cholestasis	No
Clindamycin	0.6 – 1.2	No	Yes	1.5 – 5	65 to 90%	Reduced hepatic clearance	No
Linezolid	0.5 – 0.6	Yes	Yes	3.5 – 7	31%	Pharmacokinetic changes in critically ill patients – likely non-significant	No
Colistin	0.18 – 1.5 (assuming a 60 kg patient)	Likely	Likely	2 – 7.4	Unknown	Variable according to renal function renal	No

Adapted from: Roberts JA, Lipman J. Pharmacokinetic issues for antibiotics in the critically ill patient. Crit Care Med. 2009;37(3):840-51; quiz 859.[26]
Vd – distribution volume; T1/2 – half-life; Cmax – maximal inhibitory concentration; Cmin – minimal inhibitory concentration.

Table 2 – Pharmacokinetics of fluoroquinolones and likely changes in critically ill patients

Fluoroquinolone	Distribution volume (L/Kg)	Vd increased with fluid distribution changes in the critically ill patient?	Cmax reduced with fluid distribution changes in critically ill patients?	Plasma T 1/2 (h)	Protein binding	Clearance changed with renal dysfunction?	Normal dose	Dose adjustment for renal dysfunction?
Ciprofloxacin	1.2 – 2.7	No	Yes	2 (4 – 5 h in elderly patients)	20 to 40%	No	400 mg intravenous 8 h	Yes
Levofloxacin	0.92 – 1.36	No	Yes	6 – 8.9	24 to 38%	Yes	500 – 750 mg daily (eventually increase to 1000 mg daily in sepsis critically ill patients)	CrCL = 20 49 mL/min 250 – 500 mg daily CrCL = 10 19 mL/min 250 – 500 mg 48 h
Moxifloxacin	2.45 – 3.55	No	Yes	9.3 – 15.6	39 to 52%	No	400 mg daily	No
Gatifloxacin	1.98 – 2.31	No	Yes	6.5 – 9.6	20%	Yes	400 mg daily	CrCL ≤ 400 mL/min = 400 mg starting dose, followed by 200 mg Q 24 h

Adapted from: Roberts JA, Lipman J. Pharmacokinetic issues for antibiotics in the critically ill patient. Crit Care Med. 2009;37(3):840-51; quiz 859.[26]
Vd – distribution volume; T1/2 – half-life; Cmax – maximal inhibitory concentration; CrCL – creatinine clearance.

8. Is the maximal antimicrobial dose effective and safe when compared with lower doses in severe sepsis and septic shock patients?

In a prospective cohort study of 25 ICUs, adult patients with severe sepsis and septic shock who were infected with Gram-positive bacteria were followed (**B**).[27] These patients were given continuous infusions of vancomycin with the goal of measuring the end-of-therapy serum antibiotic level. Although the patients received high doses vancomycin, the drug concentration was found to decrease as the patient's clinical status worsened; the opposite was found when the patient's condition began improving.

In a Phase II clinical trial, 274 patients with severe sepsis were randomized to receive either 1 g or 2 g of cefpirome (**B**).[28] Clinical and bacteriological response rates were not significantly different between the groups; 18 drug-related adverse events resulted in 2 cases of drug withdrawal in each group; 14 adverse events were local (5 in the 1 g group and 9 in the 2 g group). The drug was well tolerated in patients with severe sepsis for both the 1 g and 2 g twice daily dosages.

The decision to give maximal antimicrobial doses in severe sepsis and septic shock patients may be based on the pathophysiological hypothesis for the patients' septic condition, which culminates in increased renal preload.

Therefore, many infectious disease experts worldwide suggest giving maximal doses to treat these medical conditions. With respect to the optimization of antibiotic regimens in critically ill patients, Roberts and Lipman (**D**),[26] emphasize that the different associated antibiotic classes and pharmacokinetics should be considered.

Of note, the microbicidal actions of antimicrobials are dependent on different characteristics, which are based on the class of the medication. Therefore, the best activity may be achieved using the ratio of the maximal antimicrobial concentration (Cmax)/minimal inhibitory concentration (MIC), as seen for aminoglycosides; by antibiotic concentration above the MIC (time-dependent), as is the case with β-lactams; and a concentration and time combination, measured as the area under the concentrations curve above the MIC, as for fluoroquinolones.

Recommendation

• The use of maximal antimicrobial doses aims to achieve serum and tissue levels that are effective for infection control. However, the choice of antimicrobial dosage should be based on the different classes of antibiotics and their pharmacokinetic features. Based

on these characteristics, for instance, a single daily dose of aminoglycosides and continuous β-lactam infusion could be used.

9. Is antibiotic de-escalation effective and safe in comparison with non-de-escalating regimens in severe sepsis and septic shock patients?

Early broad-spectrum antibiotic therapy in septic patients is strongly recommended by clinical trials, as the risk of death increases with delays in antibiotic administration and inappropriate use (**B**).[13,29,30] Concomitantly, the prevalence of adverse events associated with this therapy is also high (**D**).[31] Therefore, several investigators in this field have sought to find a strategy able to reduce the overuse of this intervention.

De-escalation or discontinuation of therapy is a medical approach wherein broad-spectrum antibiotics are initially administered to patients with severe infections. After culture results become available, the antibiotic regimen may be reduced based on the susceptibility of the identified pathogens, limiting unnecessary exposure to antibiotics, drug resistance and nephrotoxicity (**D**).[32]

This approach is described in the literature for ventilator-associated pneumonia (**D**),[33-35] where the mortality rate was lower in de-escalated patients when compared with patients who were kept on broad-spectrum empirical therapy (**D**).[32]

Therefore, given that septic patients with pulmonary infections are representative of septic patients in the intensive care unit, this strategy is suggested in severe sepsis and septic shock patients.

This concern is shown on sepsis guidelines and updates as a suggestion rather than a therapeutic recommendation. This is expected to encourage investigators to monitor this issue by conducting randomized clinical trials.

Recommendation

• Antimicrobial de-escalation should be conducted in severe sepsis and septic shock patients after the causative agent's susceptibility tests become available or after clinical improvement; this will prevent a higher incidence of adverse events and resistance to broad-spectrum therapy.

10. Is combined antibiotic therapy effective and safe for an already identified specific agent when compared with monotherapy?

When the causative agent is identified, the antimicrobial therapy is presumed to be more effective. However, the options for using either a combination of agents or a single agent are debatable in septic patients. Therefore, finding trials on the effectiveness and safety of these interventions is important for electing the best strategy.

As a result, clear and careful methods were established in a systematic review comparing β-lactams alone (monotherapy) and β-lactams combined with aminoglycosides in septic patients (**A**).[36] Evaluating the outcome 'nephrotoxicity' in 45 studies that included 5,213 patients, the authors found that this outcome was significantly less frequent in the monotherapy group (2%) compared with the combined therapy group (9%) (RR: 0.30; 95%CI: 0.23, 0.39; DR: -7%; NNT: 14). Twenty of the 64 included studies used the same β-lactam for both study arms. In these trials, no significant inter-group difference was found (RR 1.02; 95%CI 0.76-1.38) for the outcome 'all-cause mortality'. However, treatment failure was more frequent in the monotherapy group, and in the subgroup analysis, this difference was statistically significant.

In studies comparing different β-lactams, both treatment failure and mortality were more frequent in the combined therapy group. The outcome 'failure' was highly significant, while for 'mortality,' significance was only achieved in subgroup analysis.

These studies show the advantages of using broad-spectrum β-lactams as a monotherapy when compared with more restricted spectrum β-lactams combined with aminoglycosides, although achieving similar in vitro pathogen coverage.

Although retrospective trials are less valuable in answering this question, when 183 episodes of *P. aeruginosa* ventilator-associated pneumonias were analyzed, the antibiotic appropriateness rate was significantly higher in the combined therapy group (105 of 116; 90.5%) when compared with the initial empirical monotherapy group (38 of 67; 56.7%) (p<0001) (**B**).[14] The authors concluded that initial combined therapy reduced the risk of inappropriate therapy, which was associated with increased mortality. However, administration of a single effective antibiotic or an effective combined therapy resulted in similar favorable outcomes, suggesting that the change to monotherapy after the causative agent and respective susceptibility profiles are identified is both effective and safe.

One of the reasons for controversies involving these findings may include the diversity of antimicrobial spectra of drugs used as a monotherapy.

Recommendation

• Monotherapy with broad-spectrum β-lactams may be a better option than more restrictive spectra β-lactams combined with aminoglycosides.

11. How long should the antibiotic therapy ideally last for severe sepsis or septic shock patients?

Determining the ideal time to administer antibiotics is needed to balance the use of an effective therapy versus its excessive use, in addition to reducing the risks of adverse events frequently associated with antibiotics.

To this end, inflammatory markers have been used in an attempt to identify the ideal duration of intervention in this population. A clinical trial was conducted to evaluate whether algorithms based on serum procalcitonin could shorten antibiotic administration times in severe sepsis and septic shock patients (**A**).[37] The mean antibiotic time for procalcitonin-guided therapy patients (n=39) was 6.5 days, in comparison with 9.5 days for the control group (n=40). The authors reported that no differences were observed with regard to mortality and recurrence of infection and reported a difference only for ICU lengths of stay, which were shorter for the procalcitonin-guided therapy group (p=0.03). Although this was a randomized trial, it was not specifically designed to evaluate the question of the appropriate duration of antibiotic therapy in severe sepsis or septic patients.

In a systematic review, the ideal antibiotic therapy duration was evaluated in 15 trials, which included 1,644 elderly women with lower urinary tract infections (**A**).[38]

No difference was reported for antibiotic therapy effectiveness between short- (3 to 6 days) and long-term therapy (7 to 14 days). Prolonged antibiotic therapy, however, may be associated with more adverse events. This evidence suggests that the optimal treatment of elderly women with lower urinary tract infections should be between 3 and 6 days.

In a published protocol, the authors report that they are planning to gather evidence of randomized clinical trials comparing 8 or fewer days with 8 or more days of antibiotic therapy in critically ill adults with hospital pneumonia; however, the data are not yet available (**D**).[39]

In patients with ventilator-associated pneumonia randomized to an antibiotic discontinuation strategy (mean time = 6.0 ± 4.9 days) or conventional therapy (mean time = 8.0 ± 5.6 days), no significant intergroup differences were found for mortality and ICU length of stay (**A**).[40]

These findings corroborate the Surviving Sepsis Campaign recommendations to reduce the antibiotic spectrum and the time to between 7 and 10 days, which could contribute to a reduction in bacterial superinfection and/or resistance. Source control and medical variables should always be taken into account when determining the duration of antibiotic therapy.

Recommendation

• The optimal antibiotics administration time is based on the need to optimize effectiveness while preventing the excessive use of antibiotics and their associated side effects. Although the above mentioned studies were not focused on severe sepsis and septic shock patients, they indicate that shorter therapy times may be safer for this population when appropriately guided by the clinical conditions.

12. Is empirical therapy for oxacillin-resistant *Staphylococcus aureus* effective and safe when compared to not using this criterion in septic patients?

Methicillin resistance has become a common issue in several institutions (**D**).[41] In a retrospective 4-year analysis to identify the epidemiological profile and susceptibility of 286 culture samples collected, 52.94% contained strains of methicillin-resistant *Staphylococcus aureus* (MRSA) (**B**).[42] The observed incidence of positive cultures for MRSA for two years in eastern France was 0.04 per 1,000 patients/day (**B**).[43] In Brazil, the findings of a prospective cohort study that included 1,031 patients has shown that MRSA strains are responsible for 95% of invasive device-associated staphylococcal infections in 5 ICUs at 3 hospitals (**B**).[44]

Another retrospective study from a Korean hospital emergency department included 231 cases of *Staphylococcus aureus* bacteremia. Of these, 27.3% were methicillin-resistant *Staphylococcus aureus* (**B**).[45] In this study, the mortality rate was 22%, with a mortality rate of 30.2% for MRSA patients and 19.6% for patients with antibiotic sensitive pathogens (p=0.088). In isolates of MRSA bacteremia, 81% were resistant to at least 3 antimicrobials. All MRSA isolates (63) were sensitive to vancomycin. From patients with MRSA isolates, 47.6% were started on β-lactams. The following variables were identified as risk factors for resistance: advanced age, presence of a catheter, previous hospital admission, history of surgery, and broad-spectrum antimicrobial therapy (**B**).[45-47]

In Spain, the incidence and mortality from *S. aureus* bacteremia were also high. Of 213 cases, 61% involved

MRSA; the mortality rate for MRSA bacteremia was 42.7%. For antibiotic-sensitive bacteria, however, the mortality was 16% (**B**).[48] In this study, the authors suggest that clinicians consider the cost, disease severity, and infective source, among other things, to determine whether to initiate therapy with vancomycin or other glycopeptides.

Given the high incidence of MRSA skin infections, they recommended changing empirical antimicrobial therapy to cover MRSA (**B**).[49]

Recommendation

• The prevalence of MRSA in the considered hospital should be taken into account. In sites with a high incidence of multi-resistant and oxacillin-resistant *Staphylococcus aureus*, empirical therapy of these infections should not include β-lactams. The choice could include glycopeptides or oxazolidinones, considering the selective pressure induced by these drugs.

13. Is empirical therapy for fungal infections effective and safe when compared to not using an agent that covers fungal infections in septic patients?

The growing incidence of fungal infections, mainly *Candida spp*. and *Aspergillus spp*., has been shown in epidemiological studies involving hospitals and their intensive care units, particularly in transplanted patients (**B**)[50,51](**D**).[52-54] This is reflected in the inclusion of antifungal therapy in empirical therapy regimens. The risk factors for fungal infections are numerous and include the use of broad-spectrum antimicrobial drugs, steroids, early or advanced ages, chemotherapy, malignant diseases, the use of catheters, organ transplantation, disease severity, renal failure, hospital length of stay and mechanical ventilation (**D**).[55]

A Brazilian multicenter epidemiological study observed 712 cases of fungemia (defined as isolation of *Candida spp.* from blood cultures), which corresponded to an incidence rate of 2.49 cases per 1,000 admissions and 0.37 per 1,000 patients/day (**B**).[56] The mortality rate was 54%, with mortality being more common for the following species: *C. albicans* (40.9%), *C. tropicalis* (20.9%) and *C. parapsilosis* (20.5%).

Overall, reduced fluconazole susceptibility was found for 33 (5%) of the isolates. The high susceptibility of *Candida* species to fluconazole found in the blood cultures of this study, in association with the low cost and toxicity of fluconazole, may support the selection of this antifungal agent.

Given the available epidemiological data, it is wise to consider the early use of antifungal agents with the aim of controlling fungal infections and reducing mortality rates (**B**).[56-58]

After reviewing the literature for invasive fungal infections in adult patients, infectious disease experts, clinical microbiologists and hospital epidemiologists from 5 Swiss university hospitals proposed guidelines. This study evaluated empirical therapy for patients infected with *Candida* prior to species identification. When choosing the antifungal agent, the presence (or absence) of neutropenia, severe sepsis or septic shock and recent exposure to azole drugs should be considered.

In severe sepsis and septic shock patients, caspofungin has been suggested as the first choice drug, and liposomal amphotericin B and voriconazole (in patients not previously exposed to azoles) have been suggested as alternative drugs, (**B**)[56](**D**).[59] A similar approach was recommended by the Infectious Diseases Society of America in a recent review of their guidelines for the treatment of candidiasis (**D**).[60] The expert panel recommendations are as follows:

• For non-neutropenic patients with candidemia: a fluconazole [800 mg (12 mg/kg of body weight) loading dose followed by 400 mg (6 mg/kg) daily or an echinocandin (caspofungin: 70 mg loading dose; followed by 50 mg daily or anidulafungin: 200 mg loading dose followed by 100 mg daily) as initial therapy for most patients. The experts considered echinocandins as the best option for *Candida glabrata* infections and fluconazole for *C. parapsilosis*. Conventional (0.5-1.0 mg/kg daily) or lipid (3-5 mg/kg daily) amphotericin B formulations are considered good options when toxicity to other drugs is confirmed or these other drugs are not available.

• For neutropenic patients with candidemia: for these cases, an echinocandin or lipid amphotericin B is recommended. In less critical patients who have not recently been exposed to azole drugs, fluconazole is considered a good option.

• Empirical therapy (patients with suspected invasive candidiasis): the suggested therapy is similar to those for proven candidiasis.

Despite the relevance of fungal bloodstream infections and the need for early therapy, only one randomized trial, which was published in July 2008, evaluated adding an antifungal drug to the broad-spectrum antimicrobial regimen in intensive care unit septic patients (**A**).[61] This trial included patients under broad-spectrum antimicrobial therapy for at least 4 days whose fever persisted. The patients were randomized to receive either fluconazole (800

mg daily) or placebo. The patients were followed for 4 weeks. Only 44 (36%) of the 122 fluconazole patients and 48 (38%) of the 127 placebo patients had a successful outcome with respect to their invasive fungal infection (i.e., no discontinuation for toxicity and no additional systemic antifungal required), with a relative risk of 0.95 (95% CI: 0.69-1.32; p=0.78). The primary reason for therapeutic failure was the lack of resolution of fever (51% for fluconazole and 57% for placebo). Documented invasive candidiasis was found in 5% of the fluconazole patients and 9% of the placebo patients (RR 0.57; 95% CI: 0.22-1.49). Seven of the fluconazole patients (5%) and 10 of the placebo patients (10%) experienced adverse events, leading to treatment withdrawal. Withdrawal due to abnormal liver results were found in 3 fluconazole patients (2%) and 5 placebo patients (4%).

Considering the results discussed above, the authors concluded that, in critically ill adults with risk factors for invasive candidiasis, empirical fluconazole therapy fails to clearly improve the outcome when compared with placebo.

Recommendation

• Despite the high incidence of fungal infections, particularly that of *Candida*, there is no evidence supporting the use of empirical antifungals in septic patients. Adding fluconazole for patients failing to respond to broad-spectrum antimicrobials failed to show superiority over placebo in a prospective trial; however, few patients had candidemia in both study arms.

Therefore, a potential benefit of empirical therapy cannot be excluded, and new studies evaluating larger cases series and other antifungals are necessary. Given the high incidence of *Candida spp*. bloodstream infections and the relevance of early therapy initiation, empirical antifungals may be considered in patients who are at risk for fungal infections. The high sensitivity of *Candida spp*. to fluconazole in isolates from blood cultures in a Brazilian multicenter trial, in addition to the low cost of this drug and minimal toxicity, may support the use of this antifungal drug as a therapeutic option.

However, for therapy of established or suspected *Candida spp*. infection in severely ill patients, recent reviews suggest echinocandins as the first option and amphotericin B formulations as an alternative.

RESUMO

A sepse tem alta incidência, alta letalidade e custos elevados, sendo a principal causa de mortalidade em unidades de terapia intensiva. Está claramente demonstrado que pacientes reconhecidos e tratados precocemente tem melhor prognóstico. Nesse sentido, a abordagem precoce do agente infeccioso, tanto no sentido do controle do foco infeccioso como da antibioticoterapia adequada são fundamentais para a boa evolução do paciente. A presente diretriz aborda as evidências disponíveis na literatura em relação às principais estratégias para controle e tratamento.

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