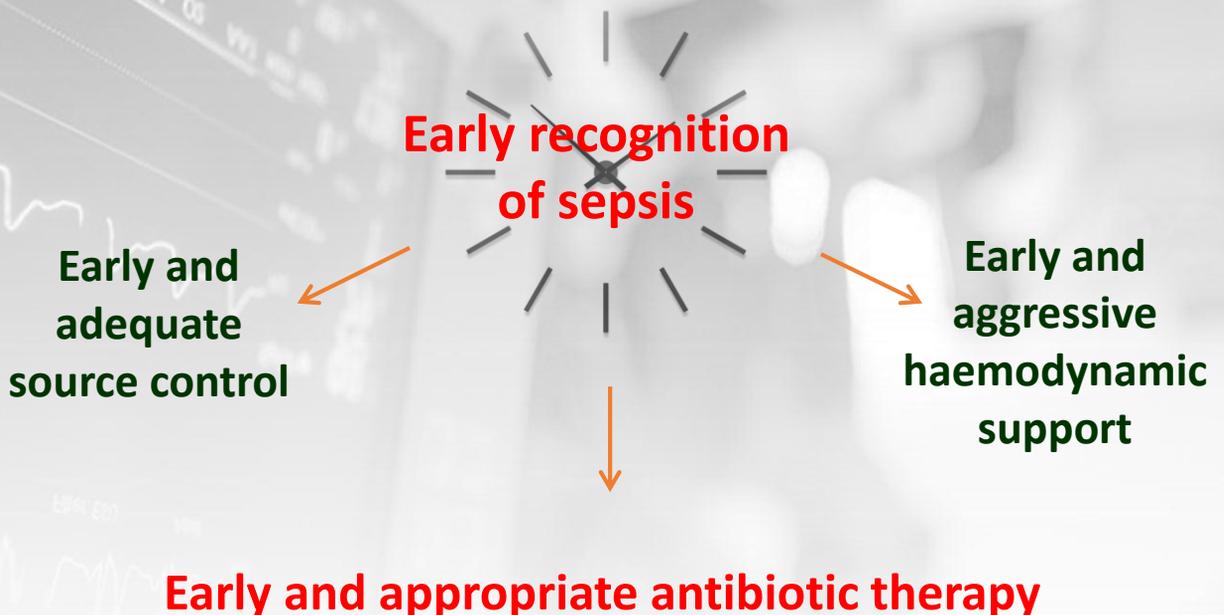




Antibiotics in patients with ongoing sepsis and septic shock



ACT NOW

Despite decades of sepsis research, no specific therapies for sepsis have emerged. Without specific therapies, management is based on control of the infection and organ support. Early antibiotics, source control, and hemodynamic support of vital organ function are the cornerstones for the treatment of patients with sepsis.

Antibiotics in patients with ongoing sepsis or septic shock

The choice of the antibiotic regimen poses serious problems for the management of critically ill patients. In patients with ongoing sepsis or septic shock an early and appropriate empirical antibiotic therapy has a significant impact on the outcome, independently by the site of infection. An inadequate antimicrobial regimen is one of the variables more strongly associated with unfavorable outcomes in critical ill patients.

International Surviving Sepsis Campaign guidelines for the management of sepsis and septic shock recommend intravenous antibiotics within the first hour after ongoing sepsis and septic shock are recognized, use of broad-spectrum agents with good penetration into the presumed site of infection, and reassessment of the antibiotic regimen daily to optimize efficacy, prevent resistance, avoid toxicity and minimize costs.

The principles of empiric antibiotic treatment should be defined according to the most frequently isolated bacteria, always taking into consideration the local healthcare setting trend of antibiotic resistance. In this era of prevalent drug-resistant microorganisms, the threat of resistance is a source of major concern that cannot be ignored. In the past 20 years, the incidence of nosocomial infections caused by drug-resistant microorganisms has risen dramatically, probably in correlation with escalating levels of antibiotic exposure and increasing frequency of patients with one or more predisposing conditions, including elevated severity of illness, advanced age, degree of organ dysfunction, low albumin levels, poor nutritional status, immunosuppression, presence of malignancy, and other comorbidities.

In recent years the changes in the pharmacokinetics in critically ill patients has received increased interest. Antibiotic pharmacokinetics describes the fundamental processes of absorption, distribution, metabolism, and elimination and the resulting concentration-versus-time profile of an agent administered in vivo. The achievement of appropriate target site concentrations of antibiotics is essential to eradicate the relevant pathogen.

When treating patients with ongoing sepsis, clinicians must be aware that drug pharmacokinetics may differ significantly between patients due to the variable pathophysiology of sepsis, and must also take into account the pathophysiological and immunological status of the patient.

Appropriate antibiotic therapy in the critically ill requires more specialized considerations than just selecting the most suitable antibiotic and adhering to traditional dosing guidelines. Unfortunately, most of the guideline recommendations are based on research that either underrepresent or exclude critically ill patients.

Appropriate antibiotic therapy in patients with ongoing sepsis and septic shock should mean prompt achievement and maintenance of optimal exposure at the infection site with broad-spectrum antibiotic agents administered in a timely manner. Appropriateness of treatment assessed in terms of adequate dosing regimens is crucial in managing critically ill patients with ongoing sepsis or septic shock. Inadequate dosing schedules may lead to suboptimal exposure at the infection site, increasing the risk for therapeutic failure or selection of resistant bacteria.

In the critically ill patients, important physiological processes that affect drug disposition are markedly perturbed. The degree of such pathologic derangements is particularly intense in septic patients.

Loading dose

In patients with ongoing sepsis, administering an optimal first dose is probably as equally important as to the timing of administration.

This optimal first dose could be described as a loading, or front-loaded dose and is calculated from the volume of distribution (Vd) of the drug and the desired plasma concentration. The Vd of hydrophilic agents (which disperse mainly in water such as beta-lactams, aminoglycosides and glycopeptides) in patients with septic shock may be altered by changes in the permeability of the microvascular endothelium and consequent alterations in extracellular body water. This may lead to lower than expected plasma concentrations during the first day of therapy resulting in sub-optimal achievement of antibiotic levels. Low plasma antibiotic levels can contribute to lower than expected antibiotic concentrations in peritoneal fluid with potentially reduced antibiotic delivery to the target tissues.

It should be kept in mind that the loading dose of lipophilic antibiotics (Macrolides, Fluoroquinolones, Tetracyclines, Chloramphenicol, Rifampicin, Linezolid) which are not influenced by the “dilution effect”, should not be influenced by the status.

Daily reassessment of the antibiotic regimen

Once appropriate initial loading is achieved, it is mandatory to reassess the antibiotic regimen daily, because the pathophysiological changes that may occur, may significantly affect drug disposition in the critically ill patients. Lower than standard dosages of renally excreted drugs must be administered in the presence of impaired renal function, while higher than standard dosages of renally excreted drugs may be needed for optimal exposure in patients with glomerular hyperfiltration.

It should be noted that in critically ill patients, plasma creatinine is an unreliable marker of renal function. The phenomenon of “augmented renal clearance” (creatinine clearance >130 ml/min/1.73 m²) can cause subtherapeutic concentrations. This phenomenon has high prevalence among critically ill patients.

Hypoalbuminaemia is another relevant cause of underdosing in critically ill patients whenever highly protein bound antibiotics are used. Hypoalbuminaemia is a frequently occurring condition in patients with ongoing sepsis as a consequence of increased albumin capillary escape rate through leaky endothelium or of fluid overload. By increasing the unbound fraction, hypoalbuminaemia may promote not only more extensive distribution but also greater renal clearance.

Time-dependent vs. concentration-dependent killing

An appropriate dosing regimen of antibiotics is required to achieve therapeutic concentrations at the site of infection such that exposure of the etiologic organisms to bactericidal concentrations achieves rapid resolution of infection. To achieve this goal, dosing regimens may need to be tailored based on the antibacterial kill characteristics.

Knowledge of the pharmacokinetic and pharmacodynamic antibiotic properties of each drug including (inhibition of growth, rate and extent of bactericidal action, and post-antibiotic effect) may provide a more rational determination of optimal dosing regimens in terms of the dose and the dosing interval.

Dosing regimen is related to the concept of time-dependent versus concentration-dependent killing. Beta-lactams exhibit time-dependent activity and exert optimal bactericidal activity when drug concentrations are maintained above the MIC. Therefore, it is important that the serum concentration exceeds the MIC for appropriate duration of the dosing interval for the antimicrobial and the organism. Higher frequency dosing, prolonged infusions and continuous infusions have been utilized to achieve this effect. For beta lactams, prolonged or continuous infusions have been advocated in order to maximize the time that the drug concentration exceeds the MIC, whereas high peak concentrations are not beneficial.

In contrast, antibiotics such as aminoglycosides exhibit concentration-dependent activity and should be administered in a once daily manner (or with the least possible number of daily administrations) in order to achieve high peak plasma concentrations.

With these agents, the peak serum concentration, and not the time the concentration remains above the MIC, is more closely associated with efficacy. In terms of toxicity, aminoglycosides nephrotoxicity is caused by a direct effect on the renal cortex and its uptake saturation. Thus, an extended interval dosing strategy reduces the renal cortex exposure to aminoglycosides and reduces the risk of nephrotoxicity.

Therapeutic drug monitoring (TDM)

The use of therapeutic drug monitoring (TDM) has been associated with higher clinical success and lower rate of toxicity. It is recommended mainly, but not only, for drugs with a narrow ratio between efficacy and toxicity, such as glycopeptides and aminoglycosides.

Critically ill patients in continuous renal replacement therapy (CRRT)

It is worth noting that appropriate dosing of antimicrobial agents in critically ill patients may be further complicated by the application of continuous renal replacement therapy (CRRT), especially when residual renal function coexists. As a general rule, drugs for which the kidney is the predominant site of clearance and that may be extracted by CRRT may need significant dosage increase as compared with the setting of renal failure or even with intermittent haemodialysis. This is usually the case for β -lactams, glycopeptides, aminoglycosides, levofloxacin and ciprofloxacin. Conversely, drugs that are not normally cleared via the renal route and that exhibit very low extraction during CRRT may need unmodified dosages in comparison with normal renal function, as in the case of linezolid and moxifloxacin. Clearly, TDM is invaluable in such cases.