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Sepsis: Antimicrobial Therapy

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1. Introduction

Twenty years ago a consensus committee of experts proposed standardized terminology and definitions for sepsis, organ failure, bacteremia, systemic inflammatory response syndrome (SIRS) and other related clinical conditions (1). Nevertheless, these terms are still a source of confusion and very often used interchangebly in clinical pratice.Whatever will be the accepted definition, sepsis is a clinical syndrome that complicates severe infection. However, in terms of antimicrobial therapy, diagnosing sepsis is not sufficient. The approach to the patient with sepsis includes also a tremendous challenge of establishing the etiologic agent, the anatomical site, the extent of the infectious problem and the possible underlying disease associated with the infection. Approximately 10 percent of patients with sepsis do not receive prompt antibiotic therapy for the implicated pathogen, and the mortality rate is 10 to 15 percent higher for such patients than for those who receive prompt, appropriate antibiotic therapy (2-3). Overall mortality from severe sepsis or septic shock ranges from 30% to 60% despite aggressive medical care (5-6). In the presence of septic shock, each hour delay in achieving administration of effective antibiotics is associated with a measurable increase in mortality (7). Therefore, antimicrobial therapy plays a central role in the management of these patients and the importance of the initial empiric regimen cannot be underestimated. The approach to critically ill patients with a suspected severe infection includes a well-accepted willingness to begin empirical broad-spectrum antibiotic therapy before the microbiological results are obtained. Intravenous antibiotic therapy should be started as early as possible and within the first hour of recognition of severe sepsis or septic shock. Appropriate cultures should be obtained before initiating antibiotic therapy, but should not prevent prompt administration of antimicrobial therapy. These recommendations are also emphasized in the recent guidelines for management of severe sepsis and septic shock (8). Nevertheless, even the broadest antibiotic regimen cannot "blindly" cover all pathogens responsible for sepsis and the choice of the initial antimicrobial therapy in sepsis should be guided by a systematic bedside evaluation, paired

with a judicious use of laboratory methods and other medical technologies. This will facilitate to determine the suspected focus of primary infection, one of major determinants in the choice of antibiotics. The antibiotic regimen should be selected taking in consideration the most common pathogens causing infections at these sites. However, even for the same site of infection choices are frequently different depending whether infections are community-acquired or health care-associated. The site of infection (e.g. central nervous system, endocardium) is also important when considering other factors such as pharmacokinetics, dosing and bactericidal properties of antimicrobial drugs. Other important factors such as knowledge of local endemic diseases, microbiological data and patterns of resistance increase the likelihood of prescribing appropriate antimicrobial therapy. Based on these principles, this review will focus on the antimicrobial therapy for the most common causes of sepsis and, in particular, discuss the most appropriate choices to be used until the causative organism and its antibiotic susceptibilities are defined.

2. Common clinical conditions and pathogens associated with sepsis

2.1. Severe community-acquired pneumonia

Several large series of patients with severe sepsis have shown that the lungs are the most commonly identified site of primary infection (9-11).Pneumonia is among the top ten most common causes of death among all age groups in the United States, the sixth leading cause of death in those 65 years or older, and the single most common cause of infection-related mortality (12). Although the majority of patients with community-acquired pneumonia (CAP) are treated as outpatients, approximately 10% of patients with community-acquired pneumonia will develop severe disease, as defined by admission to an intensive care unit (ICU) due to the presence of shock requiring vasopressors or respiratory failure requiring mechanical ventilation (13). This population represents the greatest proportion of pneumonia-related mortality and healthcare expenditure occurs among the patients who are hospitalized. Using a pathophysiological approach to characterize the causes of clinical failure, it was found that severe sepsis and cardiac deterioration are the main causes of clinical failure in hospitalized patients with CAP (14).The Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults strongly recommend direct admission to an ICU for patients with septic shock requiring vasopressors or with acute respiratory failure requiring intubation and mechanical ventilation (15).The clinical challenge of treating community-acquired pneumonia is the large number of microbial agents that can cause disease, the difficulty in making a clinical and etiologic diagnosis, and the fact that no single antimicrobial regimen can cover all the possible etiologies. Recommendations for diagnostic testing remain controversial. The most clear-cut indication for extensive diagnostic testing is in the critically ill CAP patient. Such patients should at least have blood drawn for culture and an endotracheal aspirate obtained if they are intubated. Blood cultures are positive in only 4 to 18 of patients hospitalized with community-acquired pneumonia (16); however a positive blood cultures is highly specific, may allow narrowing antibiotic use, and may

identify the presence of unusual organisms that would not be adequately covered by routine empirical antibiotic coverage (17). Other difficulties in treating these patients include a long list of bacterial, fungal, viral, and protozoal agents that may cause severe acute CAP and because, by the time of presentation, evaluation rarely results in a specific etiologic diagnosis. Therefore, antibiotic therapy is almost always begun empirically. *S. pneumoniae* and *L. pneumophila* are the organisms most commonly involved in cases of severe pneumonia, however a large number of other microorganisms must be considered. A review of 9 studies that included 890 patients with CAP who were admitted to the ICU demonstrates that the most common pathogens in the ICU population were (in descending order of frequency) *S. pneumoniae, Legionella* species, *H. influenzae*, Enterobacteriaceae species, *S. aureus*, and *Pseudomonas* species (18).In some series, *M. pneumoniae* is involved in up to 11% of patients with community-acquired pneumonia requiring intensive care (19). The following empirical antibiotic treatment is the minimal recommended by the joint IDSA/ATS guidelines for severe CAP, i.e., patients needing hospitalization in ICU (15):

1. β-lactam (cefotaxime, ceftriaxone, or ampicillin-sulbactam) **plus** either azithromycin or a fluoroquinolone (ciprofloxacin). For penicillin-allergic patients, a respiratory fluoroquinolone (levofloxacin, moxifloxacin) and aztreonam are recommended.
2. For *Pseudomonas* infection, it is recommended the use of an antipneumococcal, antipseudomonal β-lactam (piperacillin-tazobactam, cefepime, imipenem, or meropenem) plus either ciprofloxacin or levofloxacin (750-mg dose) or the above β-lactam plus an aminoglycoside (gentamicin, amikacin) and azithromycin or the above β-lactam plus an aminoglycoside and an respiratory fluoroquinolone. For penicillin-allergic patients, substitute aztreonam for the above β-lactam.
3. For community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) infection, add vancomycin or linezolid.

Infections with the overwhelming majority of CAP pathogens will be adequately treated by use of the recommended empirical regimens. The emergence of methicillin-resistant *S. aureus* as a CAP pathogen and the small but significant incidence of CAP due to *P. aeruginosa* are the exceptions. Once the etiology of CAP has been identified, antimicrobial therapy should be directed at that pathogen; however two major issues are of concern. The first is whether bacteremic pneumococcal pneumonia should be treated with dual therapy. The second is that if the patient has concomitant pneumococcal meningitis, the efficacy of fluoroquinolone monotherapy is uncertain. Therefore, discontinuation of combination therapy after results of cultures are known is most likely safe in non-ICU patients (15).

3. Nosocomial pneumonia

Nosocomial pneumonia (NP), and its most serious form, ventilator-associated pneumonia (VAP), is a major cause of morbidity and mortality in the ICU. NP accounts for up to 25% of all ICU infections and for more than 50% of the antibiotics prescribed (20).In this setting, nearly 90% of episodes of NP occur during mechanical ventilation. Rates of VAP are related to the duration of mechanical ventilation and have been estimated to be 3% per day during

the first 5 days and 2% per day thereafter (21). NP and VAP may be caused by a wide spectrum of bacterial pathogens, they may be polymicrobial, and are rarely due to viral or fungal pathogens in immunocompetent hosts (22).Time of onset of pneumonia is an important epidemiologic variable and risk factor for specific pathogens and outcomes in patients with NP and VAP. For patients who experience onset of infection within the first 4 days of hospitalization (early-onset VAP) and who have no risk factor for health care-related pneumonia or multidrug-resistant pathogens, *S. pneumoniae*, methicillin-susceptible *S. aureus*, *H. influenzae*, and antimicrobial-susceptible enteric gram-negative bacilli (e.g., *Klebsiella pneumoniae* and *Enterobacter* species) are the most common causative pathogens (22). For these patients a limited-spectrum antimicrobial therapy (i.e., ceftriaxone, a fluoroquinolone such levofloxacin or moxafloxacin, ampicillin/sulbactam, or ertapenem) may be appropriate. For patients who develop severe infection later during their hospital stay (late-onset VAP) additional antimicrobial-resistant bacteria (e.g., *P. aeruginosa*, *Acinetobacter* species, and MRSA) may also be responsible for infection (23) and a broad-spectrum combination antimicrobial therapy should be initiated promptly, with a commitment to de-escalating the treatment on the basis of serial clinical and microbiologic data. The recommended combinations (22) include an antipseudomonal cephalosporin (cefepime, ceftazidime), an antipseudomonal carbapenem(imipenem, meropenem), particularly when an extended-spectrum β-lactamase-positive strain is suspected, or a β-lactam/β-lactamase inhibitor (piperacillin–tazobactam) plus either an antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin) or an aminoglycoside (amikacin, gentamicin, or tobramycin) plus either vancomycin or linezolid (if MRSA risk factors are present or there is a high incidence locally). If an aminoglycoside is one of the agents used instead of quinolones, a macrolide (e.g. azithromycin) should also be given if *Legionella pneumophila* is suspected. Ultimately, the choice of agent should be based on ICU-specific trends in pathogens and their susceptibility patterns. VAP due to multiple drug-resistant microorganisms is one of the most dreadful complications that occurs in critically ill patients and, in this setting, infections caused by carbapenem-resistant *A. baumannii and K. pneumoniae* are of special concern because very few treatment options exist. If VAP caused by these pathogens are considered, polymyxyns (e.g. colistin) appears to be a safe and effective alternative (24). A recent prospective, randomized trial has demonstrated that fixed-dose of linezolid was more effective than a dose-optimized vancomycin regimen for treatment of methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia, although the 60-day mortality was similar (25). Cases of non-nosocomial health care-associated pneumonia, defined as pneumonia occurring within 48-72 hours of hospitalization in a patient with extensive contact with the health care system (e.g. nursing home residence, hemodialysis dependence, recent hospitalization), are treated with the same regimens recommended for NP.

4. Urinary tract infection

The term *urosepsis* is commonly used to describe the sepsis syndrome caused by urinary tract infection (UTI). In large series of patients with sepsis, the urinary tract was considered

to be source of infection in approximately 10% to 22 % of cases (9, 11). Sepsis is much more likely to occur among patients with upper UTI and complicated UTI, the latter defined as infection that occurs in a urinary tract with functionally, metabolically, or anatomically abnormalities (26). Infections occurring in patients with indwelling catheters and calculi, infection in men, pregnant women, children, and in patients who are hospitalized or in health care–associated settings also may be considered complicated (27). However, sepsis may be also a clinical presentation of acute uncomplicated pyelonephritis in young women (26). UTI in some adult patients groups, such as those with spinal cord injury, long-term catheterization, or diabetes, may progress to severe, life threatening pyelonephritis, abscess formation, or septicemia (28). In contrast to other community and nosocomial infections, there have been few new pathogens identified as important causes of UTI. *E. coli* accounts for approximately 80% of uncomplicated UTI (28); however, a broad range of bacteria can cause nosocomial UTI, and many are resistant to multiple antimicrobial agents. *E. coli*, although significantly less prevalent than in uncomplicated UTI, is still the most common cause of nosocomial bacteriuria in medical-surgical ICUs. Other gram-negative bacteria such as *Klebsiella* spp., *Serratia* spp., *Citrobacter* spp., *Enterobacter* spp., *Pseudomonas aeruginosa*, and gram-positive cocci, including coagulase negative staphylococci and *Enterococcus* spp., cause most of the other infections (29, 30). In patients with nosocomial UTI in medical-surgical ICUs reported in the U.S. National Nosocomial Infection Surveillance System from 1992 to 1998, *C. albicans* constituted 15.3% and all fungal isolates 31.2% of all urinary isolates (30). Urosepsis, in general, is easily diagnosed by positive urine and blood cultures with the same pathogens, but until microbiological results are available, empirical treatment should be selected considering the pharmacokinetics of the agent, its spectrum of activity relative to the anticipated pathogens and potential for adverse effects. Therapeutic management for uncomplicated infection has been compromised by increasing antimicrobial resistance, particularly global dissemination of the CTXM-15 extended spectrum β-lactamase (ESBL) producing Escherichia coli ST-131 strain (31).Guidelines developed by the Infectious Diseases Society of America (IDSA) and the European Society for Microbiology and Infectious Diseases (ESCMID) (32) recommends that women with pyelonephritis requiring hospitalization may be initially treated with an intravenous antimicrobial regimen, such as a fluoroquinolone (ciprofloxacin, ofloxacin) when the prevalence of resistance of community uropathogens is not known to exceed 10%. If the prevalence of fluoroquinolone resistance is thought to exceed 10%, an initial intravenous dose of a long-acting parenteral antimicrobial, such as ceftriaxone or a consolidated 24-h dose of an aminoglycoside (gentamicin), with or without ampicillin, an aminoglycoside (gentamicin), with or without ampicillin or an extended-spectrum penicillin (piperacillin, mezlocillin), with or without an aminoglycoside, or a carbapenem (imipenem, meropenem) is recommended. Patients with community-acquired urosepsis may be managed in a similar manner. Among patients with complicated nosocomial UTI the concern of multidrug resistance is much greater and the choice of antibiotic agent for empiric treatment should be based on available information, including the urine Gram-stain results, previous urine culture results, or the antimicrobial sensitivity

patterns of urinary pathogens isolated in the patient's hospital or long-term care facility (26, 29). Other potential concerns with these choices include the increasing prevalence of resistance to fluoroquinolones in institutional settings and the frequency of enterococcal infections (29). In patients with nosocomial urosepsis, one should consider a broader-spectrum drug such as piperacillin-tazobactam or a carbapenem for empiric treatment. If the urine Gram stain shows gram-positive cocci (most likely enterococci or staphylococci), treatment with vancomycin is reasonable (33). The antimicrobial regimen should be tailored as appropriate when the infecting strain has been identified and antimicrobial susceptibilities are known.

5. Intraabdominal infections

Intraabdominal infections (IAIs) are one of the most common causes of sepsis (9, 11) and they comprehend a great number of pathological conditions. According to the source, site and extension of the infections, IAIs may be classified in several manners (34); they may be retroperitoneal and intraperitoneal, primary (without an evident source) or secondary, diffuse or localized (peritoneal or visceral abscesses), community acquired or health care–associated. The term complicated intra-abdominal infections is also commonly used and it implies an infections that extend beyond the hollow viscus of origin into the peritoneal space and that is associated either with abscess formation or peritonitis (35). The bacteria that cause intra-abdominal infections are derived from the indigenous flora of the gastrointestinal tract. Anaerobic bacteria are predominant in IAIs because they are the main component of the gastrointestinal tract flora, outnumbering aerobic and facultative bacteria in the ratio of 1,000 to 10,000 to one (36). Most cases of secondary peritonitis are polymicrobial and anaerobes play a major role (37-39).The predominant aerobic are *Escherichia coli*, *Enterococcus faecalis*, *Klebsiella* spp., *Enterobacter* spp., and the main anaerobic bacteria are anaerobic Gram-negative bacilli (including *Bacteroides fragilis* group and pigmented *Prevotella* and *Porphyromonas*), *Peptostreptococcus*, and *Clostridium* spp. (40). Recently, an Expert Panel of the Surgical Infection Society and the IDSA prepared guidelines intended for managing patients with IAIs (41). These guidelines make therapeutic recommendations on the basis of the severity of infection, which is defined for these guidelines as a composite of patient age, physiologic derangements, and background medical conditions. Many of these recommendations, intended for patients with severe infection or those considered at risk of complications, are also relevant for patients with IAI and sepsis and they are summarized as follow:

1. Appropriately collected, anaerobic and aerobic cultures should be performed. These include blood cultures and specimen collected from the intra-abdominal focus of infection which are representative of the material associated with the clinical infection.
2. Appropriate source control procedures are essential for nearly all patients with IAIs. These procedures include drainage of infected foci, control of ongoing peritoneal contamination by diversion or resection, and repair of anatomic and physiological function to the extent feasible.

3. The recommended empirical antibiotic treatment of adult patients with severe community-acquired infection and all patients with health care-associated infections are similar and should include antimicrobial regimens with broad-spectrum activity against gram-negative organisms, including an carbapenem (meropenem, imipenem, doripenem), or piperacillin-tazobactam (all with excellent antianaerobic activity), or ceftazidime or cefepime in combination with metronidazole (also excellent antianaerobic activity). Quinolones (ciprofloxacin, levofloxacin) in combination with metronidazole also may be used for empirical treatment if hospital surveys indicate >90% susceptibility of *E. coli* to this class of drugs. Aztreonam plus metronidazole is an alternative, but addition of an agent effective against gram-positive cocci is recommended.

4. The empiric use of agents effective against enterococci, particularly against *Enterococcus faecalis* is also recommended in this situation and includes drugs such as ampicillin, piperacillin, piperacillin-tazobactam, or vancomycin.

5. Empiric use of vancomycin should be provided to patients with health care-associated intra-abdominal infection who are known to be colonized with MRSA or who are at risk of having an infection due to this organism because of prior treatment failure and significant antibiotic exposure.

6. Antifungal therapy is not routinely included in the empiric regimen, unless gram-stains or cultures indicate that these organisms may be involved in the infection. In this case, patients with sepsis should be treated with an echinocandin (caspofungin, micafungin, or anidulafungin)

7. All antimicrobial therapy should be tailored when culture and susceptibility reports become available.

6. Skin and soft tissue infections

The spectrum of manifestations skin and soft tissue infections (SSTI) is wide, varying from otherwise healthy people with severe infection and sepsis to patients with major co-morbidities and relatively minor infection; patients with extensive cellulitis and systemic symptoms who can be managed with antibiotics alone to patients with necrotizing limb-threatening infection that requires life-saving surgery. SSTIs have been classified in several manners, including according to the anatomical site of infection (42), to their microbial etiology or by severity (43), or clinical characteristics (44). SSTIs may be caused by a large number of microorganisms. Therefore, in establishing a diagnosis, it is critical to ask patients about animal exposure, travel history, underlying diseases, recent trauma, bites, burns, and water exposure; and to recognize the signs of different types of infection in an effort to limit the spectrum of causes to a more reasonable differential diagnosis. Eron *et al.* (45) classify these infections according to the severity of local and systemic signs, thereby developing a system that guides the clinical management and treatment decisions for patients with SSTIs. Accordingly, class 4 in this classification includes sepsis syndrome and life-threatening infection (e.g. necrotizing fasciitis), the most serious presentations of complicated SSTI. A discussion on all causes of SSTIs is beyond the scope of this chapter. Instead, we will focus

our discussion only on necrotizing fasciitis (NF), probably the most important clinical presentation of complicated SSTI associated with sepsis. NF (44, 46), is a relatively rare but often life-threatening necrotizing infection of subcutaneous tissue and fascia. About 20% of patients have no visible skin lesion. In others, the initial presentation may be a trivial lesion or that of cellulitis, which can advance very rapidly. Clinical signs that the process involves the deeper tissue planes include failure to respond to initial antibiotic therapy, a hard, wooden feel of the subcutaneous tissue, altered mental status, bullous lesions and skin necrosis or ecchymoses. According to the microbiological characteristics, NF has two major types. In type I, the polymicrobial form (most originating from the bowel flora), up to 15 different anaerobic (e.g. *Clostridium, Bacteroides, Prevotella, and Peptostreptococcus*) and aerobic organisms (*E. coli, Klebsiella, Proteus*) may be cultured. Four major clinical settings of Type I NF are recognized: (1) surgical procedures involving the bowel or penetrating abdominal trauma, (2) decubitus ulcer or a perianal abscess, (3) at the site of injection in injection drug users, and (4) spread from a Bartholin abscess or a minor vulvovaginal infection. Nevertheless, some cases are caused by a single pathogen, particularly anaerobic *Streptococcus* species. Type II NF is monomicrobial and classically has been caused by Group A Streptococcus (GAS) (*Streptococcus pyogenes*). Most cases of NF caused by GAS (also known as hemolytic streptococcal gangrene, "flesh-eating disease") are community acquired and present in the limbs. An underlying cause (e.g. diabetes, peripheral vascular disease) is common. Cases of NF that arise after varicella or trivial injuries are almost always due to *S. pyogenes*. The mortality in this group is high, approaching 50%–70% in patients with hypotension and organ failure (44).Other causes of NF are: *V. vulnificus, A. hydrophila*, anaerobic streptococci (i.e., *Peptostreptococcus* species), and community-acquired MRSA (47). A definitive bacteriologic diagnosis is best established by culture of tissue specimens obtained during operation or by positive blood culture results. Aggressive surgical intervention is the major therapeutic modality in cases of necrotizing fasciitis. Antimicrobial therapy must be directed at the pathogens and several antibiotic choices for treating NF (44) are summarized as follow:

1. Treatment of polymicrobial NF must include agents effective against both aerobes and anaerobes. Choices include: a) ampicillin which may cover susceptible enteric aerobic organisms (e.g. *E. coli*) and gram-positive organisms, such as *Peptostreptococcus* species, group B, C, or G streptococci, and some anaerobes; b) clindamycin which is useful for coverage of anaerobes and aerobic gram-positive cocci, including most *S. aureus* serogroups; c) metronidazole which has the greatest anaerobic spectrum against the enteric gram-negative anaerobes (but it is less effective against the gram-positive anaerobic cocci); d) gentamicin or a fluorquinolone (ciprofloxacin), ticarcillin-clavulanate, or piperacillin-tazobactam, which may cover resistant gram-negative rods. The practice guidelines of the Infectious Diseases Society of America for treating NF consider a combination of ampicillin-sulbactam plus clindamycin plus ciprofloxacin as the best choice of antibiotics for community-acquired mixed infections (44).
2. Necrotizing fasciitis caused by group A streptococci should be treated with clindamycin and penicillin.

3. A history of water exposure or fish injury or handling in a patient with NF is typical of infections caused by *A. hydrophila*, and, in particular, V. *vulnificus,* the most common recognized marine pathogen of SSTIs. A combination therapy with cefotaxime or ceftazidime (which are also recommended for treating infections due to Aeromonas infection) and minocycline is suggested for treating adult patients with bacteremia and severe soft-tissue infection caused by *V. vulnificus* (48).

4. *S. aureus*, particularly MRSA, is the most common Gram-positive aerobe cause of complicated SSTIs. The increased prevalence of hospital-acquired MRSA has been noted worldwide and more recently also in the community setting (CA-MRSA) (46). In the Unites States, the predominant CA-MRSA clone is USA300 which has caused several numerous outbreaks including prison innmates, professional football players and others populations (46). Therefore, the IDSA guidelines for the management of patients with MRSA infections (49), recommend that empirical therapy for MRSA should be considered pending culture data in adult hospitalized patients with complicated SSTI (deeper soft-tissue infections, surgical/traumatic wound infection, major abscesses, cellulitis, and infected ulcers and burns). In addition to surgical debridement and broad-spectrum antibiotics these recommendations include the following options: intravenous vancomycin, oral or intravenous linezolid 600 mg twice daily, daptomycin 4 mg/kg/dose IV once daily, telavancin 10 mg/kg/dose IV once daily, and clindamycin 600 mg IV or PO 3 times a day. A β-lactam antibiotic (e.g. cefazolin) may be considered in hospitalized patients with nonpurulent cellulitis with modification to MRSA-active therapy if there is no clinical response. Seven to 14 days of therapy is recommended but should be individualized on the basis of the patient's clinical response. Obviously, the oral route is not recommended for septic patients.

7. Neutropenic fever

Fever occurs frequently during chemotherapy-induced neutropenia: about 30% of patients with solid tumors and > 80% of those with hematological malignancies will develop fever during at least one of the chemotherapy cycles associated with neutropenia (50). Mortality rate of sepsis in neutropenic patients is extremely high. Bacteremia occurs in 10-15% of all patients, with most episodes occurring in the setting of prolonged and profound neutropenia (absolute neutrophil count < 100) (51-53). Substantial fluctuations in the epidemiologic spectrum of bloodstream infections have occurred over the past 40 years. Early in the development of cytotoxic chemotherapy, during the 1960s and 1970s, gram-negative pathogens, particularly *E. coli, Klebsiella* spp., *Enterobacter* spp., *Pseudomonas aeruginosa* and *Stenotrophomonas* spp., predominated. In the 1980s and 1990s, gram-positive organisms became more common, because of the increasing use of indwelling intravenous catheters (53-58). Nowadays, there is again a trend toward a predominance of infections caused by gram-negative pathogens and in particular those due to multidrug-resistant (MDR) bacteria. Extended spectrum beta-lactamase (ESBL) producing gram-negative rods, especially *Klebsiella* and *Enterobacter* species, are sometimes susceptible

only to carbapenems (59-60). Carbapenemase-producing *Klebsiella* and *Pseudomonas* species emerged recently and cause infections that are resistant to carbapenems (61). However, severe infections caused by gram-positive resistant pathogens such as MRSA and vancomycin-resistant *Enterococcus* (VRE), or penicillin resistant *pneumococci* and *viridans streptococci* are still prevalent in certain centers (62-64). An update which is intended as guidelines for the use of antimicrobial agents in managing patients with cancer who experience chemotherapy-induced fever and neutropenia was recently published by the IDSA (65). Accordingly, patients presenting with fever and neutropenia should receive empirical antibiotic therapy immediately after the initial clinical evaluation and after appropriate cultures are obtained. The initial empiric antibiotic treatment recommended for high risk patients with neutropenia, is monotherapy with an antipseudomonal beta-lactam agent, such as cephalosporin (cefepime), or a carbapenem (imipenem, meropenem), or a penicillin drug (piperacillin/tazobactam). Addition of an aminoglycoside (gentamicin, amikacin) as a combination therapy has not been proven beneficial in a meta-analysis of numerous trials (66). Modifications in the above regimens should be considered according to local epidemiological data and patient's specific risk factors. For instance, vancomycin, linezolid or daptomycin should be considered in the initial management of patients known to be colonized or previously infected with MRSA or VRE; for patients previously infected or colonized with ESBL-producing gram-negative rods, one should consider the early use of a carbapenem; colonization with carbapenem-resistant Enterobacteriacea (CRE) may justify the addition of drugs such as colistin or tigecycline. Empirical antibiotics are considered vital in febrile neutropenic patients. Although up to 23% of these episodes are associated with bacteremia (67), treatment should be continued even if blood cultures remain negative. Finally, high risk patients who have received intensive cytotoxic chemotherapy are at risk for invasive fungal infection. Yeasts which cause bloodstream infections (primarily *Candida* species), and molds which cause sino-pulmonary infections (primarily *Aspergillus species*) typically cause infections which are manifested by persistent or recurrent fever in patients with prolonged neutropenia, rather than causing initial fever in the course of neutropenia (68). Empirical antifungal coverage should be considered in high-risk patients after 4-7 days of a broad-spectrum antibacterial regimen and no identified fever source. For over 3 decades, amphotericin B was the drug used for empiric antifungal treatment, based on a study of Pizzo *et al* (69) which showed decrease mortality associated with this practice. In the last decade, a number of trials have identified roles for other antifungal agents with anti-yeast and anti-mold activity, like lipid formulations of amphotericin B, or echinocandins (caspofungin) and broad spectrum azoles (voriconazole), based on their lower toxicity compared to traditional amphotericin B (70-74).

8. Catheter related bloodstream infections (CRBSI)

Approximately 80,000 CRBSIs occur in ICUs every year (75). CRBSI is defined when bacteremia or fungemia occurs in a patient who has an intravascular device and a positive

blood culture obtained from a peripheral vein, clinical manifestation of infection, and no apparent source for bloodstream infection other than the catheter. A positive result of semiquantitative catheter tip culture (>15 cfu) with the same pathogen, or of simultaneous quantitative blood cultures obtained from catheter and peripheral blood (ratio of >3:1 cfu/ml of blood, respectively) or differential time to positivity ($\geq$ 2 hours) between catheter and peripheral vein blood culture are also required for this the definition (76). Gram staining routine culture with additional culture for fungi and acid-fast organisms as indicated, obtained from any exudate at the insertion site of the catheter, are important diagnostic tools, particularly when assessing immunocompromised patients. Several characteristics are associated with an increased risk of CRBSI with the most important being the type of the intravascular device (short-term central venous catheters are at the highest risk) (77), the intended use of the catheter (e.g. for total parenteral therapy nutrition use), the insertion site (femoral site at highest risk), the frequency with which the catheter is accessed, the characteristics of the patient, the experience of the individual who installs the catheter and the use of proven infection control measures (78-79). The pathogens that most commonly cause CRBSI differ a little according to the catheter type. In order of prevalence, the 4 groups of microbes that most commonly cause CRBSI associated with percutaneously inserted, noncuffed catheters are as follows: coagulase-negative staphylococci, *S. aureus*, *Candida* species, and enteric gram-negative bacilli. For surgically implanted catheters and peripherally inserted CVCs, they are coagulase-negative staphylococci, enteric gram-negative bacilli, *S. aureus*, and *P. aeruginosa* (79). The following discussion includes current recommendations for the management of CRBSI as updated by the IDSA in 2009 and emphasizes the most important aspects relevant to patients with CRBSI and sepsis (76). Most situations involving patients with CRBSI and sepsis require the removal of the catheter. Exceptions for this rule are patients with limited access sites and uncomplicated CRBSI involving long-term catheters (e.g., patients undergoing hemodialysis) due to pathogens other than *S. aureus*, *P. aeruginosa*, *Bacillus* species, *Micrococcus* species, Propionibacteria, fungi, or mycobacteria. In these patients treatment may be attempted without catheter removal, with the use of both systemic and antimicrobial lock therapy if there is a prompt response to antibiotic therapy (80, 81). The antibiotic lock should be changed every 24-48 hours. The concentration of the antibiotic in the lock solution should be at least 1000 times higher than the MIC of the microorganism treated (82). Although a declining incidence, MRSA represents approximately 7.5% of all reported ICU central line-associated bloodstream infections (83). In addition, coagulase-negative staphylococci are the most common cause of catheter-related infection. Most of these pathogens exhibit methicillin resistance, and this should be considered when choosing empirical therapy for catheter-related infection (84-85). Consequently, vancomycin should be recommended for the initial empiric antibiotic regimen of patients with CRBSI and sepsis. This regimen should include coverage for gram-negative bacilli using a fourth-generation cephalosporin (cefepime), or a carbapenem (imipenem, meropenem), or a beta-lactam/beta-lactamase inhibitor combinations (piperacillin/tazobactam), with or without an aminoglycoside (gentamicin, tobramicin, amikacin). Based on local antimicrobial epidemiologic and susceptibility data, empirical coverage for multidrug resistant gram-negative bacilli with

additional drugs (e.g. colistin) may also be considered. A fungal etiology, mainly invasive *Candida* infection, should be suspected in septic patients with any of the following risk factors: TPN administration, prolonged use of broad-spectrum antibiotics, hematologic malignancy, femoral catheterization, or colonization with candida species in multiple sites (86, 87). An echinocandin (caspofungin, anidulafungin) is the recommended empirical treatment for patients with recent azole exposure, patients with moderately severe to severe illness, or patients who are at high risk of infection due to *C. glabrata* or *C. krusei* (88). Therefore, this class of drugs should be preferred for the empirical treatment when sepsis is present. Transition to fluconazole is recommended for patients who have isolates susceptible to fluconazole (e.g.,*Candida albicans*) and who are clinically stable. Duration of treatment depends on the pathogen involved. CRBSI caused by coagulase-negative staphylococci should be treated for 5-7 days if the catheter is removed, and for 10-14 days in combination with antibiotic lock therapy, if the catheter is retained. *S. aureus* CRBSI should be generally treated for 4-6 weeks. A short duration of treatment (minimum of 14 days) can be considered in the absence of following conditions: a) diabetes mellitus; b) immunosuppression; c) prosthetic intravascular devices or grafts; d) endocarditis or suppurative thrombophlebitis; e) metastatic infection. The same approach may be adopted if fever and bacteremia resolved after 72 hours of treatment or if the infected catheter was removed.

9. Conclusion

Sepsis is a clinical syndrome that complicates severe infection and is associated with high mortality rates despite aggressive medical care. Antimicrobial therapy plays a central role in the management of these patients. Early institution of empirical but appropriate antibiotic treatment can influence the outcome and this is optimally done through a systematic bedside clinical evaluation, paired with a judicious use of laboratory methods and other medical technologies until the causative organism and its antibiotic susceptibilities are defined.

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