Antibiotic management of sepsis: current concepts

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Background: The development of guidelines for sepsis management has improved disease survival and reduced treatment costs. Adequate antibiotic therapy is the cornerstone of sepsis treatment. Specific rules should be established in every institution according to its profiles. Objectives: To review the current knowledge about the best drugs to be used as empiric treatment for sepsis based on their clinical efficacy and costs. Methods: Medline 1950 – 2008 was searched using the following terms: sepsis, organ failure, system failure, SIRS, septic shock, antibiotic, pneumonia, urinary tract infection, urosepsis, catheter-related infection, bloodstream, abdominal infection, and surgical wound. Results/conclusion: For most septic shock patients, monotherapy is adequate and treatment should be initiated in the first hour after first sepsis-induced organ dysfunction. The drug of choice varies in different situations and choosing the right antibiotic enables better survival, fewer complications and shorter stays in intensive care.

Keywords: abdominal infection, antibiotic, catheter-related infections, costs, guidelines, pneumonia, sepsis, urinary tract infections

1. Introduction
1.1 Epidemiology and guidelines
Sepsis is now recognized as a public health issue. Epidemiological studies suggest that there are approximately 300 cases per 100,000 population [1-3], accounting for 2% of all hospital admissions [4] and up to 30% of intensive care unit (ICU) admissions [5]. Despite recent breakthroughs, the overall hospital-mortality for severe sepsis remains high, close to 40%, which means approximately 215,000 deaths per year in the USA [3].

The need for high-complexity therapy and longer stays in ICUs places sepsis therapy among the highest costs in most hospitals. In a recent review about the economic aspects of sepsis, Burchardi and Schneider estimated that about 14.5 billion Euros are spent annually with sepsis management in North American ICUs [6].

At least three large, population-based studies [1-3] have shown that the incidence of sepsis is increasing by approximately 8.7% each year, jumping from 82.7/100,000 population in 1979 to 240/100,000 population in 2000. However, the same studies have shown a reduction in case-fatality rates from 45.0% in 1993 to 37.7% in 2000. The few sepsis-specific treatments available do not solely explain this improvement in outcomes, which have been linked to better ICU-care and development of evidence-based treatment guidelines. In fact, recent studies have shown that implementation of those guidelines are related to higher survival rates and lower costs in ICUs [7,8].

Guidelines for sepsis management have been proposed and are updated periodically [9]. However, a few recommendations on antibiotic therapy addressing
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Empirc treatment for these patients are available. There are some possible explanations. First, the consensus criteria for systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, and septic shock were created only in 1991 [10], while most trials comparing different antibiotics date from the 70s and 80s. Second, the antibiotic resistance profile of each institution is different, making the recommendation of specific antibiotic therapies difficult. Finally, sepsis patients normally use many antibiotic schemes during hospitalization, impairing the evaluation of the response to a specific drug.

This review article tries to summarize the current knowledge about antibiotic therapy in sepsis as a syndrome first, and then reviews specific therapeutic options for different conditions that can be complicated by septic shock. Again, individual aspects of each patient and the antibiotic resistance profile of the institution are essential in choosing the proper drugs. Hence, each institution should establish policies for use of antibiotics according to its unique characteristics.

1.2 Etiology of sepsis

The specific infections leading to sepsis vary according to countries or regions, institutions and over the time. However, there are some interesting points which should be considered, including i) most cases of sepsis are community acquired, despite its high incidence in hospitals. In fact, community-acquired infections are responsible for 25 – 72.3% of sepsis cases [5]; ii) sites of infection change if the infection is acquired in the hospital or in the community. Esteban et al. [11] have reported lungs (56%), genitourinary tract (20%), and digestive tract (13.5%) as the most common sites of infection among patients with community-acquired sepsis. This profile changes for hospital-acquired infections (26% pulmonary, 27% gastrointestinal, 24% genitourinary) and ICU-acquired infections (55% pulmonary, 18% urinary, 18% catheter-related). Overall, the main site of infection is the lungs, with an incidence ranging from 15.6 to 69% [12].

The distribution of infectious agents in sepsis has varied widely over the years and the most updated studies show the following incidences [2,9]: Gram-positive bacteria 40 – 52.1%; Gram-negative bacteria 37.6 – 38%; fungi 4.6 – 17%. The rate of mixed infections varies between 4.7 and 18%, and the incidence of infections due to Pseudomonas, Acinetobacter and Methicillin-resistant Staphylococcus aureus species is 14, 4, and 17%, respectively. Among fungal infections, the leading cause is Candida sp.

2. General recommendations for antibiotic use in sepsis

2.1 Empirc treatment of sepsis of unknown origin

Antibiotic therapy remains the cornerstone for sepsis patients. There is strong evidence that the inadequate antimicrobial treatment impacts negatively in survival [13], as well as the presence of shock and the delay in the beginning of antibiotic therapy [14]. The most updated sepsis guidelines recommend that empiric antibiotic therapy, with action against the most likely pathogens, should be started during the first hour of sepsis treatment, right after the sampling of cultures (Grade 1B) [9]. There are different recommendations for specimen collection in each infection related to sepsis (see below) but all patients should have two sets of blood cultures drawn (at least one percutaneously, and one from each catheter). The positivity rates for these cultures vary among studies, but approximately 30 – 50% of severe sepsis or septic shock patients will develop detectable bacteremia [15]. Predictors of bacteremia are: chills, hypotaluminaemia, renal failure and urinary tract infection, leukocytosis, left shift of neutrophils and hemodynamic compromise [16].

Since the late 70s, many good quality trials have compared the best empirical antibiotic schemes for neutropenic patients and, recently, for septic shock patients. Results were summarized in two meta-analyses, one evaluating empiric antibiotic treatment for Gram-negative bacteremia [17] and one for sepsis, regardless of causative agents [18]. Most studies compared different beta-lactams and aminoglycosides alone or in combination and concluded that monotherapy with beta-lactams was associated with lower rates of nephrotoxicity (OR: 0.36, CI 95%: 0.28 – 0.47) and had the same case fatality rates as combination therapy (RR: 0.90, CI 95%: 0.77 – 1.06). Therefore, monotherapy should be started as empirical treatment for most septic patients.

There are at least six prospective, randomized clinical trials comparing safety and efficacy of different drugs used as monotherapy for sepsis patients [19-24]. The drugs compared were carbapenems (imipenem or meropenem), a third-generation cephalosporin (ceftazidime or cefotaxime combined with metronidazole) or a ureidopenicillin with a beta-lactamase inhibitor (piperacillin-tazobactam); and no scheme proved superior to the others, so choice of treatment should be guided by each patient and each institution’s individual characteristics.

These findings are in agreement with most studies about in vitro susceptibility to antibiotics of specimens isolated from sepsis patients, which show that carbapenems, piperacillin-tazobactam and third- or fourth-generation cephalosporines remain active against most of these agents, including extended-spectrum beta-lactamase-producing Enterobacteriaceae, Pseudomonas aeruginosa and Acinetobacter baumannii [25].

However, there are some groups of patients in which these recommendations may not apply. Although most Pseudomonas aeruginosa remain susceptible to the proposed empirical antibiotics, there is a concern of resistance arising during therapy. The aforementioned meta-analysis about drug therapy for Gram-negative bacteremia [17] has found an improved outcome for patients with Pseudomonas who received combined therapy, and therefore the International Guidelines for Management of Severe Sepsis [9] recommend that patients with suspected Pseudomonas infection should receive combination
empiric treatment. There are no trials evaluating the best antibiotic in this setting, but most specialists recommend adding an aminoglycoside or a quinolone active against *Pseudomonas* to the above-mentioned empirical treatment.

Another concern are individuals or institutions with high-risk for methicillin-resistant *Staphylococcus aureus* (MRSA) infection, which include patients with skin or catheter-related infections (see below); with any kind of barrier impairment, such as mucositis; with immunosuppression; or who have recently been treated with third- or fourth-generation cephalosporines or carbapenems [26]. Vancomycin or teicoplanin should be added to the empirical therapy of these individuals. Although usually reserved for vancomycin-resistant strains, linezolid has been considered superior to vancomycin as initial treatment in one study [27]; and another one has evaluated microbiologic response with linezolid and vancomycin in ventilator-associated pneumonia due to MRSA (data not published, ClinicalTrials.gov; Identifier: NCT00572559). For resistant strains, quinupristin/dalfopristin is an alternative [28] and for salvage therapy, the recently developed drug tigecycline should be considered [29].

Finally, patients with high risk for fungal infection should receive appropriate coverage. Major risk factors for invasive fungal infections are: colonization with *Candida* of two sites (urine, rectum, gastric aspirate, vascular access site, sputum/throat swab, wounds, surgical drains), previous broad spectrum antibiotic therapy, gastrointestinal surgery and gastrointestinal perforation, acute renal and liver failure, invasive devices such as central venous catheters, immunosuppression, parenteral nutrition, high APACHE II score, and long length of stay (LOS) in ICU [30]. The vast majority of these patients will have *Candida albicans* infection and an azole should be added to the empiric antibiotic therapy, since it has been associated with similar response rates and lower adverse reactions than liposomal formulations of amphotericin B [31]. Patients recently treated with fluconazole have a higher risk of infection due to non-albicans *Candida* species, which are often intrinsically resistant to azoles. These patients should receive caspofungin, other beta-glucan inhibitors [31,32] or liposomal formulations of amphotericin B [26,33]. An alternative but less-studied drug is voriconazole [34].

Now there is evidence that adjusting antibiotic therapy following microbiological results has better outcomes than keeping original empiric therapy, and most experts recommend de-escalating antibiotic therapy after microbiological diagnosis [35]. There is also evidence that shorter courses of antibiotics do not impair clinical response and usually antibiotics may be stopped after 7 – 10 days if the patient shows signs of clinical improvement. However, if there are signs of treatment failure after 48 – 72 h, alternative diagnosis should be sought and empiric antibiotic therapy revised [9].

Recently, procalcitonin (PCT) has been advocated as a marker for guiding antibiotic therapy. PCT is elevated in bacterial infections [36], and higher levels are related to worse outcomes. In one single-center prospective study, patients with PCT levels rising for 3 days had significantly higher 90-day mortality rates than patients in which the levels stopped rising after one day of treatment (72.4 vs. 26%, p < 0.001) [37].

Many studies have concluded that stopping antibiotic therapy following a reduction in PCT levels does not increase mortality but reduces costs and ICU length of stay for community-acquired pneumonia [38,39] and ventilator-associated pneumonia [40]. However, there has been only one study evaluating a procalcitonin-guided antibiotic regimen specifically in septic shock patients. In this study, antibiotics were stopped when PCT levels had decreased at least 90% from the initial value but not before day 3 (if baseline PCT levels were < 1 µg/l) or day 5 (if baseline PCT levels were ≥ 1 µg/l). This regimen was associated to a 4-day reduction in the duration of antibiotic therapy (p = 0.003) and a 2-day shorter ICU stay (p = 0.03), with no negative impact on survival [41]. These findings are currently being evaluated by further investigation (unpublished data, ClinicalTrials.gov Identifiers: NCT00271752, NCT00472667 and NCT00407147), and results shall be available soon.

### 2.2 Sepsis due to community-acquired pneumonia

According to the Guidelines from the Infectious Diseases Society of America (IDSA) for Community-Acquired Pneumonia, any pneumonia complicated by severe sepsis should be classified as Severe Pneumonia [42]. The main causes of infection in these patients are *S. pneumoniae*, *Staphylococcus aureus*, *Legionella*, Gram-negative-Bacilli (including *Pseudomonas*), and *H. influenzae*, which are poorly covered by standard pneumonia antibiotic schemes. This partially explains the better outcomes of culture-directed therapy for these individuals [43]. What is more, these patients have a high yield of positivity for blood cultures [44], and the IDSA recommends that the following examinations should be drawn before antibiotic initiation: two sets of blood cultures; *Legionella* urinary antigen test; *Pneumococcal* urinary antigen test; endotracheal aspirate, bronchoscopy or BAL for mechanically ventilated patients; fungal and tuberculosis sputum/BAL cultures if there are cavitary infiltrates; and diagnostic thoracocentesis and pleural fluid cultures if pleural effusion is present.

No randomized controlled trials have been done yet but at least five studies have found evidence that combination therapy improves outcomes in severe pneumonia with bacteremia [45-49], and the IDSA recommends that these patients receive a beta-lactam (cefotaxime, ceftriaxone, or ampicillin-sulbactam) plus either azithromycin or a respiratory fluoroquinolone. There is some evidence of superiority for the fluoroquinolones, which have been associated with better response rates, similar to the ones from carbapenems [50-54]. Again, in patients with strongly suspected *Pseudomonas* pneumonia, the beta-lactam used should have antipseudomoccal...
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and antipseudomonal action (piperacillin/tazobactam, cefepime, imipenem, or meropenem) [55]. For patients at high risk of contracting MRSA (patients with end-stage renal disease, injection drug users, prior influenza or prior antibiotic use) vancomycin or linezolid should be added to the previous schemes.

As in all severe sepsis patients, shorter durations of therapy are not related to worse outcomes. The IDSA recommends changing therapy according to microbiology isolates and to stop therapy after 72 h of clinical stability, provided that at least 5 days of antibiotics with proper coverage (which may or may not include the empirical treatment) have been used [42]. The only exception is pneumonia due to *Pseudomonas*, in which therapy should be maintained for at least 15 days [56].

Despite proper adherence to guidelines, 6 – 15% of patients do not respond to initial therapeutic regimens and have mortality rates as high as 49% [57]. These individuals are classified as ‘nonresponding-pneumonia’ patients.

Factors associated with a higher risk for nonresponding pneumonia, include unusual agents, such as *Legionella*, Gram-negative bacteria (*Pseudomonas* will be present in 10% of these patients) and *S. pneumoniae* resistant to beta-lactams, discordant empiric therapy (not adequate to the isolated agent), and presence of cavitation, pleural effusion, infections over pulmonary emboli and others [58,59]. As both unusual bacteria and structural lung diseases are associated with this disease, new blood cultures, a chest-CT scan, bronchoscopy and thoracocentesis (when appropriate) should be done. Despite intensive workup, most cases will remain undiagnosed, suggesting that the lack of response is more related to an originally severe disease than to uncommon causes of pneumonia.

### 2.3 Sepsis due to hospital-acquired and ventilator-associated pneumonia

Pneumonia accounts for 25% of hospital-acquired infections in ICUs and 50% of used antibiotics [60]. The most common infectious agents and antibiotic profile vary among institutions but are normally composed of highly resistant bacteria, such as *Pseudomonas*, *E. coli*, *Klebsiella pneumoniae*, *Acinetobacter* and *S. aureus*, making a microbiological diagnosis mandatory. In fact, one multicenter randomized trial, showed lower mortality of a microbiological approach (after adequate empirical treatment) when compared with a clinical-only approach (HR: 1.54, CI: 1.1 – 2.16, p = 0.01) [61].

The American Thoracic Society Guidelines for Nosocomial Pneumonia [62] recommends the following examinations: two sets of blood cultures, a thoracocentesis of pleural effusions (if present) and at least one sample from lower airways (endotracheal aspirates, broncoalveolar lavage, brush from lower airways, gram stain of tracheal aspirates. None of the sampling methods has been proved clinically superior to the others [63]). However, like in any septic patient, delay in use of antibiotics is related to worse outcomes [64], and none of these procedures should delay empiric antibiotic therapy.

Empiric therapy should include a beta-lactam plus an antipseudomonal quinolone or an aminoglycoside. Specific drugs should be chosen based on local epidemiology, previous antibiotic use by the patient and likeliness of multi-drug resistant (MDR) strains. There are many risk factors for pneumonia owing to multi-drug resistant bacteria, but the most important is length of hospital stay: more than 5 days is considered a high risk regarding MDR bacteria.

Guidelines suggest ceftriaxone, levofloxacin, ampicillin/sulbactam or ertapenem for pneumonias starting within less than 5 days of hospital stay and a combination of drugs for longer stays: an antipseudomonal drug (cefepime, ceftazidine, imipenem, meropenem, piperacillin-tazobactam) plus an antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin) or an aminoglycoside. If *Legionella* or MRSA are suspected, vancomycin or linezolid should be added. Some experts recommend the combination carbapenem + levofloxacin because there is weak evidence that this scheme has a higher activity against *Pseudomonas*, *Acinetobacter* [65] and extended-spectrum beta-lactamase producing *Enterobacteriaceae* [66]; but it has never been tried in a randomized controlled clinical trial. Approximately 40% of patients following these guidelines will require changing of antibiotics after cultures (62.1% due to isolation of resistant organism, 36% lack of clinical response) [67], highlighting the importance of microbiological diagnosis.

Similar to community-acquired pneumonia guidelines, there is a recommendation of revising antibiotic therapy after 72 h of treatment and using up to 7 days’ of antibiotics (15 for *Pseudomonas*) [62].

Finally, ventilator-associated pneumonia (VAP) stands for any pneumonia developing in previously mechanically ventilated patients. From 9% to 27% of all intubated patients develop VAP after 48 h of ventilation [68] and its crude mortality varies from 24 to 76%.

The original clinical criteria for VAP (new infiltrate or worsening infiltrate on chest radiograph for 48 h plus one of the following: fever over 38°C, leucopenia or leukocytosis, purulent sputum) has been associated with a sensitivity of only 69% and specificity of 75% [69]. Therefore, many other diagnostic schemes have been proposed in the literature, including clinical scores (Modified Clinical Pulmonary Infection Score; CPIS) and various methods of tissue sampling for microbiological evaluation of lower airways. Recently, an observational study concluded that managing VAP according to severity criteria and microbiological analysis was associated with better management than the modified CPIS (80 vs 50%, p < 0.001) [70] and now most societies recommend some kind of tissue sampling.

One meta-analysis [71] concluded that bronchoscopic techniques, when compared with endotracheal aspirates, have no effect on mortality but guarantee better antibiotic management of patients, leading the American Thoracic
Society guidelines [62] to favor bronchoscopy over endotracheal aspirates. However, later trials [63,67,23] failed to show any benefit of more invasive procedures over endotracheal aspirates for diagnosis or treatment of VAP, and there is still controversy on the theme.

As in other septic patients, delayed, microbiology-driven therapy is associated with worse outcomes [74] and, therefore, empirical treatment should be started right after specimens collection. The causative agents are similar to the ones in other hospital-acquired pneumonias. However, three studies [25,75,76] demonstrate no difference in mortality or clinical improvement of combination versus monotherapy and, therefore, monotherapy with one broad spectrum agent is recommended. A recent meta-analysis [74] compared 11 monotherapy empiric regimens for VAP, most containing drugs active against *Pseudomonas*, and concluded that no regimen was superior to the other. However, the majority of these trials have included patients with likely infections due to *Pseudomonas* or MRSA, and there is a recommendation that a second drug, active against MRSA or *Pseudomonas* should be added in these cases [77].

Like in the previous situations, antibiotic therapy should be adjusted after microbiological results [35] and that treatment should be discontinued after 3 – 8 days, if there is a satisfactory clinical response [78].

### 2.4 Sepsis related to urinary-tract infections (urosepsis)

Of all septic patients, 20 – 30% will have the focus in the urinary tract. Risk factors are long-term catheters (more than 7 days) placed in the urinary tract and structural diseases, such as urinary tract obstructions, nephrolithiasis and tumors. It is beyond the scope of this review, but the management of urosepsis includes correcting (even through surgery) these conditions [79].

Urosepsis should be suspected whenever a septic patient has symptoms of the urinary tract, such as flank pain, pain at micturition and prostatic pain. These patients should have a urinalysis, urine and blood cultures and urinary tract ultrasonography done [79]. Although diagnostic, the growth of the same agent on blood and urine cultures is rare. As most patients in ICUs will have asymptomatic bacteriuria due to urinary catheters, other sources of infection must be ruled out before urosepsis is diagnosed [80].

One large prevalence trial has determined the main infectious agents in patients with urosepsis in Europe and Asia. The most common were: *E. coli* (31%), *Pseudomonas* (23%), *Enterococcus* (16%), *Klebsiella* (15%) and *Candida* (13%) [81]; and mixed infections accounted for less than 16% of cases [82]. The same study evaluated *in vitro* susceptibility to many antibiotics and concluded that the most effective was imipenem, with 83% overall sensitivity. Individually, *E. coli*, *Proteus* and *Klebsiella* had lower than 45% resistance to most antibiotics, especially second- and third-generation cephalosporines (resistance lower than 20%); however, *Pseudomonas* isolates had more than 70% resistance to most antibiotics.

Based on these results, the European Society of Urology has recommended that in community-acquired urosepsis, in which *E. coli* is the most likely cause, third-generation cephalosporines, piperacillin/tazobactam or ciprofloxacin should be used empirically, after urine culture collection. In nosocomial urosepsis, an antipseudomonal third-generation cephalosporin (ceftazidime) or piperacillin-tazobactam should be used combined with aminoglycosides or carbapenems for fluoroquinolone-resistant *E. coli* and extended-spectrum beta-lactamase producing *Enterobacteriaceae* [79]. Patients with long-standing urinary catheters (more than 7 days) should have the catheters removed and treatment should last 5 – 21 days [83].

#### 2.5 Sepsis related to bloodstream/catheter-related infections

In 18% of sepsis patients, a catheter placed in a central or peripheral vessel will be the source of infection. Clinical features suggestive of catheter-related infection are pus and > 4 mm cellulites at insertion site. What is more, some organisms growing in a blood culture suggest a catheter-related infection: *S. aureus*, coagulase-negative *Staphylococcus*, *Bacillus* sp. Fungi (specially Candida) and *Corynebacterium jeikeium* [84].

For definitive diagnosis, sets of blood cultures should be collected at the same time from every catheter and percutaneously. If quantitative cultures are done, the same organism must grow in both cultures, with a five-fold higher number of colony-forming units in the blood drawn from the catheter when compared with the percutaneous culture; if a qualitative culture is done, the culture from the catheter should become positive at least 2 h before than the percutaneous one. The quantitative analysis has a sensitivity of 93% and specificity of 97 – 100%, while sensitivity and specificity for the qualitative analysis are 89 – 90% and 72 – 87% respectively. Another approach is to take out the catheter and send it for culture by flushing the lumen, sonication, or roll tip culture methods. If the same organism grows in the culture and from a percutaneous blood culture, the sensitivity and specificity are 84 – 100% and 97 – 100% respectively [85].

There are no large trials on the epidemiology of infectious agents leading to catheter-related sepsis but it is known that the length of catheter placement plays an important role. Recent catheters (< 8 days) are colonized mainly by the skin flora of the own patient, and infections are mainly due to Gram-positive bacteria; older catheters are colonized by the flora in the catheter hub, which include fungi and Gram-negatives. Overall, the most important agents are Coagulase-negative *Staphylococci*, *S. aureus*, aerobic Gram-negative bacilli and *Candida* [84].

To our knowledge, there are no prospective randomized clinical trials about the treatment of these infections and...
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most recommendations come from observational studies. The Infectious Diseases Society of America recommends starting empirical therapy with vancomycin if there is suspicion of MRSA or with antipseudomonal-cephalosporines if Pseudomonas is a concern. If vancomycin fails for systemic therapy, options are weekly dalbavancin [86], but not linesolid, which has been associated with a higher mortality rate than other agents, according to an FDA alert of 17 March 2007. There is a recommendation that all septic patients with suspected catheter-related infections should have their catheters changed and that all tips should be sent for culture. However, if this impairs appropriate resuscitation and antibiotic infusion, the antibiotic-lock strategy should be used [84].

The antibiotic-lock consists of filling a closed catheter with some antimicrobial solution while it is not being used. Recent trials have determined that any combination of EDTA, 25% ethanol or minocycline should be used with a dwell time of 60 min for 14 days because these schemes have a higher rate of catheter sterilization [87].

If Staphylococcus aureus is isolated, there is evidence that catheter removal reduces relapse-rates [88] and this should be tried again, if not done initially. Semisynthetic antistaphylococcal penicillins should be used for susceptible strains, and vancomycin or dalbavancin are the drugs of choice for MRSA. S. aureus infections can be complicated by endocarditis and, therefore, a transesophageal echocardiogram should be done in the persistence of symptoms after 72 h of treatment. Treatment should be maintained for 10 – 14 days normally and up to 4 weeks in the case of endocarditis or metastatic infections [84].

In the case of Candida species, five prospective studies have shown a benefit of catheter removal [89,90] and it should be done within 72 h of diagnosis. Therapy should be done with fluconazole or an echinocandin (caspofungin or anidulafungin). If an azole-resistant Candida is suspected, the echinocandins are preferable. Treatment should last for 2 weeks [31].

Finally, Gram-negative bacteria have only rarely been associated with catheter-related infections. In the largest series to date, there were 149 episodes reported of S. maltophilia and other non-aeruginosa Pseudomonas [91]. In this series, failure to remove the catheter was also associated with a higher rate of treatment failure and, therefore, removal of the catheter and treatment with a 1-week course of a broad spectrum antibiotic are recommended.

2.6 Sepsis related to intra-abdominal infections

Sepsis occurs in the setting of complicated intra-abdominal infections, defined as ‘infections extending beyond the original organ, into the peritoneal cavity, through a perforated viscus, with a subsequent induction of a systemic inflammation syndrome’ [92]. Of all sepsis patients, 21.4% are surgical patients [1,5], and 20 – 38% have the primary source of infection inside the abdomen.

The main cause of intra-abdominal infections is perforation of the gastrointestinal tract, and therefore diagnosis relies on image evidence of perforation by ultrasound or CT scans. Collections identified should be drawn for gram staining and aerobic and anaerobic culture; two sets of blood cultures should also be collected.

The incidence of different infectious agents leading to intra-abdominal infection varies in different sites. However, there are some trends that deserve consideration: i) more than 50% of cases are polymicrobial and almost 80% involve at least one anaerobe [93]; ii) most causes of community-acquired infection are caused by Gram-negative bacilli and multi-resistant anaerobes, while nosocomial infections normally involve at least one MDR strain [94]; iii) risk factors for MDRs include hospitalization over 48 h; immunosuppression; postoperative infection; recent antibiotic therapy; and residence in skilled nursing care or long-term care facility [92].

In vitro susceptibility of Gram-negative bacilli is collected annually from intra-abdominal infections by the Study for Monitoring Antimicrobial Resistance Trends (SMART), an international surveillance program to monitor resistance patterns globally [95]. The SMART report from 2004, the most recent to date, evaluated 6159 Gram-negative bacilli from 5731 patients in 28 countries and determined that enteric GNB comprised 86% of isolates, including E. coli (48.4%), Klebsiella sp. (16%), and Enterobacter sp. (9%). Ten percent of E. coli, 17% of Klebsiella sp. and 22% of Enterobacter sp. produced extended-spectrum beta-lactamases, and overall, carbapenems and amikacin were considered the most active agents.

The main therapeutic approach is an adequate surgical control of the infected site, which is beyond the scope of this article. According to Guidelines of the Surgical Infection Society [96], antibiotic therapy should be offered to all patients with perforations uncorrected for more than 24 h, for extensive infections, for infections not fully removable by surgery and for persistent symptoms after surgery.

Both the Surgical Infection Society [96] and the Infectious Disease Society of America [97] recommend that high-risk patients, such as septic shock patients, should receive empiric treatment with broad spectrum antibiotics. This therapy should be effective against both Pseudomonas and Enterococcus species, which can be found in up to 25% of severe patients [98]. Meta-analyses have found no difference in response rates to carbapenems, tigecycline and moxifloxacin [99], and pharmacologic models have predicted a better response to carbapenems, piperacillin-tazobactam, ceftazidime and cefepime [100]. Therefore, normally recommended antibiotics are carbapenems (imipenem/cilastatin or meropenem), piperacillin-tazobactam, or third-/fourth-generation cephalosporines combined with metronidazole. At present, there is a recommendation to avoid fluoroquinolones, because of a high concern for the development of resistant strains [99].
studies suggest higher clinical cure rates for linezolid when compared with vancomycin [27,101] but further investigation is needed before this drug can be recommended as first-line therapy. For Enterococcus faecium, only linezolid and tigecycline have reliable effectiveness; for MDR Pseudomonas, the only option is colistin [102]; and for Candida peritonitis, caspofungin is as effective and less toxic than amphotericin B [31]; voriconazole is a salvage alternative [103].

Finally, continued therapy should be maintained until clinical signs of infection have resolved, including fever and abdominal pain, normalization of the white blood cell count, and restoration of gastrointestinal function. Provided these criteria are met, the likelihood of reinfection after discontinuation of antibiotic therapy is exceedingly small [104]. Typically, this will involve 5 – 7 days of therapy.

3. Impact of surviving sepsis campaign resuscitation bundle on survival and costs

In 2003, a group of international Critical Care and Infectious Diseases experts in the diagnosis and management of infection and sepsis, representing 11 organizations, met to develop guidelines that could be used at the bedside to improve the outcome of severe sepsis and septic shock. Two years later, the process of bedside-implementation of those guidelines in hundreds of institutions around the world began. Since then, several studies have been published showing the implications of implementing severe sepsis bundles to clinical outcome.

There are two severe sepsis bundles: resuscitation and management. The resuscitation bundle includes measuring lactate; drawing blood cultures before starting antibiotics; starting broad spectrum antibiotics in the first hour after the first sepsis-induced organ dysfunction; keeping mean arterial pressure ≥ 65 mmHg throughout fluid replacement and vasopressors; and reaching a central venous pressure between 8 and 12 mmHg and a central venous oxygen saturation above 70%. The treatment protocol for achieving hemodynamic stabilization and optimization of tissue perfusion was based on the well-known early goal directed therapy by Rivers et al. [105].

Some studies have evaluated the impact of this strategy on clinical outcome in severe septic patients. The first report was published by Gao and co-workers [106] showing a mortality relative risk reduction of about 50%. Also, a before-after study from Kollef’s group [107] has shown that the implementation of SSC guidelines in the Emergency Department was associated with lower mortality rates (48.3 vs 30.0%, p < 0.040). The authors have also reported a greater volume resuscitation (2825 ± 1624 vs 3789 ± 1730 ml, p < 0.002), and greater administration of appropriate initial antibiotic (71.7 vs 86.7%, p < 0.043) when compared with patients in the before group. Similarly, a German retrospective cohort study [108] has assessed the impact of a ‘standard operating procedure (SOP)’ based on the SSC guidelines (basically early-goal directed therapy, glycemic control, hydrocortisone and activated protein C administration) on outcome of septic shock patients. Again, the mortality rate was lowered from 53 to 27% after implementation of the SOP. More recently, a nationwide observational study performed in 59 medical-surgical Spanish ICUs has showed an association between sepsis bundles implementation and relative risk reduction in the hospital mortality rate [8]. Taking together these studies, we could easily conclude that the implementation of evidence-based sepsis bundles is associated with mortality rate reduction. In some of these studies, increased adherence to early antibiotics administration was also associated with better outcomes.

The economic impact of the above described protocol implementation was evaluated in two studies. In the first [109], the authors were able to show a decrease in total costs ($16,103 vs $21,985, p < 0.008) and an increase in surviving rate (70.0% vs 51.7%, p < 0.04) following the protocol’s adoption. The cost reduction was associated with a shortening of length of stay. The second study [110] evaluated costs and cost-effectiveness of a sepsis integrated protocol implementation. The authors reported that this implantation resulted in a mean increase in cost of $8,800 per patient but was associated with a longer life expectancy and more quality-adjusted life years. The protocol was associated with an incremental cost of $11,274 per life-year saved and a cost of $16,309 per quality-adjusted life year gained. These studies have demonstrated that the implementation of a standardized protocol to manage patients with severe sepsis is, at least, cost-effective.

4. Conclusion

In summary, empiric intravenous antibiotic therapy should be started as early as possible after recognition of the first sepsis-induced organ dysfunction and be adjusted after microbiological results. Appropriate cultures should be taken before initiating antibiotic therapy. Although the choice of adequate antibiotics depends on clinical characteristics of the patients and the microbiological profile of the institutions, there are several evidence-based guidelines that could be implemented.

5. Expert opinion

Sepsis is a major challenge in critical care medicine. Every institution should orientate its care providers to create strategies to manage this syndrome adequately. This approach should include the creation of a multidisciplinary team involving physicians, nurses, respiratory therapists, nutritionists, clinical pharmacists and microbiological and lab departments, among others. This team should implement a ‘standard operating procedure’ of evidence-based sepsis interventions. One of the key interventions that lowers mortality rate is an
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adequate antibiotic therapy. The concept of ‘adequate antibiotic therapy’ in severe sepsis should include not only appropriate spectrum of activity and tissue penetration but also early administration. Hence, the challenge of facing a severe sepsis patient is to provide a fast diagnosis including the source of infection, which should also drive the choice of the antimicrobial agents and their prompt infusion (establishing a supply of premixed antibiotics for such urgent situations), and a reassessment of the chosen regimen after microbiological results.

Another huge challenge has been the management of sepsis due to multi-drug resistant microbes, especially *Pseudomonas*, *Acinetobacter*, ESBL producing strains of *Klebsiella* and *E. coli*, and methicillin-resistant *Staphylococcus aureus*. Several institutions have already used polymyxin B as the last option for dealing with *Pseudomonas* and *Acinetobacter* infections, and perspectives to deal with these conditions are lacking. Indeed, when we look at the future of antibiotics in terms of new developments, the scenario is disturbing, owing to the progressive decrease in the search for new drugs. Since antibiotics are semisynthetic drugs that can be easily produced and made generic, there is a trend towards less investment for the research and development of new antimicrobial agents. On the other hand, research has been increasing for antifungal agents, since the prevalence of fungi infections is increasing, as well as fungi-associated burden in outcome.

**Declaration of interest**

The authors state no conflict of interest and no payment has been received in preparation of this manuscript.

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Papers of special note have been highlighted as either of interest (*) or of considerable interest (**) to readers.

   • First populational study of sepsis based on hospital discharge records. Describes and validates this study protocol, used in other articles in this review.
   • Large populational study, based on hospital discharge records, which estimates annual incidence of sepsis in the USA and describes comorbid conditions, infectious agents and system failures.
   • Large populational study, based on hospital discharge records, which estimates the annual incidence of sepsis in the USA and describes trends in sepsis epidemiology from 1993 to 2003. The incidence seems to be increasing, but case fatality decreasing.
   • Results from the SOAP study: large, prospective, multicenter, international epidemiological analysis of sepsis in European ICUs.
   • Reviews articles about ICU costs related to sepsis. Concludes that newer, sepsis-specific therapies are cost effective, basically because they enable better survival and shorter ICU length-of-stay.
   • Most updated guidelines on sepsis diagnosis and management.
   • Prospective study in three tertiary Spanish Hospitals. Compares the characteristics of sepsis patients in the ICU and in the wards.
   • Retrospective analysis of ED charts from patients with suspected sepsis. Concludes that most cases of sepsis are community-acquired and are initially treated in the ED.

**Meta-analysis of 17 studies, concludes that combination therapy is not superior to monotherapy in sepsis patients, unless when Pseudomonas aeroginosa is a concern.**


**Meta-analysis done by the Cochrane Collaboration, pools results from 64 trials and concludes that adding an aminoglycoside to a beta-lactam, does not improve survival in sepsis patients, nor even in individuals with high risk for Pseudomonas infection.**


• Evaluates 720 patients with ventilator-associated pneumonia and concludes that targeted antibiotic therapy is associated with less antibiotic use, shorter ICU length of stay and no negative impact on mortality.


• Meta-analysis of 59 studies comparing procalcitonin to c-reactive protein as a marker of systemic inflammatory response syndrome due to bacterial infection. Procalcitonin was better, with a Q value of 0.78 (vs 0.71 for CRP, p = 0.002). The closest to 1, the more likely a test is to discriminate between individuals with and without a characteristic.


• Prospective study of procalcitonin levels in sepsis patients. Higher levels related to higher mortality rates.


• Randomized controlled trial of usual treatment protocols versus procalcitonin-guided protocols for patients with suspected community-acquired pneumonia. The procalcitonin group had shorter treatment courses (5 vs. 12 days, p < 0.001) and no negative impact on survival.

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** Only prospective, randomized trial of procalcitonin-guided antibiotic therapy for severe sepsis patients. Seventy-nine patients were enrolled in a single institution. Procalcitonin-guided therapy was related to shorter durations of antibiotic therapy, with no negative impact on survival.


** IDSA/ATS 2007 guidelines for diagnosis and management of community-acquired pneumonia.


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