Chapter 3

Clinical Aspects of Sepsis: An Overview

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Abstract

Sepsis is one of the oldest and most elusive syndromes in medicine. With the confirmation of germ theory by Semmelweis, Pasteur, and others, sepsis was considered as a systemic infection by a pathogenic organism. Although the germ is probably the beginning of the syndrome and one of the major enemies to be identified and fought, sepsis is something wider and more elusive. In this chapter clinically relevant themes of sepsis will be approached to provide an insight of everyday clinical practice for healthcare workers often not directly involved in the patient's management.

Key words Sepsis, Severe sepsis, Septic shock, Sites of infection

1 Definition

Severe sepsis or septic shock is a complex syndrome defined in a consensus conference of many different and important scientific societies in 2001 [1]. This syndrome includes infection, suspected or documented, and presence of any of the diagnostic criteria shown in Table 1. This table has been adapted from the last available version of "Surviving Sepsis Campaign," published in 2013 [2]. Both former SIRS (systemic inflammatory response syndrome) criteria and organ dysfunction criteria are present.

These items are based both on clinical and laboratory parameters. Severe sepsis is defined as sepsis with an organ dysfunction.

Interestingly, over the years, tissue perfusion variables, especially lactatemia, have received great attention, and a threshold value of hyperlactatemia is nowadays included in the definition of severe sepsis, defining sepsis as "severe" also without clear organ involvement.

Septic shock is defined as persistent hypotension, with systolic blood pressure <90 mmHg or mean arterial blood pressure <70 mmHg, after adequate fluid resuscitation.

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Table 1
Criteria for severe sepsis and septic shock

Infection (proved or suspected) and any of the following
General variables
Fever (>38.3 °C) or hypothermia (core temperature <36 °C)
Heart rate > 90 bpm or >2 SD normal value for age
Tachypnea
Altered mental status
Significant edema or positive fluid balance (>20 ml/kg in 24 h)
Hyperglycemia (plasma glucose >140 mg/dl or 7.7 mmol/l) without diabetes
Inflammatory variables
Leukocytosis (WBC >12,000 cells/microL^{-1}) or leukopenia (WBC < cells/microL^{-1} 4,000)
Normal WBC with >10 % immature forms
Plasma C-reactive protein >2 SD above normal value
Plasma procalcitonin >2 SD above normal value
Hemodynamic variables
Arterial hypotension (SBP<89 mmHg, MAP<70 mmHg, or a SBP decrease > 40 mmHg)
Organ dysfunction variables
Arterial hypoxemia ($PaO_2/FiO_2 < 300$)
Acute oliguria (urine output <0.5 ml/kg/h for at least 2 h despite adequate fluid resuscitation)
Creatinine increase >0.5 mg/dl or 44.2 micromol/l
Coagulation abnormalities (INR > 1.5 or aPTT > 60 s)
Ileus (absent bowel sounds)
Thrombocytopenia (PLT < 100,000 microL^{-1})
Hyperbilirubinemia (>4 mg/dl or 70 micromol/l)
Tissue perfusion variables
Hyperlactatemia (>1 mmol/l)
Decrease capillary refill or mottling

Sepsis is defined by infection (suspected or documented) and general or inflammatory variables. *Severe sepsis* requires at least one organ dysfunction
Septic shock is defined by persistent arterial hypotension despite adequate fluid resuscitation that requires inotropes or vasopressors
SD standard deviation, *WBC* white blood cells, *SBP* systolic blood pressure, *MAP* mean arterial pressure, *PaO_2* arterial partial pressure of oxygen, *FiO_2* fraction of inspired oxygen, *INR* international normalized ratio, *aPTT* activated partial thromboplastin time, *PLT* platelets. Adapted from Dellinger et al [2]

Despite this highly standardized definition of sepsis, there is up to 20 % variability in the incidence of severe sepsis and septic shock, due to variations in interpretation of SIRS criteria [3].

2 Epidemiology

According to Kumar [4], the rate of hospitalization for severe sepsis in the United States has increased from 143 to 343 every 100,000 people from 2000 to 2007. Mortality rates for severe sepsis exceed those of common medical conditions, such as myocardial

infarction and stroke. In the last 20 years, mortality rates for severe sepsis decreased from over 50 % to almost under 30 % [5], with an odds reduction similar to that observed for other severe conditions, like congestive heart failure or surgery for intracerebral hemorrhage.

An apparently surprising observation is that, despite the reduction in mortality, nowadays hospitalized patients have higher rates of organ failure (respiratory, renal, and cardiovascular failure being the most commonly diagnosed) and also a higher probability of experiencing septic shock than only severe sepsis [4]. Nevertheless, mortality has decreased. This is probably related to advances in supportive care for the critically ill such as implementation of bundled care processes, low tidal volume ventilation for acute respiratory distress syndrome, and possibly extracorporeal membrane oxygenation.

The trend of increase in sepsis is expected to increase due to aging of the population, enhanced survival to chronic health conditions, and a wider access to advanced treatments, like high invasive surgery, transplant program, chemotherapy, and immunosuppressive therapy.

It is unclear if the trend in mortality reduction will continue also. Several important trials studying new therapeutic weapons failed to show survival benefits, either regarding new drugs [6, 7] or use of old drugs with new indications [8]. Even a promising drug as drotrecogin alfa or recombinant activated protein C, after some published efficacy data, failed to confirm its efficacy in two randomized controlled trials and has been removed from the market by the producer [9, 10]. Some reports of a similar drug (but in the zymogen form) are interesting, but high-quality evidence is still missing [11, 12]. Hospital-acquired infections have increased and account for 4.5% of admissions [13]. An alarming scarcity of new antibiotic classes in the pipelines of the pharmaceutical industry reduces availability of new molecules and has forced the healthcare community to optimize the therapeutic potential of currently available antibiotics [14], but pan-drug-resistant bacteria are reported.

3 Etiology

Etiology of sepsis is classically approached by considering the site of infection and the microbiological responsible pathogen.

1. The lungs represent the most common site of infection and pneumonia is associated with the highest mortality. According to Table 2, showing some of the most important (published after 2012 on journal with impact factor superior to 6, including at least 100 randomized patients) recent randomized studies on several sepsis treatments, the lungs were the site of

Table 2
Recently published major randomized studies on septic shock or severe sepsis

First author	Schortgen	Annane	Ranieri	Morelli	Brunkhorst	Guntupalli	Perner	Opal
Patients included	200	411	1,696	154	600	194	798	1,961
Population	SSH	SSH	SSH	SSH (a)	SeS, SSH	SeS	SeS	SeS
CA/HA	na	78/22 %	77/23 %	na	50/50 %	na	25/75 %	na
Lung	84 %	67 %	44 %	64 %	41 %	48 %	55 %	51 %
Abdomen	7 %	11 %	30 %	33 %	38 %	14 %	8 %	24 %
Genitourinary	6 %	17 %	12 %	<1 %	12 %	21 %	13 %	21 %
Bloodstream infection	na	14 %	5 %	0	3 %	0	0	5 %
Soft tissue, bones, joints	na	8 %	5 %	0	7 %	14 %	11 %	9 %
Others	14 %	8 %	8 %	0	15 %	na	10 %	8 %
Unknown site	5 %	4 %	na	0	na	na	na	na
Gram positive	26 %	40 %	na	na	54 %	51 %	na	27 %
Gram negative	41 %	44 %	na	na	49 %	27 %	na	32 %
Others (fungi, virus, anaerobia, etc.)	0 %	12 %	na	na	29 %	7 %	na	2 %
Mixed organisms	5 %	na	na	na	(b)	30 %	na	11 %
No pathogen identified	25 %	27 %	41 %	na	8 %	na	na	26 %

Type of population, major sites of infection, and causative pathogen in some of the major published randomized controlled studies on severe sepsis and septic shock
SSH septic shock, *SeS* severe sepsis, *na* not available, *CA/HA* community/hospital acquired. Causative pathogens sum may exceed 100 % because some had more than one infection site; (a) selected population; (b) already included in other groups

infection for 41[15]–84 % [16] of enrolled patients. Secondarily, genitourinary tract, especially in young women, and intra-abdominal sepsis in surgical cohorts, account for, respectively, 1–21 % [7, 17] and 7–38 % [15, 16] of cases.

Bloodstream infections are expected to increase due to the higher number of implantable devices utilized, such as pacemakers and long-lasting central or peripheral inserted venous catheters. In some series, these could be responsible for up to 14 % of etiology of sepsis [10].

Knowing the site of infection is very important. Even though severe sepsis and septic shock are syndromes involving the whole body, the identification of the specific site of infection causes important subsequent actions.

First, it has been proved that the choice of the correct antibiotic molecule must consider its penetration and activity in the site of infection. It is well known, for example, that important molecules against severe pathogens like MRSA (*methicillin-resistant Staphylococcus aureus*), such as daptomycin, are very effective against the bloodstream infection but completely useless in lung disease, due to surfactant inactivation.

Second, the site of infection is associated with the risk of death. Urinary tract and intravascular catheter infections are less likely to be lethal than sepsis involving the lungs, abdomen, or soft tissues.

Third, some sites of infection will require adjunctive therapies other than antibiotics to obtain infection control. Drainage of abscess, revision of anastomosis, and debridement of tissue necrosis are sometimes fundamental to obtain source control in sepsis. Galeno's adage *ubi pus ibi evacua* (where there is pus, there evacuate it), from 150 b.C. is still very valid (nowadays probably not with extensive surgery, but with more accurate and conservative radiological guided procedures, as a percutaneous drainage of an abscess).

2. Many important data on the causative pathogens come from EPIC II study, an international collaborative study that enrolled 1,265 intensive care units (ICUs) all around the world in 2007 [18]. This study confirmed the respiratory tract to be the first site of infection but extensively evaluated causative microorganisms.

   Among pathogens, gram negative account for majority of isolates (62 %), with *Escherichia coli* in the prominent position (16 %). Gram positive account for 47 %, with *Staphylococcus aureus* (SA) in the first line (21 %).

   Pseudomonas species and fungi are important pathogens in sepsis nowadays (respectively, 20 % and 19 %).

   According to Table 2, it is important to notice that, even in highly controlled settings, the probability of missing the causative agent of sepsis is still too high: up to 41 % [9]. Missing

pathogen identification could have important outcome on choice, tailoring, and escalation of antibiotic treatment. It is well known that missing efficacy of first-line antibiotics has a severe and important impact on patients' outcome [19].

Pathogen identification can also help to stratify patients' risk of death and advise on appropriate setting for treatment (ICU versus general ward) and intensity of clinical and laboratory monitoring.

Cohen and colleagues [20] reviewed half a thousand papers, including more than 55,000 patients with microbiologically confirmed infections. Analyzing in detail the interaction between the site of infection and the causative pathogen, they showed that SA involved in skin and soft tissue infections causes death in 0–25 % of patients, while the same pathogen in the lung causes death in 31–84 % of patients.

Therefore, the site of infection and the identification of the pathogen involved are both of paramount importance and strongly interrelated and should be considered together when approaching the evaluation or treatment of patients with severe sepsis or septic shock.

4 Overall Clinical Picture

Patients with severe sepsis suffer more than from just the consequences caused by the primary site of infection, whatever it is.

Some studies have addressed the question of how many patients with sepsis (or infection) will progress to severe sepsis or septic shock. There is great variability in this proportion, probably related to the population considered (only ICU or general ward patients): in the ICU 70 % of septic patients will develop severe sepsis and 17 % septic shock [21], and when considering general wards, 39 % of patients will develop severe sepsis [22], probably due to the less severe disease compared to the ICU.

The number of organs involved in severe sepsis is variable. An international research on severe sepsis, enrolling more than 1,900 patients [22] affected by severe sepsis within 12 h from the first organ dysfunction, showed that half of the patients had lung localization, followed by intra-abdominal and genitourinary tract infection.

In Table 3, a very common distribution of organ dysfunction is shown. About one third of patients have only one organ dysfunction. Another third of patients have two organ dysfunctions, and the last third are composed by patients with three or four organ dysfunctions. Overall, the majority of patients have a multi-organ disease.

The most common clinical picture is a patient presenting with infection and two or three organ failures (cardiovascular, renal, and respiratory dysfunction being the most frequent). Even if often not

Table 3
Distribution and frequency of organ dysfunction

Organ dysfunction	Percent	Mean SOFA score
Arterial Hypoxemia	23 %	2.7
Thrombocytopenia	16 %	0.6
Arterial Hypotension	82 %	3.3
Acute renal failure	36 %	1.9
Impaired neurological status	na	1.6
Number of organ failure	**Percent**	**Cumulative percent**
1	34 %	34 %
2	35 %	69 %
3	22 %	91 %
4	8 %	99 %
5	<1 %	100 %

Distribution of organ dysfunction in more than 1,900 patients affected by severe sepsis or septic shock and mean SOFA (sequential organ failure assessment) score for each dysfunction. For arterial hypoxemia, mean patient had a PaO2/FiO2 ration between 200 and 300, and for arterial hypoxemia, had infusion of mild to high dose of vasopressor. Mean glasgow coma scale was between 14 to 10 and platelet count more than 150,000 cell/microL1. Adapted from Opal et al. [6]

formally classified, up to 50 % of patients will also experience encephalopathy [23], representing a further failing organ.

The clinical picture often includes: impaired neurological status, varying from confusion to coma; signs of shock like hypoperfusion, oliguria or anuria, and high lactate levels; clinical signs of hypovolemia, due to temperature or to effective losses (in the third space or in the abdomen); vasodilation; and respiratory impairment even though respiratory mechanics could be normal (especially in young patients and in extrapulmonary localization) with tachypnea due to the attempts to compensate the metabolic acidosis; shock is often associated with a reduction of systemic blood pressure and a worsening of kidney function or cerebral performances; when severe cardiac impairment causes a low output syndrome, instead of the classic reddish due to vasodilation, the skin can become whitish; either fever or hypothermia can be present in sepsis.

Above this general picture, signs of the primary site of infection can be present and can guide the clinician to diagnosis. Elevated aminotransferase levels, paralytic ileus, altered glycemic control, thrombocytopenia and disseminated intravascular coagulation, euthyroid sick syndrome, and adrenal dysfunction are all common in patients with severe sepsis.

Mortality of severe sepsis and septic shock has dramatically reduced when compared to that reported 30 years ago, when they were typically lethal (often exceeding 80 %) [24]. Advances in training, better surveillance and monitoring, prompt initiation of therapy to treat the underlying infection, and support of failing organs have brought mortality down to 20–30 % in many series [25]. Numerous studies have suggested that patients who survive to hospital discharge after sepsis remain at increased risk of death in the following months and years. Those who survive often have impaired physical or neurocognitive functioning, mood disorders, and a low quality of life [26].

5 Major Sites of Infection

5.1 The Lung

5.1.1 Community-Acquired Pneumonia

Community-acquired pneumonia (CAP) [27] should be considered in any patient who has newly acquired respiratory symptoms (cough, sputum production, and/or dyspnea), especially if accompanied by fever and auscultatory findings of abnormal breath sounds and crackles. Standard posteroanterior and lateral chest radiographs are valuable in these patients and may also suggest specific etiologies or conditions such as lung abscess, tuberculosis, and acute respiratory distress syndrome. Computerized tomography of the thorax can add important sensitivity and specificity to chest X-rays and is helpful also to set mechanical ventilation (when necessary).

More recently, lung ultrasound (LUS) has gained importance in the diagnosis of CAP, being at least as accurate as chest radiography. Air bronchogram within an echo-poor area is the most important parenchymal criterion. At the same time, LUS allows the diagnosis of interstitial syndrome, showing the presence of multiple diffuse bilateral B-lines [28]. Ideally, physical examination and LUS at the bedside could allow immediate diagnosis of CAP.

In CAP every effort should be made to identify a specific etiologic pathogen in a timely manner, with focused and appropriate testing. If the etiology is identified, therapy can be focused, but this goal should account for two considerations. First of all, according to sepsis survival guidelines, therapy should be started within 1 or 3 h (if diagnostic tests lead to a delay in therapy, they are associated to adverse outcome). Even if microbiological sampling should be done before administration of the first dose of antibiotics, microbiological tests with great sensibility even after antibiotic administration exist (e.g., those based on antigen or polymerase chain reaction).

Secondly, in CAP, coinfection of a bacteria and an atypical pathogen is possible. Atypical bacteria may be harder or longer to identify; therefore consideration of a full course of effective therapy should be granted, even with negative or pending microbiology assays. When possible, a Gram stain of sputum could be useful.

Two sets of blood cultures should be drawn before initiation of antibiotics in CAP patients, as in any other patients with severe sepsis or septic shock. For patients with suspect of *Legionella* infection, measurement of urinary antigen is valuable [29].

Many invasive diagnostic techniques to obtain lower airway specimens exist (transtracheal aspiration; bronchoscopy with lavage or brush, protected or not; needle aspiration of the lung). These procedures are not indicated in most patients with CAP, but could be useful in patients whose illness is not resolving in spite of an apparently appropriate therapy.

5.1.2 Hospital-Acquired, Ventilator-Associated, and Healthcare-Associated Pneumonia

Hospital-Acquired, Ventilator-Associated, and Healthcare-Associated Pneumonia (HAP, VAP, and HCAP) are important causes of morbidity and mortality despite advances in antimicrobial therapy, better supportive care, and a wide range of preventive measures. HAP incidence varies between 5 and 15 cases per 1,000 hospital admissions. Pneumonia in ventilated patients is 6- to 20-fold higher than in non-mechanically ventilated patients.

HAP is defined as pneumonia that occurs 48 h or more after admission, which was not incubating at the time of admission. VAP refers, traditionally, to a pneumonia that arises more than 48–72 h after tracheal intubation [30]. HCAP is included in the spectrum of HAP and VAP, and patients with HCAP need therapy and, more generally, care as HAP patients. The Centers for Disease Control and Prevention (CDC) recently proposed an algorithm that uses objective, readily available data elements to identify a broad range of conditions and complications occurring in mechanically ventilated patients, including but not limited to VAP, introducing new conditions like ventilator-associated condition (VAC, an elevation in the demand of oxygen and pressure), infection-related VAC (IVAC, also an abnormal temperature or white blood cell count and the starting of a new antimicrobial agent), and, lastly, VAP that requires that patients have IVAC and laboratory and/or microbiological evidence of respiratory infection [31].

The etiology of these kinds of pneumonia is considerably different from CAP, being commonly caused by aerobic gram-negative bacilli like *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Acinetobacter* species or gram-positive cocci, such as *Staphylococcus aureus*, with a great incidence of methicillin resistance.

The CDC introduced new categories also because the diagnosis of HAP is difficult, due to reduced use of cultures of protected specimen (e.g., bronchoalveolar lavage) and because chest X-ray interpretation is often challenging in patients with long hospitalization or concomitant cardiac diseases. Even adding invasive strategies to diagnostic techniques in VAP doesn't seem to affect survival [32].

Generally, two approaches can be applied for the diagnosis.

The clinical approach defines the presence of pneumonia as a new lung infiltrate plus clinical evidence that the infiltrate is of an infectious origin. This grants the starting of a new antibiotic treatment, with the execution of microbial sampling before starting the new plan of therapy.

The bacteriologic strategy uses quantitative cultures of lower respiratory secretions (endotracheal aspirate, BAL, or protected brushing) to define both etiology and presence of pneumonia. Growth below some threshold, based on the methodology of collection of sampling, is assumed to be due to colonization or contamination, and new antibiotics are administered following quantitative microbiologic results. The incompressible delay of 48–72 h for complete antimicrobial testing, including antibiotic susceptibility, has enforced the development of rapid molecular testing to optimize the choice of initial drugs and to avoid the overprescription of broad-spectrum molecules. Such tools should reliably identify both the most common pathogens and their most frequent resistance genotypes in 2–6 h. Real-time PCR, in situ DNA hybridization, and mass spectrometry are some of the leading investigation methods [33].

When therapy decisions have been based on bacteriologic strategy, fewer patients have been treated with antibiotics and a narrow spectrum of therapy used, compared to the clinical approach. Major concerns with this approach are that a false-negative culture can lead to a failure to treat the patients and that positive results, after at least 48 h of waiting, lead to a strong delay in starting new antibiotic treatment and this could worsen the outcome.

An important factor causing false-negative cultures is a recent start or change in antibiotic treatment as this can alter positivity of cultures itself or amplitude of bacterial growing. Therefore, ideally, all quantitative cultures should be obtained before any antibiotic manipulation. When this is not possible, changes in the diagnostic threshold may be helpful. Taken together these considerations imply an important alliance between the clinician and the laboratory: knowledge of the kind of sampling and history as well as timing of antibiotic treatment could be important in evaluating and interpreting microbiological results.

Guidelines are available in leading treatment of all forms of pneumonia. Therapy is complex and depends on patient's adjusted risk of atypical pathogens, multidrug-resistant pathogens, and MRSA involvement. Attention should be also paid to the pharmacodynamic and pharmacokinetic properties of every molecule and their penetration in the lung parenchyma.

Notably, pneumonia treatment, especially in patients requiring mechanical ventilation, is the way the patient receives mechanical ventilation itself [34, 35], and great attention should be done to avoid both volutrauma and barotrauma, by meticulously controlling

tidal volume. In the most severe patients, with refractory hypoxemia or impossibility to use protective mechanical ventilation, extracorporeal support of oxygenation is possible today and, despite necessity of definitive evidence, results are encouraging [36, 37]. As extracorporeal support can't be delivered in every hospital due to the high complexity of this treatment, many countries have developed a system of centralization of more severe cases, in a hub-and-spoke structure.

In conclusion, an increasing burden of pneumonia, in its many different forms, can be expected in the coming years, due to many factors, like progressive aging of population, increasing of comorbidities, and intensification of cares. Both diagnosis and treatment of pneumonia remain challenging and grant an intensive work for research and development of new clinically efficient instruments [38].

5.2 Abdominal Infection

Intra-abdominal infections (IAIs) represent a wide variety of conditions that involve lesions of all intra-abdominal organs. They include also intra- and retroperitoneal abscesses and parenchymal abscesses. They are divided as uncomplicated, when localized to one organ, and complicated, when causing peritonitis. Complicated IAIs are classified according to the cause of the associated peritonitis (primary, secondary, and tertiary) and the extension of the inflammation (local or diffuse) [39]. Similarly to pneumonia, they can also be divided into community-acquired (CA-IAI) and hospital-acquired (HA-IAI) with important differences regarding antimicrobial treatment [40].

IAIs are an important cause of ICU morbidity and mortality. Mortality is approximately 30 % and up to 50 % when peritonitis arises from a complication of a previous surgical procedure or recurs during ICU admission [41].

Gastrointestinal perforation with leakage of alimentary or fecal contents in the peritoneal cavity is the main cause of IAIs. Perforation can be caused by appendicitis, diverticulitis, ulcer, cancer, trauma, and medical procedures (like colonoscopy, gastroscopy, or biliary tract procedures). A second group of IAIs is related to biliary tract diseases (e.g., acute cholecystitis, cholangitis). The third group includes postoperative intra-abdominal infections (anastomosis leakage is an important cause of HA-IAIs and correlates with a very severe prognosis) [42].

The typical clinical presentation of IAI includes abdominal pain and tenderness with signs of peritoneal irritation on physical examination. Diffuse pain suggests generalized peritonitis, while localized pain suggests a walled-off process arising from an organ in the anatomic vicinity.

The epidemiology of IAIs is largely dominated by aerobic gram-negative bacteria (AGNB). In a study of 239 patients [43], abdominal drainage cultures revealed 53 % of AGNB, with

Escherichia coli being the most frequent. Interestingly, more than 30 % of patients had isolations of more than one pathogen. The incidence of gram negative is higher in distal (like colorectal and appendix) than in proximal perforation. Fungi are often involved in IAIs, being isolated in 20 % of patients, especially in proximal (gastroduodenal) perforations. Gram positives are also represented, up to 40 %.

Treatment of IAIs is challenging due to the high demand of a multi-faced therapy: surgery (as definitive or source control), antimicrobials, and an aggressive support of organ dysfunctions that often requires ICU management and full life support.

Antimicrobial therapy itself could be challenging due to: frequent polymicrobial infections, multidrug resistance for both in-hospital and out-of-hospital patients (especially due to community-acquired extended-spectrum beta-lactamase-producing bacteria), and fungi involvement.

Appropriate microbiological sample should be taken, possibly before antimicrobial starts but avoiding any possible delay in the first dose. Dosage consideration should include using high loading doses (patients with IAIs often have higher volume of distribution) and reduced further doses, because of the frequent association of IAIs with renal dysfunction.

Apart from blood sampling that should be done as in any other septic or septic shock patients, cultures should be taken from intra-abdominal samples during surgical or interventional drainage procedures, ensuring sufficient volume (at minimum 1 ml of fluid or tissue) and using transport systems that properly handle the samples so as not to damage them or compromise their integrity.

Concluding, IAIs are an important cause of preventable morbidity and mortality. The responsible disorders are numerous. Etiology often includes gram-negative pathogens, but also gram positive and fungi can be isolated and should be considered in treatment. Close collaboration between the surgeon, the radiologist, the microbiologist, and the intensive care specialist is imperative to ameliorate outcome.

5.3 Urinary Tract Infection

Urinary tract infection includes urinary infection, acute nonobstructive pyelonephritis, and, in men, bacterial prostatitis. The urinary tract is the source of infection of up to 30 % of severe sepsis or septic shock patients in some series [44]. In Table 2, this proportion is slightly lower, varying from 6 to 21 % [7, 16].

At the same time, few patients with urinary tract infection develop severe sepsis or septic shock. In an Israeli study including women with complicated pyelonephritis, only 13 % developed severe sepsis [45]. Ideally, progression of an uncomplicated urinary infection to severe sepsis should suggest an underlying complicating factor or the presence of a severe comorbidity (e.g., poorly controlled diabetes, liver cirrhosis), immune modulation, or suppression.

An indwelling catheter is of paramount importance to differentiate between urosepsis [46].

For non-catheterized patients, an evidence of infection by culture of pathogen directly from the infected tissue (not urine) is required or from fever, urgency, localized pain, tenderness at involved site, a compatible analysis of urine (pyuria, more than 10^5 cfu/ml, positive Gram stain), or a compatible imaging study.

For the catheterized patients, criteria for diagnosis of infection are more stringent due to the possibility of contamination or colonization. A direct evidence of infection or a positive culture above certain threshold associated with clinical compatible signs is required.

Urine culture should be collected in any patient with a suspected infection and could lead to definitive diagnosis, etiology determination, and therapy guidance. Since systemic antimicrobial therapy will usually sterilize the urine within minutes, it is very important that specimen for culture should be collected before initiation of therapy. Special attention should be given when urine sampling is done through an indwelling catheter, especially if it has been in situ for more than 2 weeks [47].

Blood cultures should also be collected, are frequently positive (up to 30 %) even in patients that will not progress to severe sepsis or shock, and might identify the most important strain in patients with multiple organism isolated from urine culture with implications in the tailoring of antibiotic therapy [48].

Treatment should be done according to available guidelines, usually including an extended-spectrum cephalosporin, a fluoroquinolone with mainly renal excretion, and, sometimes, a molecule with antipseudomonal activity [49].

Severe sepsis and septic shock have a relatively low mortality (10–20 %) in urosepsis [48], probably because of a relative straightforward approach to source control and a lower impairment of vital function (e.g., ARDS) [50].

6 Sepsis Management

Surviving Sepsis Campaign is an international consortium of professional societies involved in critical care and in infectious diseases. It recently issued the third iteration of clinical guidelines for the management of severe sepsis and septic shock [2] that provides extensive information on how to treat a sick septic patient.

Since guidelines have little immediate impact on bedside behavior, tools to increase guideline adherence and to speed their application have been developed.

6.1 Clinical Management

Clinical management of sepsis is grouped into interventions (or bundles) to be completed within 6 h and management bundles to be accomplished in the ICU.

The 6-h bundle includes initial volemic resuscitation with goal-directed fluid challenge, diagnosis of infection with microbiological sampling coupled with imaging studies, treatment of infection with antibiotics (also with surgery or radiological procedures when appropriate), and hemodynamic support with vasopressors or inotropes if volemic resuscitation fails to reverse hypoperfusion defects.

The management bundle after 6 h includes optimization of organ support and monitoring, avoidance of further complications, and de-escalation of care when possible. Routine critical care support therapy should be started: management of anemia and coagulation abnormalities, ventilation according to ARDSNet protective strategy, glycemic control, renal support, deep vein thrombosis, stress ulcer prophylaxis, and feeding. The only immune-modulating therapy is, in selected circumstances, a short course of hydrocortisone.

In patients with severe sepsis and septic shock, it is important to discuss goals of care and prognosis with patients and families. The goals of care, including any end-of-life care planning or the use of palliative care principles should be accomplished as appropriate [51].

6.2 Sepsis Performance Improvement Programs [51, 52]

Guidelines in sepsis should serve as a resource document for the creation of treatment protocols that, when coupled with audit and feedback as a part of a formal hospital-based performance improvement initiative, can change bedside practice and grant a real change in patient's outcome. Therefore sepsis treatment, as described in the guidelines, is only a part of a more complex group of actions that should be taken at a higher level, usually involving the full hospital and, in some instances, also the health service.

Programs to improve the performance start with hospital-wide education initiatives, centered around early identification and familiarity with the treatment protocols that will be applied once the patient is identified. Protocols can be successful in changing bedside behaviors only with the application of education and commitment of physician, nurse, and other healthcare professionals from key areas of the hospital (ICU, emergency department, and hospital floors).

Success of severe sepsis performance improvement programs requires multidisciplinary commitment from physicians, nurses, pharmacists, and administration. Programs must be multispecialized as well and include medicine, surgery, emergency medicine, microbiology, and others. Establishing support from key ICU, emergency dept., and floor leaders is crucial. Interdepartmental communication and collaboration facilitate seamless steps in the continuum of care and give the best chance of success.

7 Conclusions

Severe sepsis and septic shock are a frequent cause of mortality and morbidity. This syndrome is increasingly diagnosed over time, caused by many pathogens with an everyday harder profile of sensibility to antibiotics, one of the main cornerstones in the treatment of sepsis. Besides that, bundle approach and organization efforts are very important issues. The lung, abdomen, and urinary tract are still the major sites of sepsis, but other sites of infection, as the skin and blood, are increasing.

Early diagnosis and expedited treatment based on evidence-based medicine can decrease sepsis morbidity and mortality. Extensive collaboration between many figures (intensivists, surgeons, infectivologists, microbiologists, pharmacists, nurses, and many others) is required to get this goal. Over that, institutions and healthcare systems are also very important players in sepsis fight.

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