Management of sepsis: from evidence to clinical practice

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ABSTRACT

Sepsis is one of the leading causes of death in hospitalized patients and its management involves a lot of specialist. Internist is required to demonstrate his competence since the beginning when the diagnosis is not so easy to be clarified. A rapid clinical suspicion permits a prompt management of the patient that means important mortality reduction. However, it is essential to understand the source of infection and echography represents a rapid, economic, useful and widespread tool with whom Internist should become more and more confident. The following review is a practical guide to manage septic patients according to the most recent literature, underlining aspects of antibiotic therapy, hemodynamic stabilization and supportive therapy. To limit sepsis mortality, a valid Internist should be culturally prepared and especially able to cooperate with other specialists, because a strong enemy requires a strong team.

Introduction

Sepsis is defined as the presence (probable or documented) of infection together with systemic manifestations of infection. Severe sepsis is defined as sepsis with organ dysfunction, sepsis shock as sepsis with hypotension despite adequate fluid resuscitation[1] (Appendix Tables 1 and 2).

Sepsis and severe sepsis are important public health problems. Currently, severe sepsis is a leading cause of death in the United States and the most common cause of death among critically ill patients in non-coronary Intensive Care Units (ICUs).[2]

In general, sepsis occurs in approximately 2-4% of all hospitalizations in developed countries.[3,4] In most developed countries, the incidence of severe sepsis has been identified between 50 and 100 cases per 100,000 people in the population.[5] The incidence of sepsis is increasing in all areas of the world where epidemiology studies have been conducted. A two-decade study of US hospitalizations identified an increase in the incidence of sepsis among hospitalized patients by 8.7% per year.[6-10] This trend is expected to continue, due to aging of the population, increasing burden of chronic health conditions, increased use of immunosuppressive therapy, transplantation, chemotherapy and invasive procedures.[11] Mortality depends on quantity of organs involved and varies from 6% in case of sepsis, to 65% when 4 organs are involved.[12] The type of organism causing severe sepsis is an important determinant of outcome.[13] Gram-positive bacteria as a cause of sepsis have increased in frequency over time and are now almost as common as gram-negative infections, likely due to greater use of invasive procedures and the increasing proportion of hospital-acquired infections.[14]

Over the past 2 decades, the case-fatality has declined due to advances in supportive care for critical ill and a better understand of the physiopathology of sep-

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sis.[1] Despite falling proportional fatality rates of sepsis, the total number of people dying from sepsis each year continues to increase due to the growing number of cases. What we should do is to make diagnoses of sepsis as soon as possible, permitting a rapid therapy. Machiavelli stated *hectic fever, at its inception, is difficult to recognize but easy to treat; left unattended it becomes easy to recognize and difficult to treat*. 500 years have passed but this statement is still valid.

The diagnostic tools in sepsis

In the initial diagnostic evaluation of sepsis, the Guidelines recommend to perform at least 2 blood cultures, each one to be collected before antibiotic therapy by using aerobic and anaerobic bacteria's kits, and with at least 1 venipuncture and by taking 1 blood sample from each vascular access, which has been inserted for more than 48 h. If clinically indicated, other biological samples should be collected (urine, cerebrospinal fluid, expectoration or other biological fluids that can be considered as infected). In severe sepsis, the collection of culture tests samples should not delay the start of antibiotic therapy over 45 min.[1]

The blood culture's success is determined by many factors. Collection of blood samples should be made 60-90 min before temperature onset, with the assistance, if possible, of signs and symptoms (chills, marbling, abnormal neurological status, *etc*.).[15] The sample should contain at least 10 mL per bottle[16] and is defined as positive in the presence of at least 3 colony-forming units.

In case of intravascular catheter-related bloodstream infections[17] (CRBSI), a blood sample taking from the intravascular catheter is performed to assess bacterial colonization. In this case the diagnosis is made if the growth of the same organism from both the catheter tip culture and the blood culture sample took by venipuncture is demonstrated, or if the simultaneous positivization of blood cultures collected from both intravascular catheter and venipuncture is demonstrated with a faster or higher positivization of the sample taken from intravascular catheter rather than the sample taken from a peripheral vein. In case of severe sepsis and CRBSI, intravascular catheters should be removed assessing the true cost-benefit of a rescue treatment.

If an invasive candidiasis is suspected, the guidelines recommend dosage of 1-3 β-D glucan and/or mannan and anti-mannan antibody (Ab).[1] Blood cultures are often falsely negative or lately positive.

Anti-Candida Ab are unreliable in frequently immunocompromised patients and they might be false negative/positive, because this fungus is a gastrointestinal tract colonizer. For this reason, it is recommended to use the test to take over directly the fungus antigen.[18] The 1,3-β-D-glucan is a Candida cell wall component and in case of invasive candidiasis there will be high blood concentration of it. This test is not specific for Candida, but it can be positive in case of various fungal infections[19] (invasive *Aspergillosis*, *Pneumocystis jirovecii pneumonia*) with a high predictive negative value.[20] In case of invasive fungal infections, a high concentration of 1,3-β-D-glucan showed a good diagnostic capacity both in non-neutropenic patients[21] (sensitivity 80-90% in case of candidiasis) and in neutropenic patients.[22]

Mannan is a polysaccharide component of Candida cell wall; its presence in the blood correlates with invasive candidiasis.[23] The search for anti-mannan Ab has considerably improved the diagnostic possibilities of invasive candidiasis: in patients with candidiasis, the diagnostic sensitivity of a positive test for both mannan and anti-mannan Ab is greater than 80%.[24]

In addition to lab-tests, Sepsis Guidelines recommend the rapid execution of instrumental tests to identify the possible source of infection.[1] The clinical judgment is essential for choosing proper exams with the greatest cost-advantage, also considering their availability and the risks of transporting a critical patient; in this setting bedside-ultrasound can play an important role.

In course of infections and bacterial sepsis, endotoxins, exotoxins and some cytokines (interleukin-1 β, tumor necrosis factor α, interferon γ) stimulate production of procalcitonin (PCT), mainly by leukocytes (monocytes and macrophages), lung and intestine neuroendocrine cells; the same plasmatic protein, in normal metabolic conditions, is synthesized by thyroid C cells. In septic patients, PCT can be detected within 2-6 h and reaches peak values after 12-48 h. It has a half-life of about 20-35 h with decrementing values in few days in the absence of further stimulus.[25] PCT, due to its pharmacokinetic, can be considered an important biomarker of bacterial infection (high PCT levels are quickly detectable, persist along with the inflammatory process, tend to correlate with the disease outcome), however it can also increase during major surgery, cardiogenic shock, severe organ perfusion abnormalities, lung microcytoma, medullary C-cell cancer, polytrauma, burns. PCT can facilitate diagnosis of bacterial infection, provides prognostic information, directs therapeutic choices. Several trials have attempted to validate a decisional algorithm related to PCT values. In patients with the suspect of sepsis, empirical antibiotic therapy should be started independently of PCT values and serial evaluations may lead to suspension of antibiotic therapy;[26] although this approach can be useful in decision-making, further studies are needed to identify a specific algorithm and a reliable cut-off of PCT.[27]

Antibiotics

Intravenous administration of antibiotic therapy should be made as soon as possible (*golden hour*: within 1 h) after diagnosis of severe sepsis with or without shock. Each hour delay in achieving administration of effective antibiotics is associated with an increased mortality in several studies.[28-30] When sepsis is determined by a clear infection of an organ, the most recent guidelines published on the topic should be considered.[31-39] Empirical antimicrobial therapy should be composed of one or more drugs that have activity against all likely pathogens and adequate tissue penetrance. The choice of empirical therapy depends on: the patient's medical history, its origin (community or nosocomial infection), recent antibiotics assumption (previous 3 months), data on local antibiotic resistance and the presence of particular pathogens that have previously colonized or have been a source of infection for the patient.[7] Every patient should receive the dose in relation to renal and hepatic function and the serum concentration[10,40-41] of some antimicrobials should be monitored.

The most common pathogens that cause septic shock in hospitalized patients are Gram-positive bacteria, followed by Gram negative and mixed bacterial micro-organisms. Other uncommon pathogens should be considered in selected patients, for example, neutropenic patients.[42] A combination of empiric therapy is recommended in neutropenic patients with severe sepsis and in patients with *difficult-to-treat* infection by multi-resistant bacteria, such as *Pseudomonas* and *Acinetobacter* spp.

Clinician should also consider using antifungal therapy, when there are important risk factors for Candida infection, including immunosuppression, prior intense antibiotic treatment and colonization in multiple sites. The choice of empirical antifungal therapy should be tailored to the local pattern of the most prevalent Candida species and any recent exposure to antifungal drugs.[43] The recent Infectious Diseases Society of America (IDSA) guidelines recommend the use of fluconazole or echinocandin (Table 1), taking into account the local pattern of resistance to some antifungal agents.[21]

Antiviral therapy should be initiated as early as possible in patients with severe sepsis or septic shock of viral origin. Recommendations include the early use of antiviral treatment in severe influenza or in patients at higher risk for influenza complications.[44,45]

The role of cytomegalovirus and other herpesviruses as significant pathogens in septic patients remains unclear.[46-48] At the moment, the guidelines do not recommend any treatment. In patients with severe primary or generalized varicella-zoster virus infection, and in rare patients with disseminated herpes simplex infection, the use of an antiviral agent, such as acyclovir, can be highly effective if started early in the course of infection.[49]

Antimicrobial treatment should be reassessed daily for potential de-escalation to prevent the development of resistance, to reduce toxicity, costs, and the development of superinfection by other pathogenic or resistant organisms such as Candida species, *Clostridium difficile* or vancomycin-resistant *Enterococcus faecium*. However, in some cases[11] (*Pseudomonas* species, only susceptible to aminoglycosides; enterococcal endocarditis; *Acinetobacter* species susceptible only to polymyxins), it is recommended to continue with a specific combination of antimicrobials.

Table 1. Candidemia therapy.

	First choice	Alternative	Comments
No-neutropenic patient	Fluconazole 800 mg (12 mg/kg) loading dose, then 400 mg/daily (6 mg/kg) days following or echinocandin (anidulafungin: 200 mg loading dose then 100 mg/daily; caspofungin: 70 mg loading dose, then 50 mg/daily; micafungin: 100 mg/daily)	Amphotericin B (lipid formulation-LFAmB) 3-5 mg/kg/daily; or AmBd 0.5-1 mg/kg/daily; or voriconazole 400 mg (6 mg/kg) twice daily for 2 doses and then 200 mg (3 mg/kg) twice daily	Choose echinocandin in severe impairment and for patients recently exposed to treatment with azoles. Treatment duration: 14 days after the detection of the first negative blood culture and resolution of signs and symptoms of candidemia. Ophthalmologic examination is recommended in all patients. Remove all intravascular catheters, if possible
Neutropenic patient	Echinocandin (anidulafungin: 200 mg loading dose then 100 mg/daily; caspofungin: 70 mg loading dose, then 50 mg/daily; micafungin: 100 mg/die) or amphotericin B (lipid formulation-LFAmB) 3-5 mg/kg/daily	Fluconazole 800 mg (12 mg/kg) loading dose, then 400 mg (6 mg/kg) days following; or voriconazole 400 mg (6 mg/kg) twice daily for 2 days and then 200 mg (3 mg/kg) twice daily	Echinocandin or amphotericin B (LF) are preferred in most cases. Fluconazole is recommended for patients who have not been recently treated with azoles and are not critical. Voriconazole is recommended when you want additional cover for other fungi (*Aspergillus*). The removal of intravascular catheters is recommended but still controversial

Adapted from Pappas et al., *2009.*[21]

Duration of antibiotic therapy varies according to clinical response, presence of undrainable foci of infection and type of infection (*Staphylococcus aureus bacteremia*, some fungal and viral infections or immunologic deficiencies, including neutropenia).

It is important to seek and diagnose or exclude as rapidly as possible the source of infection and implement measures (including surgery) to control it within the first 12 h after diagnosis. The effective intervention to control the source of infection should be the one with the least insult (*e.g.*, percutaneous rather than surgical drainage of an abscess). If intravascular access devices are a possible source of severe sepsis or septic shock, they should be removed promptly after another vascular access has been established.

Role of echo-bedside in patient with sepsis

Symptoms, signs and laboratory tests are not always sufficient for the etiological diagnosis. It is often necessary to use instrumental examinations. Among instrumental tests, ultrasound is extremely useful. Ultrasound has indeed many advantages in septic patients. The close correlation of ultrasound with clinical evolution gives us simple answers and supports for specific issues. Ultrasound is cheap, non-invasive, repeatable and simple to perform at bedside.

The contribution of ultrasound in the management of septic patients is based on two main components: i) *diagnostic*; ii) *monitoring*.

Identification of a source of infection is essential: it enables to narrow the antibiotic spectrum and to perform interventional and surgical procedures. Monitoring is essential to assess the effectiveness of therapy especially in the next 6-72 h.

Research of septic foci

Study of abdominal organs

Ultrasound holds the greatest sensibility and specificity for the study of liver, biliary tree and pelvic organs, with accuracy greater than 90% in experienced hands. A second imaging study should be carried out only in case of negative or non-diagnostic ultrasound [first computed tomography (CT) scan].

Kidney and urinary tract

Kidneys are retroperitoneal organs easily accessible with ultrasound. Appendix Table 3 shows features to look for an exhaustive study of kidney and urinary tract.

Hydronephrosis and acute pyelonephritis should be searched to support urinary sepsis. Hydronephrosis refers to distension and dilation of the renal pelvis and calyces, usually caused by obstruction of the free flow of urine from the kidney. Untreated, it leads to progressive atrophy of the kidney.[50] In cases of hydroureteronephrosis, distention of both the ureter and the renal pelvis and calices can be easily visualized. Dilatation of the ureter is usually recognizable in proximal or distal tract (last 3 cm of ureter). Ultrasound is highly sensitive and specific for the detection of hydronephrosis.

Hydronephrosis is divided into three grades: i) mild (dilatation of calices and renal sinus; Appendix Figure 1); ii) moderate (more evident dilatation of calices and renal sinus; Appendix Figure 2); iii) severe (important dilatation with compression and reduction of the renal parenchyma; Appendix Figure 3).

Renal stones, clots, tumors or extrinsic compressions can cause hydronephrosis.[51] Renal calculi are the main cause of pelvic and ureteral obstruction. Calculi are usually visible if larger than 3-4 mm as typical echoic image with sharp, distal acoustic shadowing. Their detection is not influenced by their chemical structure, but only by their dimension and anatomical position (intrarenal, proximal ureter, distal or intramural ureter and bladder).

Pyelonephritis has nonspecific ultrasonographic findings. Usually we can observe renal enlargement (Appendix Figure 4), increase in thickness of the renal cortical with compression and reduction of the renal sinus, abnormalities of structure (areas of decreased or increased echogenicity), focal areas corresponding to abscesses (Appendix Figure 5) (round, thick-walled, hypoechoic complex masses with posterior shadowing and internal mobile debris and septations), focal or diffuse absence of color Doppler signals.

Bladder is easily studied with ultrasound scan. It is best evaluated when moderately filled as an anechoic formation with well-demarcated regular wall.[51] We can evaluate the degree of filling and the presence of urinary retention. Other pathological findings are: bladder diverticula, calculi, debris or clots, wall thickening and sign of ureteral obstruction.

Gallbladder and biliary tree

Evaluation of the biliary tract is one of the most appropriate and effective application of ultrasound examination. The cystic nature of the gallbladder and the bile ducts, particularly when dilated, provides an inherently high contrast resolution in comparison with the adjacent tissues.[52]

CT scan is considerably less sensitive in the diagnosis of gallstones and bile duct stones. Magnetic resonance cholangiopancreatography and endoscopic ultrasound show comparable sensibility ad specificity but they are more expensive and invasive.

Gallbladder is an anechoic organ with thin wall and variable shape. Usually the longitudinal diameter is <10 cm, the transversal diameter is <4 cm and wall thickness is <2-3 in normal fasting, <5 mm after meal (anterior wall).[53]

Common bile duct is an anechoic tubular structure with thin echoic wall. The diameter of common bile duct is <6 mm. After cholecystectomy or in older patients it is generally between 8-10 mm. It can be studied at the level of the portal vessels, but it is not always completely recognizable up to the ampulla of Vater (intestinal gas, lack of an adequate acoustic window).

The intrahepatic biliary tree is normally not visible, unless in case of pathological dilatation. Stones in the biliary tree can be seen as echoic images, but they are rarely associated with posterior acoustic shadowing. An important and diagnostic sign is the presence of dilatation of the upstream biliary tree.[52,53]

Inflammation of gallbladder (cholecystitis**)** is usually associated with gallstones, which are present in 90% of patients as one or more mobile echogenic images in the lumen of gallbladder with strong posterior acoustic shadowing (Appendix Figure 6). When gallbladder is completely filled with stones, it will appear as an echogenic line with strong posterior shadowing. It is also detectable the presence of sludge (Appendix Figure 7), amorphous, low-level echoes within the gallbladder in a dependent position, with no acoustic shadowing. Other findings suggestive of acute cholecystitis are distention of the gallbladder lumen (transversal diameter >4 cm and longitudinal diameter >10 cm), thickening of the gallbladder wall (Appendix Figure 8) (>3 mm often striated with a hypoechoic intermediate layer). Murphy's sonographic sign is positive in 95% of patients. Finally, pericholecystic fluid collection and hyperemic gallbladder wall can be present. The sonographic findings of acute cholangitis include thickening and dilation of the biliary tree, lithiasis or sludge, pneumobilia and hepatic abscesses.[54]

Abscesses

Ultrasound has a primary role in the study of abscesses, not only for diagnosis but also for therapy through the placement of a percutaneous drainage. The three main abdominal organs usually involved are liver, spleen and kidney. CT scan or magnetic resonance imaging (MRI) must be reserved for selected patients, to complete sonographic findings, to assess complications and in case of non-diagnostic sonography.

Hepatic abscesses can appear as single or multiple nodular lesions in the hepatic parenchyma with variable echogenicity and shape depending on the infectious cause and the evolutive phase.

Appendix Table 4 shows the main features of bacterial and mycotic abscesses (Appendix Figures 9-11).

Splenic bacterial and pyogenic abscesses are coarse round hypoechoic or anechoic lesion, single or multiple, with variable size and irregular shape.

Splenic fungal abscesses are usually multiple, round and small nodules, with regular rims. Echogenicity can be variable (hypoechoic, wheels-within-wheels, hyperechoic).

Renal abscess is a single round complex mass: hypo or anechoic nodule with internal debris and septations, thick wall, internal gas and posterior shadowing. At the Doppler interrogation, we usually observe increased signals outside the mass and no signals within the abscess (minus images).

Abdominal effusions

Normally, peritoneum and peritoneal cavity cannot be explored with ultrasound. Usually, free fluid is not present in the abdominal cavity (unless a minimal amount in the pouch of Douglas in female subjects).[55]

Sonography has a great sensibility and specificity in detecting even small amounts of free fluid in the peritoneum. This fluid can be loculated around elective site of infections or free in the peritoneal cavity (Appendix Table 5).

Ultrasound can also help to distinguish the fluid features, anechoic in transudate fluid and particulate in exudate fluid as blood, pus or in tumoral conditions.

In acute appendicitis, we observe appendix as a blind ended non-peristaltic tube (*cul de sac* image in longitudinal section and target lesion in transversal section) arising from the cecum. It is non-compressible, with the typical gut signature and contains free internal echoes. Frequently pericecal collections and local adenopathies can be seen if complications occur (perforation and abscess formation).

In diverticulitis, we can appreciate thickening of part of the gut (especially colon) with hypoechoic appearance, loss of typical gut signature and fluid collections.

Pelvic and scrotal pathology

Ultrasound is the first-choice test. CT and MRI are usually necessary when sonography is non-diagnostic or when an evaluation or staging of a tumoral disease is required.[56]

With suprapubic view, we can observe inflammatory pathologies of fallopian tube, ovary, endometrium, pelvic abscesses and peritonitis. In ovarian[57] inflammation, ovaries are enlarged with multiple cysts and indistinct margins. In salpingitis[56,57] fallopian tubes are dilated and filled with fluid (hydrosalpinx), with or without internal echoes (pyosalpinx) up to tubo-ovarian abscess[58] (complex multiloculated mass with variable septations, irregular margins, and scattered internal echoes). Usually free fluid in the Pouch of Douglas is present. In male patients, infectious disease of the scrotum, epididymis and testis are easily recognized.

In epididymitis, an enlarged and thickened epididymis is present. In orchitis testis are enlarged, hypoechoic and with abnormal texture. In both conditions, Doppler signals are increased.

Study of chest: lung as a cause of sepsis

Pulmonary consolidation

In inflammatory processes, the distal air spaces fill with liquid material or lose some of their air content: in this situation, ultrasound shows a hypoechoic area[59-60] which is defined *consolidation* (expression of increased density and reduction of air content), that sometimes looks similar to liver parenchyma (Appendix Figure 12). The consolidated area[61] is easily seen when it reaches the pleural line, the so-called *paradox of the lung* for which this organ, minimally explored in normal conditions, shows significant acoustic windows. The pulmonary consolidation[62] reaches the pleural line in 98.5% of cases: ultrasound has a high sensitivity and specificity (both 96.5%) in detecting parenchymal lesions radiologic-occult (sensitivity of chest radiography 66%).

Pneumonia[63,64] appears during the ultrasound scan as a hypoechoic area with variable size, irregular margins and shape (triangular base projected to the pleural surface or irregular and poorly defined edges) with posterior acoustic shadowing and reduction-absence of sliding.

The structure of consolidation[65,66] is irregular because there may be images of air or fluid trapped in the airways, defined as air or fluid bronchograms.[67,68] In the first case, there are ventilated bronchi with thickened air (hyperechoic spots, with typical reverberation artifact and arborescences) (Appendix Figure 13). In the second case, there are bronchi with fluid content (hypo-anechoic) and absent ventilation, expression of airway obstruction. Air bronchograms can be static or dynamic: only in the dynamic bronchograms air artifact moves consensually with breaths (element evaluated by exploiting the dynamic ultrasound examination in *real time*) and the presence of dynamic air bronchograms allow excluding atelectasis. Infectious lung diseases present in 70-97% of cases dynamic air bronchograms: therefore, this element is a valuable tool for the definition of the etiological consolidation integrated with symptoms, physical examination and biochemical data of the patient. The static air bronchogram is expression instead of trapping air inside the bronchus.

Interstitial syndrome

The interstitial syndrome[69] is an expression of increased *extra vascular water*: it shows an ultrasound picture characterized by an excessive number of B lines, located in a single region, *interstitial focal syndrome* or in all lung fields, *homogeneous diffuse interstitial syndrome*, or in more than two fields for each hemithorax, *diffuse non-homogeneous interstitial syndrome.*

Interstitial Focal Syndrome can be present in different pathological pulmonary processes: pneumonia, atelectasis, contusion, heart attack, cancer, pleural disease. Therefore, the integration of ultrasound with anamnestic and biochemical data is mandatory to achieve a correct diagnosis. In pneumonia B lines appear in the early stages of the inflammatory infectious process, localized in the peripheral regions of the consolidation and they replace consolidation when it resolves.

The most frequent case of *homogeneous diffuse interstitial syndrome* is cardiogenic pulmonary edema. The ultrasound technique is able to recognize a very early lung overload with a sensitivity of 100% (higher than the sensitivity of 65% of chest X-ray). A normal ultrasound excludes pulmonary edema since its interstitial phase.

The specificity of the B lines for cardiogenic pulmonary edema is not absolute: similar situations can be observed in all interstitial lung diseases such as acute respiratory distress syndrome (ARDS), interstitial pneumonia and diffuse parenchymal lung diseases, as pulmonary fibrosis.

An example of *diffuse not homogeneous interstitial syndrome* is ARDS. We can see bilateral B lines with patchy distribution and presence of areas of savings. Other elements that can move towards ARDS, are the presence of small subpleural consolidations, absence or reduction of the sliding and abnormalities of the pleural line that appears thickened and irregular.

Pleural effusion

Pleural effusion[70,71] appears as an anechoic subpleural space (free effusion) or a hypo-anechoic space with echoic areas (organized effusion). Thoracic basal posterior scans are used to detect or exclude the presence of pleural effusion. In the absence of effusion, the lung bases create a typical picture with downward movements of the ventilated lung toward abdominal organs that are partially covered (*curtain sign*). Effusion is interposed as an anechoic image between the chest wall and/or the diaphragm and the lung parenchyma. The sonographic appearance of effusion may be indicative of the nature of the collection: generally, transudates have homogeneously anechoic appearance, free effusion, (Appendix Figure 14), while exudates, empyema or hemorrhagic effusion, always look irregular with hypo or hyperechoic images (organized effusion) (Appendix Figure 15).

In 34-61% of pneumonia, free basal effusion is present and in 9-42% of cases effusion is localized (perilesional). In the diagnosis of pleural effusions, chest ultrasound has a very high accuracy, above 90%, with sensitivity and specificity >90%. Its use in the ICU[72] (constantly supine patients) is relevant with an accuracy of 93% in the diagnosis of pleural effusion, much higher than clinical examination (61%) and chest radiograph (47%).

Assessment of intravascular volume status and monitoring

In sepsis, assessment of hemodynamic status is based on: i) echocardiographic evaluation of the heart (especially volume and size of heart chambers, systolic function of the left and right ventricle, identification of pericardial effusion, evaluation of heart valves); ii) evaluation of the filling fluid status: study of the inferior vena cava and capillary wedge pressure.

This allows a rapid diagnosis of shock and its causes besides a continuous control of the patient.

Role of echocardiography

Echocardiography[73,74] provides static measurements (ventricular wall thickness, size of the heart chambers, presence of pericardial effusion, valvular abnormalities) and dynamic measurements (contractility, blood flow, valvular movements).

This information will be integrated with clinical features to identify previous heart diseases (*e.g.*, any heart hypokinetic cardiopathy limiting filling fluid challenge), acute ventricular dysfunction, and acute cardiac complications with the ultimate purpose of optimizing patient therapy.

Global left ventricular function

In critical patient pressure, resistance and flow bind together according to precise mathematical equations. In particular, the systemic vascular resistances (SVR) (Appendix Figure 16) have a value between 900 and 1300: i) SVR <900: low resistances, *e.g.*, in sepsis, anaphylactic shock, spinal shock, adrenal insufficiency, hyperthermia; ii) SVR >1300: high resistances, *e.g.*, in severe heart failure, cardiogenic shock, vasopressor use, hypothermia.

This is expressed by the following formula:

$$SVR = \frac{(MAP - \text{right atrial pressure}) \times 79.9}{\text{Cardiac output (CO)}}$$

where:
MAP is mean arterial pressure (mmHg);
right atrial pressure (mmHg) corresponds to central venous pressure (PVC) and it is estimated with ultrasound by the caliber and the variations of the inferior vena cava;
CO, cardiac output (L/min), is sonographically evaluated through various methods more or less accurate according to performer's echocardiographic knowledge.

A first coarse estimation of the cardiac output and contractility can be made by simply observing the volume and variation of the left ventricle during systole and diastole (Appendix Figure 17): ventricular walls in conditions of good contractility almost come in contact during systole. However the most used and easiest method to estimate cardiac output is the calculation of ejection fraction (EF), generally performed in apical route.[75,76] The EF is defined as:

100 × [(End-diastolic volume of left ventricle – End-systolic volume of left ventricle) / End-systolic volume of left ventricle]

Pericardial effusion

Pericardial space is normally a virtual space; in the presence of effusion the two pericardial layers are separated by anechoic or hypoechoic liquid (also particulate effusion, irregular or organized according to the etiology). Effusion is usually first seen posterior to the left ventricle, then anterior to the right ventricle and finally circumferential (parasternal and apical routes).

When pericardial effusion increases (Appendix Figures 18 and 19), heart is compressed and we can detect pericardial tamponade with severe hemodynamic alterations. Sonographic features are: i) movement of the interventricular septum to the left with compression of the left ventricle during inspiration (equivalent of the paradox pulse for increased venous return and increased right volume in inspiration); ii) collapse of the heart chambers in diastole (at the beginning right atrium, then right ventricle, lastly left ventricle); iii) dilatation of the inferior vena cava with minor variations during respiratory cycle.

Ultrasound plays a diagnostic and therapeutic role guiding the performance of pericardiocentesis.

Heart valves

Echocardiographic study of the heart valves can highlight the presence of previous stenosis or regurgitation and guides us in the search for potential septic foci. It is possible to demonstrate through transthoracic echocardiography both the onset of new valvular defects, and the presence of hyperechoic images on the free surface of the valve leaflets, suggestive of endocarditis (usually vegetation can be observed if superior to 2 mm in size) (Appendix Figure 20).

The sensitivity and specificity is not high (40-60%); therefore, a negative exam does not rule out clinical suspicion, but it is necessary a transesophageal study, still the gold standard for the diagnosis of endocarditis. With this approach, we can recognize small vegetating masses, extravalvular involvement and valvular abscesses (thickened perivalvular areas with irregular hypoechoic appearance). In case of strong suspicion of endocarditis but negative transthoracic and transesophageal examination, investigations should be repeated in 7-10 days to highlight any new development.

Evaluation of central venous pressure

In septic patients, ultrasound is a simple, rapid, reliable, repeatable and cheap tool for the assessment and control of intravascular volume status through the measurement of inferior vena cava and its variation. Sensibility is extremely high in case of hypovolemia, lower in case of hypervolemia. A diameter superior to 2 cm is not strictly correlated with hypervolemia or otherwise an *effective volemia*: it is necessary to evaluate the right ventricular systolic function (acute systolic dysfunction, pulmonary embolism, right ventricular infarction, pericardial tamponade). In these conditions the reduced right output leads to caval hypertension.[77,78]

The inferior vena cava (IVC)[79,80] is a large bore, extremely compliant, vessel (Appendix Figure 21); its size correlates with the patient's volume status (Appendix Table 6); the vessel contracts and expands with every respiratory cycle and the variations of the size give us a reliable estimation of the right atrial pressure and of PVC.

The study is technically based on the measurement in longitudinal section of the diameter of inferior vena cava in inspiration and in expiration[81] at the confluence in right atrium (hepatic vein and inferior vena cava junction or if not visible 2-3 cm from the confluence in right atrium). Serial measurements are possible at the admission of the patient and during fluid therapy up to the achievement of optimal therapeutic response (estimated in the collapse of 30% of the inferior vena cava).[82]

Non-invasive evaluation of pulmonary wedge pressure (right atrial pressure)

The pulmonary capillary wedge pressure (PCWP) is another important hemodynamic parameter in the evaluation of septic and critic patient: it is essentially an image of *the pulmonary congestion* of the patient, of the filling and tolerance to fluid therapy. PCWP is nothing more than the equivalent of PVC on the pulmonary side, equivalent to the left atrium pressure.

This indicator is normally used by intensivists and measured with Swan-Ganz catheter.

We can evaluate PCWP with ultrasound in a simple and repeatable way, at the bed of the patient, using the tissue Doppler method (TDI).

The TDI is based on a particular type of pulsed Doppler (Appendix Figure 22) and it directly measures the speed of excursion of the lateral portion of the mitral annulus.

The main evaluated parameters are: i) the peak speed of Em wave (NV >10 cm/s); ii) the ratio of the E-wave peak velocity of trans mitral flow and the Em wave (E/Em ratio). This ratio is normally <8, abnormal between 9 and 14 and pathological >15 (Appendix Table 7). It has been widely shown that E/Em ratio correlates linearly with the PCWP measured with invasive method.

We can conclude that typical pattern of the patient with sepsis/septic shock consists of: i) IVC totally collapsed and not identifiable, or diameter <1 cm and caval index >50%; ii) small left atrium; iii) left ventricle with normal end-diastolic volumes, hyperkinetic, with greatly reduced systolic volume (sign of *kissing ventricle*, the ventricular walls collapse and touch during systole); iv) absence of B lines in the lung; v) ratio E/Em <8 in tissue Doppler of mitral annulus (reduced PCWP).

Septic shock: pathophysiology and hemodynamic resuscitation

The microcirculation is a critical element of the pathogenesis of severe sepsis and septic shock[83-88] and microcirculatory failure is associated with increased mortality.[83,89,90] Septic shock pathophysiology is complex and not fully understood. The specific response in any patient depends on causative pathogen (load and virulence) and the host (genetic characteristics and coexisting illness). Proinflammatory reactions are thought to be responsible for collateral tissue damage in severe sepsis such as dysfunction of the vascular endothelium, accompanied by cell death and loss of barrier integrity, giving rise to subcutaneous and body-cavity edema.[91] Further several factors (hypotension, reduced red-cell deformability and microvascular thrombosis) contribute to diminished oxygen delivery in septic shock.[92] As well known, the major pathophysiologic changes in patients with severe sepsis and septic shock include vasoplegic shock (distributive shock), myocardial depression, altered microvascular flow, and a diffuse endothelial injury.[93,94] According to the Surviving Sepsis Campaign[1] (SSC), the principles of the initial management bundles are to provide cardiorespiratory resuscitation that requires the use of intravenous fluids and vasopressors (Appendix Tables 8-10). The exact components required to optimize resuscitation (choice and amount of fluids, type and intensity of hemodynamic monitoring) remain the subject of ongoing debate and clinical trials.

None of the currently used solutions are really physiological or *balanced*: colloid solutions are more effective in expanding intravascular volume and maintaining colloid oncotic pressure, but they are expensive and impractical to use as resuscitation fluid.[95] Albumin can be used in severe sepsis and septic shock when patients require substantial amounts of crystalloids,[1] but it should not be used in patients with traumatic brain injury.[95,96] Moreover, instead of its theoretical benefits in septic patient,[97,98] the SAFE study showed no significant difference between saline and albumin in ICU patients.[96] Semisynthetic colloids

as hydroxyethyl starch solutions should not be used because of the increased mortality and risk of renal replacement therapy.[1,99,100] Crystalloids are inexpensive and widely available and have an established, although unproven, role as first-line resuscitation fluids. Isotonic saline is the most commonly used crystalloid, but the administration of large volumes of saline results in a hyperchloremic metabolic acidosis[101,102] which is associated with an increased risk of renal dysfunction.[102-104] Some authors suggest that dilutional-hyperchloremic acidosis is related to large volumes of saline administration and the effect remains moderate and relatively transient.[105]

Although there is still no answer to the best choice for volume resuscitation in sepsis,[106] recent data[102,107-109] suggest that isotonic balanced solutions could be the preferred resuscitation fluids for the majority of acutely ill patients and saline could be considered in patients with hypovolemia and alkalosis.[95] By the way, the new GIFTAHo NICE guidelines recommend the measure of serum chloride anytime a solution containing chloride more than 120 mmol/L is used.[110] No clear indications exist of what adequate endpoint for resuscitation should be, but avoiding fluid overload is recommended: several studies demonstrated how an excessive fluid accumulation following the acute phase of resuscitation is associated with poor outcome.[111] In patients with sepsis and acute kidney injury (AKI), excessive fluid therapy, despite optimal systemic hemodynamic and a high rate of diuretic use, may worsen gas exchange[112] and may precipitate or worsen AKI.[113] Vasopressor therapy is recommended to sustain life and maintain perfusion (Appendix Table 9). The initial target of mean arterial pressure (MAP) with vasopressor therapy is 65 mmHg. Norepinephrine is recommended as the first choice vasopressor,[1] because of its α-adrenergic properties and its modest β-adrenergic effects that help to maintain cardiac output. Recent trial demonstrated no advantage of dopamine over norepinephrine and it is associated with higher rates of death among patients with septic shock.[114,115] Dopamine should be carefully considered only in patients with a low risk of arrhythmias and either known marked left ventricular systolic dysfunction or low hear rate.[1,92] Inotropic therapy, such as dobutamine infusion up to 20 mcg/kg/min should be used or added to vasopressor in the presence of myocardial dysfunction (elevated cardiac filling pressures and low cardiac output) or ongoing signs of hypoperfusion, despite achieving adequate intravascular volume and adequate MAP.[1] Although currently used septic shock guidelines focus on the importance of detecting central venous pressure and central venous oxygen-saturation, recent data may challenge this milestone. In the proCESS trial,[116] septic patients managed without protocols had the same outcome of those managed with protocols. A previous study[117] demonstrated that serial measurement of blood lactate levels was non-inferior to central venous oxygen-saturation measurement. These results anyway should be carefully interpreted. Actually, they probably suggest that early recognition of sepsis, early administration of antibiotics, early adequate volume resuscitation are essential elements of the management of sepsis, and less invasive measurements are probably required for the assessment of the circulation support.[116]

Non-invasive ventilation, bicarbonate, steroid and immunoglobulin in sepsis

The lung is a target organ that often contributes to morbidity and mortality[118] in patients with sepsis. Actually, the majority of patients with severe sepsis and septic shock requires intubation and ventilation and 50% of them develops acute lung injury and/or ARDS.[119] Limiting tidal volume ventilation to 6 cc/kg[120] is helpful to prevent barotrauma and to reduce mortality in ventilated patients with ARDS. The previous widespread belief to normalize PCO_2 has been supplanted by the *permissive hypercapnia* resulting in less lung injury[121.] The direct manipulation of the acid-base balance with the decrease in PCO_2 or bicarbonate administration has lost certainties.[122] On the contrary, we should aim at correcting the underlying metabolic acidosis with adequate perfusion and oxygenation of the tissues. The initial fraction of inspired oxygen (FiO_2) may be high, but it should be reduced to avoid oxygen toxicity whenever possible.[119] Positive end-expiratory pressure (PEEP) permits to keep alveoli open at the end expiration[123] and its ideal settings depends on compliance and thoracic volume. PEEP may decrease cardiac output in patients dependent on preload.[124] The supine body position can be considered in patients with poor oxygenation,[125] after having optimized ventilation parameters. Non-invasive ventilation (NIV) applied as first-line intervention in ARDS avoided intubation in 54% of treated patients in expert centers. A simplified acute physiology score II >34 and the inability to improve PaO_2/FIO_2 after 1 h of NIV were considered predictors of failure.[126] NIV is not indicated in patients with depressed mental status, septic shock, signs of fatigue, poor oxygenation or in whom it is required protection of the respiratory tract.[121,126] Latest sepsis guidelines do not recommend the use of sodium bicarbonate therapy in patients with hypoperfusion-induced lactic acidemia with pH ≥7.15, because bicarbonate administration has been associated with sodium and fluid overload, an increase in lactate and PCO_2, and a decrease in serum ionized calcium. No studies have examined the effect of bicarbonate administration on outcomes.[1] Patients with refractory hypotension after fluid therapy and vasopressors should receive steroid.[1,127] A large meta-analysis of Annanne *et al.* demonstrated that low doses

of steroids for 7 days decreased mortality in severe sepsis and in septic shock.[128] However, Sprung in a large controlled trial showed no difference of mortality in steroid treated patients who received vasopressors for any time.[127] The same authors, in a subgroup analysis considering the same inclusion criteria of Annanne *et al.*[128] (longer period of hypotension and vasopressor administration, higher overall mortality), found the same benefits on mortality. In the study of Sprung *et al.* 300 of the 800 subjects (required for a proposed 80% power to demonstrate a 10% reduction in mortality) are missed.[127] The use of corticosteroids as immunosuppressant (higher doses than 300 mg/day hydrocortisone) in patients with sepsis has not proven effective.[128] The addition of a mineralocorticoid, such as 0.05-0.2 mg of fludrocortisone, has been suggested by some authors, but hydrocortisone at a dose of 200 mg has properties equivalent to 0.05 mg of fludrocortisone and is probably sufficient.[127] Further mineralocorticoid is administered orally with probable variable absorption. Intravenous immunoglobulin as an adjunctive treatment in sepsis was regarded as promising by a Cochrane meta-analysis of small trials with some methodological flaws. The only large study showed no effect.[129] Therefore, using intravenous immunoglobulins is not suggested in severe sepsis or septic shock.[1,130]

Supportive therapy

Nutrition

Early enteral nutrition has theoretical advantages (*e.g.*, supporting the metabolic and immune response, preserving gut integrity), but unfortunately no clinical trial has evaluated its real benefit among septic patients. Enteral feeding should be preferred to total parenteral nutrition, which seems to be associated with higher risk of infectious complications.[131-133] Although the most recent Surviving Sepsis Campaign[1] suggests low dose feeding (*i.e.*, up to 500 kcal/day) in the first week, the force of the recommendation is weak (2C) and other studies contradict this approach, suggesting higher doses.[134]

Venous thromboembolism prophylaxis

Most recent guidelines[1] recommend daily pharmacoprophylaxis against venous thromboembolism for patients with severe sepsis. Attention should be focused on the glomerular filtration rate (GFR) as it determinates the most appropriate pharmacological regimen (*i.e.*, unfractionated heparin for GFR ≤30 mL/min).

Patients who have contraindication for anticoagulation (*e.g.*, active bleeding, coagulopathy, recent cerebral hemorrhage) should be treated with mechanical devices such as graduated compression stockings or intermittent compression devices and bleeding risk should be re-assessed daily.

Glucose control

Hyperglycemia is a common finding in critically ill patients. Stress conditions, steroid and nutritional therapies in patients with underlying glucose metabolism disease may lead to abnormally high blood glucose levels. Many studies have shown a reduction in ICU mortality associated with glucose lowering strategies.[135,136] Insulin therapy should be started for blood glucose levels ≥180 mg/dL and it should aim at a target of 140-180 mg/dL. Lower levels are associated with higher risk of hypoglycemia-related complications. Computer-based algorithms should be encouraged as they reduce the risk of hypoglycemia.[137]

Blood products administration

Although the ideal threshold for red blood cell transfusion is unknown,[138] the early goal-directed therapy protocol[139] recommends it as the hematocrit falls below 30% to achieve adequate tissue perfusion. Once tissue hypo-perfusion has resolved and in the absence of other indications (*e.g.*, active hemorrhage, coronary artery disease) transfusion is recommended when hemoglobin levels falls below 7 g/dL to target a hemoglobin concentration of 7.0 to 9.0 g/dL. According to international guidelines[1] based largely on consensus opinion, platelets should be infused: i) prophylactically if counts are ≤10,000/mm^3; ii) prophylactically if counts are ≤20,000/mm^3 and the patient is at high risk of bleeding (*e.g.*, temperature >38°C, recent minor hemorrhage, rapid decrease in platelet count, coagulation abnormalities); iii) to target ≥50,000/mm^3 in the presence of active bleeding or planned invasive procedures. Fresh frozen plasma should be used only for correcting clotting abnormalities in the presence of active bleeding or planned invasive procedures.

The management of patient with sepsis

Rationale and objective

Sepsis is a challenge for Internists as it often represents a probable diagnosis, which should be clarified and treated rapidly. Prompt and accurate management reduces mortality and needs a multidisciplinary team and a multispecialty collaboration to improve the chance of success.[1] In this context Internists have the main role, especially at the beginning, when the site of infection is often unknown. Therefore, the goal of this work is to raise awareness of the clinical management of *sepsis* through a better knowledge of its diagnosis and treatment.

Methodology

In order to provide evidence-based recommendations for the management of patients with sepsis, we first verified the existence of guidelines on the matter. Therefore, we conducted a search using the following database-guidelines:
- Scottish Intercollegiate Guidelines Network (SIGN);
- ICSI;
- NICE (NHS Evidence);
- National Guideline Clearinghouse;
- Canadian Medical Association (CMA Infobase);
- New Zealand Guidelines Group;
- National System Guidelines;
- Clinical Practice Guidelines Portal;
- EGuidelines.

The research was carried out by six authors independently, using terms *sepsis*, *infection* as key words, when the site included the search function, and in other cases we listed the last guidelines manually stored in the database or made reference to the *infective illness*. The results obtained separately were then compared and discussed together. Thus, the guidelines obtained were independently evaluated by 6 authors using the Appraisal of Guidelines, Research and Evaluation II, 22 (AGREE II) instrument.[140] AGREE II assesses compliance with 23 requirements, meeting 6 domains as the explanation of the purpose, the clarity, the involvement of all stakeholders, the rigor of development, applicability and editorial independence of the same. Each author assessed the compliance of individual requirements with a score from 1 (disagree completely) to 7 (complete agreement). The scores assigned by each author were added within individual domains and reported with the highest and the lowest score possible within the domain based on the number of requirements included and the number of evaluators.

Results

Through the databases listed above, we identified 6 guidelines which we evaluated with AGREE method (Table 2).[1,39,108-111] Other references were excluded because too specific and non-functional for our purpose. We analyzed three guidelines that deal with particular aspects of septic patients, such as pregnancy, neutropenic sepsis in cancer patients and infections of the urinary tract.[39,141,142] By using AGREE criteria we judge the NICE guidelines on neutropenic sepsis to be the best. Actually, it contains excellent description of target population, objectives and purpose, it clearly demonstrates economic aspects of a single strategy and does not forget to consider target-population preferences. Obviously, as it is specific, it lacks some important aspects of septic patient management such as hemodynamic stabilization. Therefore, it is incomplete and medical culture cannot be based only on this guideline. On the contrary in the SSC guideline[1] all important aspects are treated and documented with exhaustive references. Messages are clear, elaborated with many tables and easy to access. The main pity remains the economic aspects and the barriers to the implementation of the guideline, which are marginally considered. Canadian guideline[143] is really easy to assess and schematic. It lacks explanations of the asserted items and it does not deal with economic aspects. NHS guideline is not strictly a guideline,[144] but it looks like a consensus statement, a valid toll for the diagnosis and management of sepsis. The guideline on bacterial sepsis in pregnancy considers some particular aspects of sepsis in pregnant woman, following the milestones of the SSC. It is not always well-documented but it is important to consider that some particular obstetrician items are not corroborated by significant literature. Lastly the guideline on urinary infection is a really exhaustive guideline on all the aspects of urinary tract infection, well organized and schematic, rich in references and complete. It lacks some important aspects of sepsis, but at the end of the chapter you can find some links and references where to examine in depth these items. Sepsis is an important chapter of medical diseases and it needs continuously updating. Currently, the SSC guideline contains some parts that should be updated according to more recent papers.[116] For this reason, the evidence-based medicine management of sepsis was obtained also by the analysis of reviews and articles on sepsis.

Table 2. Evaluation of the guidelines on sepsis using AGREE method.

Guideline	AGREE evaluation
Neutropenic sepsis[109]	6
Surviving Sepsis Campaign[1]	5
Urological infections[39]	4
Canadian Association of Emergency Physicians[110]	4
Bacterial Sepsis in Pregnancy[108]	4
National Health System[111]	2

Clinical approach to patients with sepsis

Diagnose and staging gravity

The most important thing is quite obvious: early identification of sepsis. Clinical suspicion is the first step and has to be based on meticulous history taking and complete clinical examination (Table 3). Procalcitonin and other inflammatory markers are important data but they should be interpreted carefully in the context of medical history and physical examination.[145] After having produced a hypothesis of sepsis[146] clinicians should immediately stage gravity (Appendix Figure 23). Alterations of traditional hemodynamic parameters such as blood pressure and heart rate are only some predictors of the presence of septic shock. Clinicians should focus their attention on other signs of vitality such as respiratory rate, SaO_2, level of consciousness, capillary refill, urinary output and lactic acid level.[147] Almost all of these signs can be assessed in few minutes. Respiratory rate and capillary refill lack specificity, but they are both very sensitive in identifying patients at risk. Obviously, they should be considered in the context of full bedside assessment.

Hemodynamic support

It represents the hottest topic of sepsis and it is still a matter of debate. The importance of the hemodynamic support is incontrovertibly demonstrated in patients with severe sepsis or septic shock[139] (Appendix Tables 8-10). In any circumstances, you should administer crystalloids 30 mL/kg for hypotension.[1] Albumin and colloids have been definitely abandoned.[148,99-100] Amine support should be considered only in septic shock, and norepinephrine represents the best choice.[1] Actually, dopamine has a role in low heart beat patients and dobutamine in ventricular dysfunction. Epinephrine, vasopressin and phenylephrine can be considered in case of norepinephrine failure.

Understand the source of infection

The key role of early intervention has been recognized in the creation of the term *the golden hour* as it relates to therapy of life-threatening conditions.[139] For effective treatment of severe sepsis and, particularly, septic shock, early elimination of the pathogenic bioburden that drives the septic process and resuscitation are equally important (Table 4). Blood cultures should be collected before antibiotic therapy administration.[1] At least 2 sets are necessary with at least 1 drawn percutaneously and 1 drawn through each vascular access device, unless the device was recently (<48 h) inserted. Cerebrospinal fluid, urine, expectoration or other body fluids that may be the source of infection can be collected if clinically indicated. In case of suspected candidiasis, use of the 1,3-β-D-glu-

Table 3. Diagnosis of sepsis.

History taking	Clinical examination	Laboratory
Symptoms (onset, duration)	Localization sign (examine all body)	CRP
Travel	Temperature	Procalcitonin
Recent invasive procedure	Heart rate	Lactatemia
Immunosuppression	Tachypnea	Glycemia; creatinine
Altered mental status		Capillary refill; platelets
Blood pressure		WBC

CRP, C-reactive protein; WBC, white blood cells count.

Table 4. Tools for source control.

Tool	Clinical suspect
Fluid cultures	Sepsis
1,3-β-D-glucan, mannan, anti-mannan	Fungal infection
Thorax radiography	Broncopneumonia
Lung echography	Broncopneumonia
Abdomen echography	Abdominal abscess; cholecystitis; globe bladder with possible urinary tract infection; hydronephrosis
Echocardiography	Endocarditis
Abdomen computed tomogrphy	Retroperitoneal abscess

can assay, mannan and anti-mannan antibody assays should be performed. Imaging depends on clinical suspects and should be performed rapidly in order to confirm a potential source of infection.

Antibiotic therapy

The successful treatment of septic patients with a high risk of death depends on early and aggressive antibiotic treatment.[28] It should be administered within one hour in patients with severe sepsis.[1] Administration of appropriate antibiotics along with source control (Figure 1) should be done in parallel with resuscitative therapy. If the source of infection is not determined, therapy should consider broad-spectrum antibiotics. Combination empiric therapy for neutropenic patients with severe sepsis and for patients with difficult-to-treat, multidrug-resistant bacterial pathogens such as *Acinetobacter* and *Pseudomonas* are suggested. In neutropenic cancer patients with a low severity sepsis, piperacillin-tazobactam is a reasonable choice.[142] If the source of infection is determined, guidelines on specific infection can be applied.[31-39] When causative pathogen has been identified, de-escalation should be performed by selecting the most appropriate antimicrobial agent that covers the pathogen.[1] Therapy should be continued typically for 7 to 10 days, longer courses may be appropriate in patients who show a slow clinical response, present undrainable foci of infection or bacteremia with *S. aureus* or some fungal and viral infections or immunologic deficiencies, including neutropenia. Procalcitonin can be useful to decide to stop antibiotic therapy in septic patients, but it is still uncertain what cut-off has to be considered.[33] Further procalcitonin can be useful to stop antibiotic therapy in a patient who appears septic at the admission, but has not any subsequent evidence of infection. Echinocandins or triazoles should be started whenever a candidemia is suspected.[1] In case of severe sepsis, it is preferable to use echinocandins but the choice should be tailored to the local pattern of the most prevalent Candida species and any recent exposure to antifungal drugs (Table 1). The antiviral therapy should be initiated as early as possible in patients with severe sepsis or septic shock of viral origin.[1,44-49]

Other measures

Clinicians should consider a series of other measures discussed in recent years (Table 5). Considering *ARDS*, a serious complication of sepsis, NIV can represent an opportunity to avoid intubation.[126] Internists should think of it, but the choice has to be discussed with Intensivists, because intubation delay can worse mortality. *Steroids* should be used only in septic shock without response to vasopressor therapy and immunoglobulins cannot be suggested due to the lack of convincing efficacy.[1] *Insulin therapy* should be administered in diabetic patients or in stress hyperglycemia to limit mortality.[136] It is advisable to keep glycemia between 140 and 180 mg/dL.[137] *Nutrition support* should be considered in septic patients and enteral nutrition should be preferred to parenteral one. At the moment, there is not enough evidence to recommend more precise advice regarding doses and timing.[131-133] *Venous thromboembolism prophylaxis* should be encouraged.[1] *Blood and platelets transfusion* are suggested on expert opinion and few papers. Clinicians should focus on patient's clinical conditions.

Special cases

In a critically ill pregnant woman, birth of the baby may be considered if it would be beneficial to the mother or the baby or to both.[141] A decision on the timing and mode of birth should be made by a senior ob-

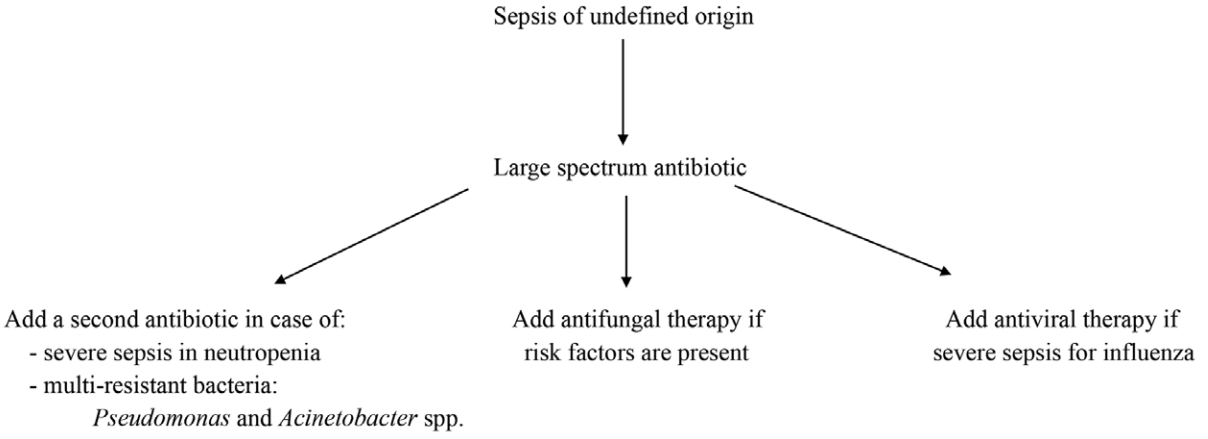

Figure 1. Antibiotic therapy in sepsis.

stetrician following discussion with the woman if her condition allows.

Clinical governance and management of sepsis: an extended audit about the appropriateness of empirical antimicrobial therapy

We can no longer think that effectiveness of care is an isolated professional matter: if we are aiming at quality, then we need to consider the healthcare service as a mosaic composed of different pieces, each expression of a different point of view. Clinical governance represents a systematic and structured approach for quality that integrates the perspectives of staff, patients, caregivers, and those charged with managing the health service.[149]

Clinical audit is a component of clinical governance and offers the greatest potential to assess the quality of healthcare. In its essence, clinical audit is a systematic review of care, and is based on the comparison with explicit criteria; from this comparison, it is easy to identify the deviations and to design the subsequent interventions to implement the change: the audit methodology is effectively applied into an environment supporting it (*using the method, creating the environment*).

Clinical audit is described as a continuous cycle (Figure 2), to underline that we should not define a definitive arrival point in a continuous quality improvement process.

What, is the objective, defined by predefined explicit criteria and sought in clinical practice, to be identified as achieved or missed.

If the objective is missed, *why*, is the deviation from explicit criteria that suggests the priority of the change.

Therefore, *doing* is the intervention needed to implement the change and to verify its realization, so to achieve the objective. And, then, the cycle starts again.

To expand the circle, and clearly define the sequence of steps to apply the audit methodology, we need a pathway that, on the one hand defines the method and, on the other hand, underlines the role of the environment for a successful audit (Figure 3).

Thus, from *Learning from Bristol: Report of the Public Inquiry into Children's Heart Surgery at the Bristol Royal Infirmary 1984-1995* (Department of Health, 2001):

> *143: The process of clinical audit… should be at the core of a system of local monitoring of performance.*
>
> *144: Clinical audit must be fully supported by trusts. They should ensure that healthcare professionals have access to the necessary time, facilities, advice, and expertise in order to conduct audit effectively. All trusts should have a central clinical audit office that coordinates audit activity, provides advice and support for the audit process, and brings together the results of audit for the trust as a whole.*
>
> *145: Clinical audit should be compulsory for all healthcare professionals providing clinical care and the requirement to participate should be included as part of the contract of employment.*

The project of Young Group of the Federation of Associations of Hospital Doctors on Internal Medicine (FADOI) is: to learn to use *the audit method*, to review their clinical practice basing on scientific evidence; to stimulate the creation of an environment conducive to sustain necessary changes; to start developing an environment where individuals form a whole that shares, cooperates, integrates, manages into a vision as univocal as possible.

The present project is based on the implementation of the audit method to the prescriptive appropriateness of empirical antibiotic therapy.

The clinical guidelines edited by SSC on the management of severe sepsis and septic shock provide

Table 5. Other measures in sepsis.

Measure	Circumstances
NIV	Can substitute intubation in ARDS. Do not insist if it does not work
Steroid	In case of septic shock without response to amines
Insulin	To keep glycemia between 140 and 180 mg/dL
Venous thromboembolism prophylaxis	Always encouraged
Nutrition	Possibly enteral
Blood transfusion	In expert opinion. Consider patient complexity
Platlets transfusion	In expert opinion. Consider patient complexity
Birth delivery	Consider beneficials to mother and baby

NIV, non-invasive ventilation; ARDS, acute respiratory distress syndrome.

well definite recommendations about the parameters to be measured and the diagnostic and therapeutic actions to be fulfilled, with clear-cut references of timing, modalities, and doses of treatment.[1]

The bundles recommended by SSC could represent an outright reference standard check list; the proposal to perform a test, and therefore, in essence, a comparison of our clinical practice against such a check list, greatly ease the testing activity, requiring, ultimately, only the collection of the data generated by such testing activity.

The only limit of the recommendations is related to the empirical antibiotic therapy.

However, the following items show a great evidence in literature: i) the timing: within 1 h from recognition of septic shock (1B) or severe sepsis without septic shock (1C); ii) the essential quality: administration of an effective therapy, because the treatment of patient with severe sepsis and septic shock allows a very narrow margin of error; iii) the complexity of the choice, to be made very early, depending on issues related to:

- the causative agent - all likely pathogens (bacterial and/or fungal or viral). It implies the knowledge of the pathogens more frequently involved in different types of infections, their susceptibility to the different classes of antibiotics, the entity and quality of antimicrobial resistance;
- the antimicrobial agent and its adequate concentration into the tissues presumed to be the source of sepsis. Confidence with pharmacokinetics and pharmacodynamics of drugs, especially during sepsis (impaired/unstable kidney or liver function, abnormally high volumes of distribution due to the aggressive fluid resuscitation required during the first steps of treatment);
- the host, considering factors as: i) history of allergy; ii) recent exposure to antimicrobials (over last 3 months); iii) comorbidities and/or chronic therapies related to immunodeficiency; iv) risk factors for a multi-drug resistant pathogen (residence in healthcare facilities; presence of devices; hemodialysis).

The microbes are educated to resist penicillin and

Figure 2. The clinical audit cycle.

a host of penicillin-fast organisms is bred out… In such cases the thoughtless person playing with penicillin is morally responsible for the death of the man who finally succumbs to infection with the penicillin-resistant organism. I hope this evil can be averted (Sir Alexander Fleming New York Times, 26/06/1945.)

Antimicrobial agents have many different peculiarities.

The administration of every drug has effects on the patient; antimicrobial agents are the only drugs that have effects both on the patient and on its surrounding environment, through the selection of pathogens and/or resistances. This aspect increases more and more the responsibility of the prescribing physician: in 2010, World Health Organization (WHO) identified the antibiotic resistance as one of the three more dangerous threatens for public health. Considering the link between antimicrobial use and the selection of resistant pathogens, the rate of inappropriate antimicrobial prescriptions is often used as a surrogate marker for the avoidable impact on antimicrobial resistance.

Hence, this issue is the basis for institution of antimicrobial stewardship programs: to indicate programs of structured interventions aimed to measure and improve the appropriate prescription of antimicrobial agents, promoting the selection of therapeutic regimens optimized in relation to the choice of the drug, the dose, the administration route and the duration of therapy.[150]

The primary goal of these programs is to optimize clinical outcomes while minimizing unintended consequences of antimicrobial use, including toxicity, the selection of pathogenic organisms (such as *Clostridium difficile*) and emergence of resistances; the secondary goal is to reduce the sanitary costs, without a negative impact on the quality of care.

Although evaluation of the antimicrobial stewardship programs is beyond our aims, it is useful to point out that, in the paper *Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America Guidelines for Developing an Institutional Program to Enhance Antimicrobial Stewardship*[151] only two recommendations are proposed with level of evidence *A* and strength *I*: i) perspective audit of antimicrobial use with direct interaction and feedback to the prescriber can result in reduced inappropriate use of antimicrobials; ii) multidisciplinary development of evidence-based practice guidelines incorporating local microbiology and resistance patterns can improve antimicrobial utilization.

Moreover, in March 2014, the FADOI Education Department has developed a questionnaire to understand the update/education needs of the FADOI members; this questionnaire explored the context of clinical

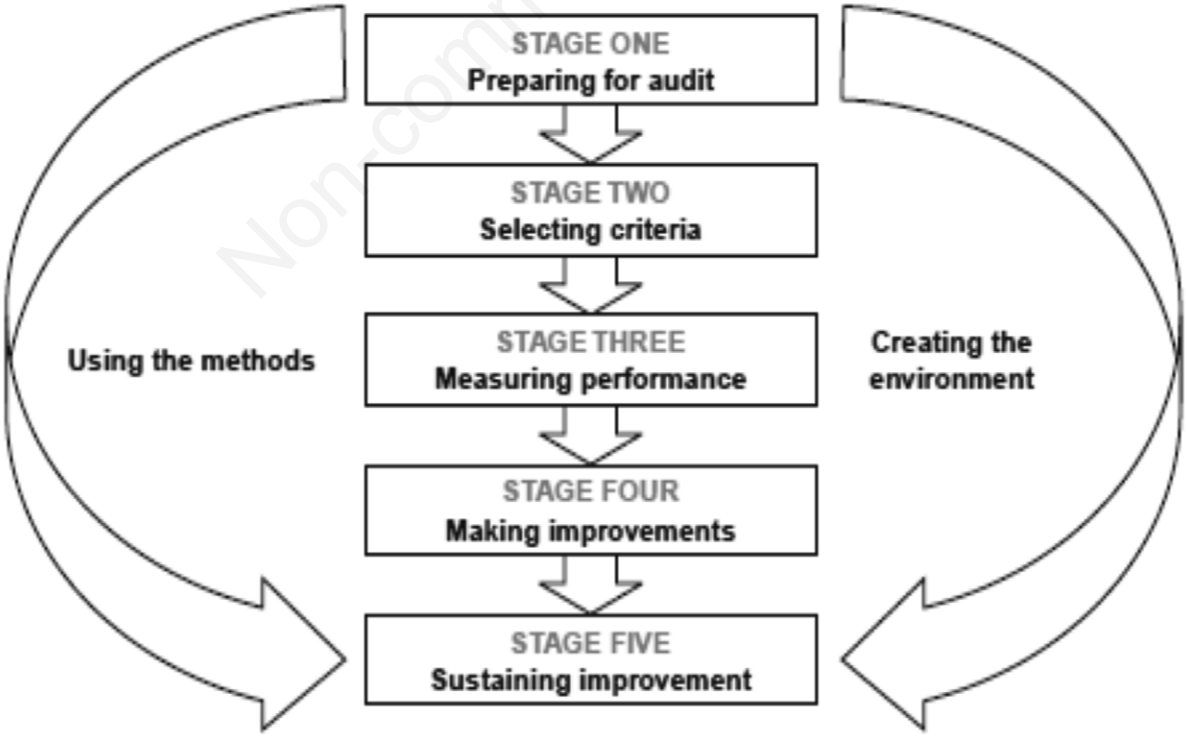

Figure 3. The stages of clinical audit. Clinical audit involves the use of specific methods, but also requires the creation of a supportive environment.

knowledge with multiple open choices. In June 2014, the questionnaire was sent to all the 1810 FADOI members; there was a feedback from about 30% of the contacts. Sepsis and infections/antimicrobial therapy - 157 and 141 respectively - resulted at the first and second place of the expressed needs with an overall result of 298 indications, corresponding to 53.6% of the whole sample. Most of the members expressed not only the preferred topic, but also the preferred educational tool, clearly requiring a practical approach; for example, in the context of our project: organ/system specific protocols of empiric therapy; rational choice of the antimicrobial agent in sepsis; protocols of empiric antibiotic therapy of nosocomial infections.

Therefore, our aims are: i) to perform a systematic search for the existing clinical guidelines on the empiric antimicrobial therapy, separated on the basis of the system involved and of the clinical syndrome (sepsis, pneumonia, urosepsis, skin and soft tissues infections); ii) to assess the clinical guidelines with the AGREE method, to define the quality of each guideline as a whole; iii) to compare, also on the basis of AGREE scores, the recommended schemes of empiric antimicrobial therapy expressed by the different guidelines; iv) to arise a standard reference therapeutic scheme for each system involved and/or clinical syndrome, implementable into different internal medicine settings with the lowest possible error; v) to submit the result of the work to the opinion of an infectious diseases expert for further validation.

In the meanwhile, we will start up a data collection about the prescription of empiric antibiotic therapy by the FADOI members involved in the editing of the present work (five members from Young FADOI and four members of *Area Permanente of Clinical Governance*): for this purpose, we will use a form containing all elements that allow to reason about the empirical antibiotic therapy. The data collection will be retrospective; we will include the data of the inpatients receiving an antibiotic therapy and admitted to our wards during a period of 30 days. Then, the data will be compared against the standard reference therapeutic schemes so that any deviations can be identified.

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