Chapter

Empiric Antimicrobial Therapy in Critically Ill Septic Patients

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Abstract

Sepsis is a medical emergency and life-threatening condition due to a dysregulated host response to infection, which is time-dependent and associated with unacceptably high mortality. At the bedside of a patient with sepsis or septic shock, clinician must make immediate life-saving decisions including empirical initiation of broad-spectrum antimicrobials; the most likely to be appropriate. The empiric regimen should be initiated within the first hour of diagnosis and determined by assessing patient and epidemiological risk factors, likely source of infection based on presenting signs and symptoms, and severity of illness. Optimizing antibiotic use is crucial to ensure successful outcomes and to reduce adverse antibiotic effects, as well as preventing drug resistance. All likely pathogens involved should be considered to provide an appropriate antibiotic coverage. Herein, we tried to make suggestions of empirical therapeutic regimens in sepsis/septic shock according to most likely pathogens in cause and sepsis source based on the recent recommendations of learned societies. Some suggestions were adapted to an environment of low-resource regions where the ecology of multi drug resistant organisms is of concern.

Keywords: empiric, antimicrobial, sepsis, septic shock, intensive care

1. Introduction

Sepsis is a clinical syndrome characterized by systemic inflammation due to infection (presumed or confirmed). There is a continuum of severity ranging from sepsis to septic shock. Diagnosing sepsis remains difficult because it is not a single disease but a syndrome with various pathogen and host factor-associated symptoms. Sepsis-3 was established to improve risk stratification among patients with a suspected infection focusing on organ failures [1]. Sepsis should be immediately recognized because it is the primary cause of death from infection, especially if not diagnosed and treated promptly. Mortality has been estimated to be ≥10 percent and ≥ 40 percent when shock is present [1, 2]. In the United States, it is estimated that there are 270 000 deaths a year due to sepsis and 35 000 deaths attributable to antibiotic resistance [3, 4]. Herein, we discussed the immediate management of sepsis and septic shock mainly the empiric antimicrobials in critically ill patients.

2. Immediate conditioning

Correcting hypoxemia and establishing venous access for the **early** administration of fluids and antibiotics are priorities in the management of patients with sepsis and septic shock [5, 6].

2.1 Oxygenation

Intubation and mechanical ventilation (MV) may be required to support the increased work of breathing that typically accompanies sepsis. Oxygenation should be monitored continuously with pulse oximetry. Once MV is indicated, rapid sequence intubation (RSI) should incorporates a rapidly acting sedative (ie, induction) agent, in addition to a neuromuscular blocking (ie, paralytic) agent, to create optimal intubating conditions. Then ensure analgesia sedation throughout the duration necessary for the sepsis/septic shock management while regularly monitoring the possibility of weaning from ventilator.

2.2 Venous access

Venous access is essential in the immediate management of sepsis/septic shock. The peripheral access has the advantage of the quickness of its putting in (at least 2 lanes of good caliber). But anyway, we are going to need central venous access. Preferably, it is advisable to set up a central venous catheter (CVC) but that should not delay the administration of resuscitative fluids and antibiotics. A CVC is useful to infuse intravenous fluids, medications (particularly vasopressors) and antibiotics. As well as, it can be used to monitor the central venous pressure (CVP) and the central venous saturation ($ScvO_2$).

2.3 Initial investigations

Concomitantly to the initial conditioning including oxygenation and venous access, must be carried out: a history with a physical examination of rapid orientation, biological, microbiological and imaging examinations. This may allows having an orientation towards the source and sometimes the pathogen in cause and thus guiding the empirical choice of antibiotics.

- Laboratory tests include complete blood counts, Arterial blood gas (ABG), analysis of renal and liver functions, D-dimer level, Procalcitonin and serum lactate.

- Microbiologic samples include peripheral blood cultures (aerobic and anaerobic cultures from at least two different sites), and other samples depending of suspect sites should be obtained (e.g., cyto-bacteriologic examination of sputum if pneumonia suspected or urine if urinary tract infection evoked, catheter tip if catheter-related infection (CRI) evoked, surgical site, etc.). Regarding the bloodstream cultures, it is unnecessary to draw blood through a catheter, given the risk of contamination by skin flora. The sample should be taken from a peripheral venipuncture site.

- Imaging target at the suspected infection site is warranted (eg, chest radiography, computed tomography of chest and/or abdomen).

2.4 Rapid restoration of perfusion (first three hours)

Aggressive administration of intravenous fluids, usually crystalloids given at 30 ml/kg, started by one hour and completed within the first 3 hours following presentation.

Some patients may require higher than recommended volumes, particularly those who demonstrate clinical and/or hemodynamic indicators of fluid-responsiveness. The clinical and hemodynamic response and the presence or absence of pulmonary edema must be assessed before and after each bolus using passive leg raising, CVP variation, $ScvO_2$, pulsed pression variation (PPV) or ultrasound indicators etc.... Intravenous fluid challenges can be repeated until blood pressure and tissue perfusion become acceptable.

2.5 Vasopressors

Vasopressors on CVC if the blood volume is optimized and persistent hypoperfusion or immediately if the diastolic blood pressure is less than 40 mmHg.

Based on the SSC (survival sepsis campaign) guidelines 2016 [5], the response should be assessed using the following targets within 6 hours: $ScvO_2 \geq 70\%$, CVP 8–12 mmHg, mean arterial pressure (MAP) ≥65 mmHg, and urine output ≥0.5 ml/kg/hour.

3. Empiric antimicrobial therapy (EAT)

Initial selection of particular antimicrobial agents is empiric and is based on an assessment of the patient's underlying host defenses, the potential sources of infection, and the most likely pathogens depending on the locally epidemiological data. EAT is preferably administered within the first hour.

3.1 Times to antibiotics

Once a presumed diagnosis of sepsis or septic shock has been made, optimal doses of appropriate intravenous antibiotic therapy should be initiated, preferably within one hour of presentation and after cultures have been obtained. The Infectious Diseases society of America (IDSA) opts to that prompt administration of antibiotics is recommended once a presumed diagnosis of sepsis or shock has been made by the treating clinician [7]. The Surviving Sepsis Campaign recommends immediate antibiotics for all patients with suspected sepsis and septic shock, ideally within 1 hour of recognition.

The literature review does not find a clinical trials evaluating specially the target time of one hour to start antimicrobials. That is understandable given the enormous ethical concern that results. But almost all observational studies agree that a delay exceeding one hour is related to poor outcomes; as well as inadequate doses and inappropriate antibiotic therapy [8–14]. Ferrer R, et al. in a large population of patients with severe sepsis and septic shock (17,990 patients) demonstrated a linear increase in the risk of mortality for each hour delay in antibiotic administration [9]. In a retrospective study of 35,000 patients treated in emergency department, the increase in absolute mortality associated with an hour's delay in antibiotic administration was 0.3% ($p = 0.04$) for sepsis, 0.4% ($p = 0.02$) for severe sepsis, and 1.8% ($p = 0.001$) for shock [11].

In a large database study comparing patients with sepsis and septic shock treated with various types of protocolized treatment bundles (that included fluids and antibiotics, blood cultures, and serum lactate) versus those in whom a three-hour bundle (blood cultures before broad spectrum antibiotics and serum lactate level) was completed within the three-hour time frame [12]. Each 3-hour bundle delay achievement increased in-hospital mortality by 1.04 per hour [12]. In addition, a delayed completion of a fluid bolus did not increase mortality significantly (OR = 1.04) as the delay of antimicrobials [12].

3.2 Identification of suspected source/responsible pathogens

Establishing an accurate diagnosis of the infection site is a priority objective that must be fulfilled as soon as possible.

Sometimes the patient arrives with a visible source of infection (e.g. infected wound, cellulitis etc). In the case where the source is unclear, the process of its identification is based on a good anamnesis for collecting the medical and surgical history and a careful and exhaustive physical examination looking for local inflammatory signs or function loss. If the source is identified, targeted imaging and microbiological sampling should be done and therefore empiric antibiotic therapy should be initiated.

In the case where the source remains unclear, it is necessary to complete by an exhaustive imaging or even a whole body CT scan and extensive sampling.

Table 1 summarizes the most common sources of infection with a potential risk of progress to a sepsis and septic shock and the additional tests to be performed.

Additional diagnostic testing or interventions may be required to identify the anatomic site(s) of infection. In particular, in addition to antibiotics, closed space infections should be promptly drained or debrided (eg, empyema, abscess) for effective source control.

Besides bacteriological examinations, imaging is often essential to recognize sites of infection (chest radiography, ultrasound, tomography and MRI).

Sometimes in structures with limited resources, imaging is not always available, as are interventional radiology techniques. In this case, blood cultures before the administration of antibiotics becomes an essential measure and ideally that should be obtained from two sites.

3.3 Regimen to choose

The choice of empirical antibiotic therapy is not a simple attitude and must be reasoned upon the presumed primary focus, the history of the patient ((eg, recent antibiotics received, previous organisms) and its co-morbidities (eg, diabetes, organ failures, immune defect..), invasive devices, nosology (eg, community- or hospital-acquired) and the bacterial ecology and resistance patterns of the unit where the patient is hospitalized [13, 14, 16–18]. It must be preceded by directed bacteriological samples.

Also, the choice of the molecule is made according to its spectrum of action and its pharmacodynamics/pharmacokinetics (PK/PD) properties and the spectrum of the selected combination must be efficient against gram-positive, gram-negative, and anaerobic bacteria because all of these classes of organisms produce similar clinical presentations.

Regarding the administration route and dosing, it is recommended that the intravenous is mandatory and at high doses to achieve bactericidal serum levels. This later correlated with clinical improvement rather than the number of antibiotics prescribed.

Suspected site	Symptoms/signs	Suggested initial tests
Upper respiratory tract	Pharyngeal inflammation plus exudates ± swelling and lymphadenopathy	Throat swab for aerobic culture Cyto-bacteriological exam of sputum PCR-SARS CoV2 if pandemic context
Lower respiratory tract	Productive cough, pleuritic chest pain, consolidative auscultatory findings	Sputum of good quality, rapid influenza testing, urinary antigen testing (eg, pneumococcus, legionella) PCR-SARS CoV2 if pandemic context
Urinary tract	Dysuria, urination scorch	Urine culture, renal ultrasound (obstructive calculus)
Vascular catheters: arterial, central venous	Redness or pus at insertion site	Culture of blood (from the catheter and a peripheral site), catheter tip bacterial exam after removal
Abrasion, wound, burn, diabetic foot lesion	Erythema, pus, lymphangitis	Local swabs gram stain and culture, sampling of pus or per cleaning
Skin/soft tissue	Lividities, cyanic spots, subcutaneous crepitation, local hypo- or anesthesia, induration exceeding erythema, local necrosis	Culture of flowing liquid or draining pus, preoperative tissue samples
Urinary system	May differ by gender low abdominal pain and vaginal discharge in women, Dysuria, incontinence, cloudy urine, prostatic tenderness in men	Vaginal and endocervical sampling in women and cytobacteriological examination plus culture in both sexes
Deep intra-abdominal focus	abdominal pain depending on the organ affected, vomiting	Aerobic and anaerobic culture of abdominal fluid collections drained percutaneously or surgically
Gastrointestinal	Diarrhea, vomiting and intestinal spasms	Coproculture, parasitological stool examination
Meninges and brain	Meningitis: stiff neck, sign of Kernig and Brudzinski, osteotendinous hyper-reflexia Encephalitis: Altered state of consciousness, motor deficit, seizures	Lumbar puncture for exhaustive examination of the CSF (cytological, chemical, bacteriological, search for soluble Ag, culture and PCR if indicated)
Peritoneal catheter	Cloudy fluid, local inflammatory signs	Direct examination and culture of the discharged fluid
Bones and joints	Pain, Inflammatory signs	MRI, peroperative cultures or by interventional radiology Arthrocentesis, blood cultures

PCR: polymerase chain reaction, SARS CoV2: severe acute respiratory syndrome coronavirus 2, CSF: cerebrospinal fluid; PD: peritoneal dialysis; MRI: magnetic resonance imaging.
Source: Reference [15]

Table 1.
Identification of sources of sepsis and additional tests.

The regimen to choose should consider antipseudomonal in patients with neutropenia or burns and anti-anaerobes in intra-abdominal/perineal infections.

Antimicrobial choice should be tailored to each individual. In any case, appropriate cultures should be obtained which include two sets of blood cultures obtained before antibiotics are started and cultures of other suspected sites of infection (sputum, urine, etc.) obtained as soon as possible.

For most patients with sepsis without shock, antimicrobials may be administered in monotherapy or in combination. Anyway, the empiric chosen regimen must cover all the maximum number of pathogens most likely involved (ie gram-positive and gram-negative bacteria, fungi if presence of invasive candidiasis factors or immune-compromised for aim *Pneumocystis jirovecii*, and rarely viruses (eg, influenza, Cytomégalovirus (CMV)). For SARS CoV2, all the therapeutic means tried so far (chloroquine, macrolides, tocilizumab, remdesivir, monoclonal antibody, colchicine ...) are designed for immunomodulatory purposes and no treatment is directed specifically against COVID-19.

Patients with septic shock, in whom gram negative bacilli are suspected, must be treated with at least two antimicrobials from two different classes according to the considered likely organisms and local antibiotic susceptibilities. That is commonly called combination therapy defined as more than one antimicrobial agent given in the aim to improve efficiency against a known or suspected pathogen.

Escherichia coli, *Staphylococcus aureus, Klebsiella pneumoniae,* and *Streptococcus pneumoniae,* are the most common isolated organisms from patients with sepsis. Thus, these organisms should be taken into account when choosing empiric regimen [19]. Betalactams such carbapenem, piperacillin-tazobactam, in combination or not with aminosides or quinolones are a good alternative to cover a large batch of gram negative and positive organisms.

When nosocomial nature of sepsis or septic shock is suspected, the multiresistant profile of microorganisms (mainly non fermenting gram negative bacilli including *Acinetobacter Baumannii*) should be covered [20, 21].

Otherwise, the following pathogens must be included in the spectrum of antibiotics to be chosen and this according to the risk factors for their presence:

- **Methicillin-resistant *S. aureus*:** Today, methicillin-resistant *S. aureus* (MRSA) is no longer classified among the pathogens of healthcare-related infections since it is increasingly described in community infections [22, 23]. That is why empirical intravenous vancomycin (be careful with the doses if renal impairement) should be added in subjects with sepsis/septic shock at risk of MRSA. Linezolid if MRSA refractory (VISA or GISA of susceptibility profile) or a contraindication to vancomycin can also be suggested as an anti MRSA. Daptomycin may be prescribed in cases of extra-pulmonary MRSA infection. In skin and soft structures infections, IDSA update 2014 proposed vacomycin, linezolid, clindamycin, daptomycin and ceftaroline/fosamil may be proposed.

- ***Pseudomonas aeruginosa*:** if *Pseudomonas* is a likely pathogen and depending on local antibiotic susceptibility patterns, antimicrobials proposed are:

  - Antipseudomonal cephalosporin (eg, ceftazidime, cefepime), or

  - Antipseudomonal carbapenem (eg, imipenem, meropenem), or

  - Antipseudomonal beta-lactam/beta-lactamase inhibitor (eg, piperacillin-tazobactam, or Fluoroquinolone with good anti-pseudomonal activity (eg, ciprofloxacin), or Aminoglycoside (eg, gentamicin, amikacin), or Monobactam (eg, aztreonam)

- **Enterobacteria** (eg, *E. coli*, *K. pneumonia, Proteus, Providencia, Serratia*): They are pathogens treated, for a long time, by a regimen which combines several antibiotics although this is not proven by studies. Indeed, in the old meta-analysis of Safdar N, et al. the summary odds ratio was 0·96 (95% CI

0,70–1,32), indicating no mortality benefit with combination therapy compared to monotherapy with a third generation cephalosporin or a carbapenem [24]. Furthermore, the combination to an amino-glycoside was related to an increase of nephrotoxicity [24].
Therefore, it is recommended to administer a single antimicrobial agent known to have proven efficacy and the least possible toxicity. Patients with neutropenia or in whom *Pseudomonas* is suspected are to exclude from this rule and combination therpay should be contemplated.

- **Carbapenemase-producing *Enterobacteriaceae* (CPE)** are becoming an emerging concern worldwide. Infections caused by these pathogens are associated with high morbidity, mortality and costs while they are difficult to treat since only a small number of therapeutic options are available. Only a few clinical studies, often size-limited and retrospective, have been conducted mainly on infections caused by KPC - producing *Klebsiella pneumoniae* whereas there are more in vitro and animal data. In some cases, β-lactams can be used, such as carbapenems (if MIC ≤8 mg/L), aztreonam or ceftazidime. A double-carbapenem regimen also seems to be promising, with ertapenem. Polymyxins and tigecyline (with a loading dose and high dosages) are possible alternatives in combination. Aminoglycosides (especially gentamicin) in monotherapy are choice options for the treatment of urinary tract infections. Fosfomycin may be used in combination but there is a risk of emergence of resistant mutants during therapy. For the treatment of severe infections (bacteremia and pneumonia), combination therapy should be used since risks of clinical failure and mortality are significantly lower than with monotherapies in the majority of studies. The most frequent combinations are polymyxins-carbapenems, tigecycline-carbapenems and polymyxins-tigecycline, knowing that carbapenem-based regimens (if MIC ≤8 mg/L) must be favored [25].

Acinetobacter Baumannii: *Acinetobacter* are opportunistic and ubiquitous bacteria that occur in the form of Gram-negative coccobacilli. Among the species of this genus, *Acinetobacter baumannii* is the most implicated in nosocomial infections, especially in ICU [26]. This bacterium is involved in a wide range of infections such as VAP, bacteremia, CRI, urinary tract infections, secondary wound infections or postoperative meningitis.
A.baumannii exhibits a remarkable ability to acquire mechanisms of resistance to antibiotics, rapidly leading to multi-resistance to almost all commercially available antibiotics and sometimes to therapeutic dead ends [27].
Acinetobacter baumannii is one of the ESCAPE organisms (*Enterococcus faecium*, *Staphylococcus aureus*, *Clostridium difficile*, *Pseudomonas aeruginosa*, and Enterobacteriaceae), a group of clinically important, predominantly health care-associated organisms that have the potential for substantial antimicrobial resistance [28].

Independent risk factors for colonization or infection with resistant strains of *Acinetobacter* include the following [29–32]: prior colonization with MRSA, prior beta-lactam (particularly carbapenems) or fluoroquinolone use, bedridden status, current or prior ICU admission, presence of a CVC, recent surgery, Mechanical ventilation, Hemodialysis, malignancy, steroids therapy.

Empiric antibiotic therapy for *Acinetobacter*, before results of antimicrobial susceptibility testing are available, should be selected based on local susceptibility patterns. In general, it should consist of a broad spectrum cephalosporin, a combination beta-lactam/beta-lactamase inhibitor (eg, a combination including

sulbactam), or a carbapenem. An additional agent may be warranted if local resistance rates to the chosen antibiotic class are high (eg, greater than 10 to 15%).

When rates of resistance to the selected antimicrobial agent are low (ie, below 10 to 15 percent), monotherapy is likely adequate as there are no data to clearly demonstrate that combination therapy improves outcomes through synergistic effect. However, when rates of resistance are higher, it is reasonable to use one of the agents above in combination with an antipseudomonal fluoroquinolone, an aminoglycoside, or colistin to improve the likelihood of administering an antibiotic agent that retains activity. While there are no clear clinical data to support this practice for *Acinetobacter* infections, many experts favor empiric combination therapy for serious infections with these and other potentially resistant gram-negative organisms because of the increased mortality associated with inappropriate empiric therapy.

A prospective cohort study was made in 70 ICU patients with nosocomial sepsis/septic shock in whom imipenem/colistin was prescribed as first line antibiotic therapy [33]. The main findings were: this regimen was only appropriate in 52% of cases and inappropriateness was associated with an increased ICU mortality risk (OR = 6.27, 95% CI [1.83–21], p = 0.003) [33].

- If isolates susceptible to first line agents**:** we favor choosing the agent with the narrowest spectrum of activity. Other considerations in selection of a regimen include patient drug allergies or intolerance; need to cover additional infections, and hospital formulary.

- If resistant isolates: in the setting of resistance to first line agents, therapeutic options are generally limited to polymyxins (colistin [polymyxin E] and polymyxin B), and tigecycline. We generally use polymyxins, for which there is the most clinical experience in treating extensively drug-resistant *Acinetobacter*.

Susceptibility testing for these agents should be performed as well prior to their use given the possibility of resistance.

We generally favor using a second agent, such as a carbapenem, tigecycline, or rifampin, in addition to polymyxins for serious infections (eg, bacteremia, pneumonia, critical illness) with resistant isolates.

There are no definitive clinical data that demonstrate improved outcomes with combination versus monotherapy, and some randomized trials have suggested that certain combinations (colistin and rifampin or colistin and meropenem or fosfomycin) resulted in comparable clinical outcomes as monotherapy with colistin [34, 35]. Nevertheless, infections with multidrug-resistant *Acinetobacter* are associated with high mortality rates, and we are concerned that the use of a single agent is not adequate, particularly since resistance can develop during therapy, leaving no therapeutic alternatives. The synergistic pharmacological tests are a great contribution to the choice of treatment and consultation with an expert in the management of such infections is advised.

In case of ventilator acquired pneumonia (VAP) caused by *Acinetobacter,* additional considerations include the possible use of adjunctive inhaled antibiotics. Inhaled colistin may be beneficial in select patients [36–38], although not all studies suggest a benefit [39]. We favor use of inhaled colistin among patients with severe pneumonia due to *Acinetobacter* only sensitive to colistin, since intravenous colistin yields low lung concentration. The optimal dose of inhaled colistin is uncertain and ranges from 75 to 150 mg colistin base activity (2.25 to 4.5 million international units CMS) twice daily. Higher doses, up to 5 million international units colistimethate sodium (approximately 167 mg colistin base) every eight hours, have also been used for VAP with *Acinetobacter* [40].

- **Invasive fungal infections:** Fungal infections are a feared complication in ICU patients. Their epidemiology has deeply changed linked to major changes in medical practices (induced immunosuppression, organ transplants, cytotoxic chemotherapy, ICU invasive procedures, parenteral nutrition, and prolonged antimicrobial). Moreover, several factors depend on patient's morbidities (chronic liver or renal failure, diabetes, surgery, septic shock or multisite *Candida* colonization).

  The Arsenal antifungal therapy has also broadened considerably with new molecules, such echinocandins, well tolerated than amphotericin B. The use of an empiric antifungal in patients exhibiting sepsis and septic shock has been widely debated with a rather converging towards the absence of a favorable effect on mortality [41–44]:

Cortegiani A, et al. in a meta-analysis including 22 studies (total of 2761 participants) concluded that the use of untargeted antifungal is not associated with a significant reduction in all-cause mortality and may be associated with a reduction of invasive fungal infection among ICU patients [41]. Empiric antifungal treatment (mostly fluconazole) not decreased risk of mortality or occurrence of invasive candidiasis in ICU patients receiving mechanical ventilation for at least five days [42]. In addition, the multicenter randomized trial conducted in ICU (known as EMPIRICUS, n = 260 patients colonized with *Candida* and having sepsis), micafungin administered for 14 days did not improve 28 day-survival without infection [43].

In a 8-years retrospective double cohort (empiric antifungal group, n = 125 versus no empiric antifungal group, n = 122), no improvement of 28-day survival was found. Moreover, no preventing effect on a new episode of candidemia. Nevertheless, a beneficial effect of empiric antifungal on survival was found in patients with an Acute Physiology and Chronic Health (APACHE) II score < 16: OR = 0.68; CI 95% [0.53–0.87]; p = 0.002 [44]. That means; it is the less severe patients who can benefit from an empiric fungal.

However, if *Candida* or *Aspergillus* is strongly suspected or if neutropenia is present, echinocandin (for *Candida*) or voriconazole (for *Aspergillus*) are often appropriate [45].

Even if our focus here is the empirical choice of antibiotic therapy in septic ICU patients, but it would be wise to suggest a list of the more common potential pathogens that would need to be treated. The main pathogens to be considered in **community infections** depending on the infected site are:

Community acquired pneumonia (CAP): *Streptococcus pneumoniae, Mycoplasma pneumoniae, Chlamydia pneumoniae, Legionella pneumophyla, Haemophilus influenzae, Enterobacteria, anaerobies, Staphylococcus aureus.*

Community meningitides: *Streptococcus pneumoniae, Nesseria meningitis, Listeria monocytogenes Haemophilus influenzae, Enterobacteria, Streptococcus sp.*

Urinary tract infections: *Escherichia coli, Proteus mirabilis, Klebsiella pneumoniae, Staphylococcus saprophyticus, Enterobacter sp, Enterococcus sp.*

Skin and soft tissues infections: *Streptococcus pyogenes, Staphylococcus aureus, anaerobies.*

Intrabdominal infections: *Escherichia coli, Klebsiella pneumonia, anaerobies (Bacteroides fragilis) Enterobacter sp, Enterococcus sp, Streptococcus pneumoniae, Pseudomonas sp.*

For nosocomial infections, Gram-negative bacilli are mostly involved followed by Gram-positive cocci. The main multidrug-resistant bacteria (MDRs) to be considered are: Methicillin-resistant *Staphylococcus aureus* (MRSA), *Enterobacteriaceae* producing Extended spectrum beta-lactamases (ESBL) or hyperproducing cephalosporinases (HPCase), *Pseudomonas æruginosa, Acinetobacter Baumannii* and *Enterococci* Vancomycin Resistant (EVR).

Suspected source of sepsis/ septic shock	
Unknown Source (includes catheter related blood stream infection)	Vancomycin* **PLUS** Cefepime 1 g/6H or Aztreonam 2 g/8H or imipenem 1 g/ 8H (if known high incidence of MDR GNB in the unit) **+/–** Tobramycin 7 mg/kg IV EIAD+ + Consider addition of antifungal in those at high risk for candidemia (caspofungine 70 mg followed by 50 mg daily or anidulafungine 200 mg the 1st day relayed by 100 mg daily or micafungin 100 mg daily).
Intra-abdominal Source	Piperacillin/tazobactam 4 g/6H **OR** Ertapenem 1 g/d **OR** Aztreonam 2 g/8 h **OR** Cefepime 1 g/6H (failing cefotaxime 1 g/4H) **PLUS** Metronidazole 500 mg/8H **+/–** Gentamicin 5–7 mg/kg IV (adjust the dosing with dosage of the max and residual concentration +)
Urinary Tract	Cefotaxime 1 g/6H or Ceftriaxone 2 g daily +/– Gentamicin 7 mg/kg If History ESBL colonization: Ertapenem 1 g/d **OR** Aztreonam 2 g/8 h **PLUS** Gentamicin 7 mg/kg If history of MDR pathogen or Pseudomonas: Imipenem 1 g/8H PLUS Amikacine 25 mg/Kg/d
Skin/Soft Tissue Infection: Necrotizing Skin/Soft Tissue: Gas Gangrene or Necrotizing Fasciitis	**If MRSA not suspected:** Piperacillin/tazobactam 4 g/ 6H PLUS gentamycin 5–7 mg/Kg EIAD +/– Clindamycin 900 mg/8H (**only** if toxic shock present) **If MRSA suspected:** Vancomycin 30 mg/kg/d in 2 divided doses* +/– Clindamycin 900 mg/8H OR Linezolid 600 mg/12H OR Ceftaroline 600 mg/12H
Severe CAP	Ceftriaxone 2 g/24 h **PLUS Levofloxacin 500 mg/ 12 h OR** Azithromycin 500 mg /24 h Severe beta-lactam allergy: only Levofloxacin 500 mg /24H and Consider addition of vancomycin OR Linezolid 6oo mg/12H if MRSA is suspected (CT features+)
Severe CAP with the following Risk factors: □Hospitalized ≥5 d in the past 90 days □Broad spectrum or IV antimicrobial for ≥5 days in the past 90 days □Known respiratory tract colonization with an MDR organism □Residence in a long-term care facility	Imipenem 1 g/8H OR Piperacillin/tazobactam 4 g/6H OR Cefepime 1 g/6 h **PLUS** Azithromycin 500 mg/24 h **+/–** Vancomycin IV or Linezolide 600 mg/12H if MRSA suspected **+/–** Tobramycin 7 mg/kg IV (if *Pseudomonas* colonization *such* COPD, cystic fibrosis…)
HAP/VAP: Risk factors: □Hospitalized ≥5 days □Broad spectrum or IV antimicrobial for ≥5 days in the past 90 days □Known respiratory colonization with an MDR organism □Septic shock	Imipenem 1 g/8H OR Meropenem 1 g/8 h OR Aztreonam 2 g/ 6 h **PLUS** Colistin 9MU in loading dose relayed by 4,5 MU /12H +/– Vancomycin (if MRSA suspected) Consider adjunction of inhaled colistin if high incidence *Acinetobacter* only susceptible to colistin

**Vancomycin dosed per pharmacy consult. Typically with loaded with 20–25 mg/kg dose initially (max 2 g initial dose).*
MDR GNB: multi drug resistant gram negative bacilli, ESBL: Extended spectrum betalactamases, MRSA: Methicillin-resistant Staphylococcus aureus, CAP: Community Acquired Pneumonia, HCAP: healthcare acquired pneumonia, HAP: hospital acquired pneumonia, VAP: ventilator acquired pneumonia.

Table 2.
Suggested regimens for empiric antimicrobials in sepsis/septic shock.

Table 2 displays suggested regimens for empiric antimicrobials in sepsis and septic shock according to the suspected Source (all antibiotics are to be administered intravenously).

3.4 Dosing and modality of administration

Maximizing the dose in patients with sepsis and septic shock is a judicious attitude. This strategy is based upon the known increased volume of distribution that can occur in patients with sepsis due to the administration of fluid and the action of inflammatory cytokines [46, 47] and that higher clinical success rates have been reported in patients with higher peak concentrations of antimicrobials [48, 49]. Continuous infusions of antibiotics as compared with intermittent dosing regimens remain investigational at this time [50].

The meta-analysis of Chen CH, et al. [51] (9 RCTs plus 4 retrospective studies, 1957 participants) compared continuous and intermittent groups. A significant difference was showed with mortality which was higher in the subgroup of continuous infusion (OR 1.433, 95% CI: 1.139–1.801). In this same group, length of stay in ICU was shorter and antibiotic duration was longer but without significance [(OR 0.834, 95% CI: 0.542–1.282) and (OR 1.055, 95% CI: 0.659–1.689) respectively] [51].

However, authors were unable to recommend continuous infusion of intravenous antibiotics better than traditional intermittent infusions of antibiotics at routine clinical care.

In general, the choice of the administration modality depends above all on the PK/PD characteristics of the antibiotic. Time-dependent antibiotics (eg betalactamins, vancomycin) their bactericide are based on the time of contact with the

Antimicrobial	**Dose**
Imipenem-cilastatin	0.5 to 1 g intravenously every 6 hours to 1 g every 8 hours
Meropenem	1 to 2 g intravenously every 8 hours
Doripenem	0.5 g intravenously every 8 hours
Gentamicin[¶]	1 to 2.5 mg/kg intravenously every 8 to 12 hours or 7 mg/kg every 24 to 48 hours depending on creatinine clearance
Tobramycin[¶]	1 to 2.5 mg/kg intravenously every 8 to 12 hours or 7 mg/kg every 24 to 48 hours depending on creatinine clearance
Amikacin[¶]	5 to 7.5 mg/kg intravenously every 8 hours or 15 mg/kg every 24 to 48 hours depending on creatinine clearance
Ciprofloxacin[¶]	400 mg intravenously every 8 hours
Colistin[Δ]	2.5 to 5 mg/kg/day as **colistin base**[Δ] intravenously in two to four divided doses
Polymyxin B	25,000 units/kg (2.5 mg/kg) loading dose followed by 12,500 units/kg (1.25 mg/kg) intravenously every 12 hours
Minocycline	200 mg single dose, followed by 100 mg intravenously every 12 hours
Tigecycline[◊]	100 mg single dose, followed by 50 mg intravenously every 12 hours; 100 mg every 12 hours in serious infections

¶Aminoglycosides and fluoroquinolones are generally used in combination with another agent.
Source: Reference [52, 53]
[Δ]means that the recommended dosage corresponds to that of colistin base, the conversion is: 1 mg colistin base = 2.67 mg colistimethate = 33.3 IU. Thus 2.5 to 5 mg / kg / day of colistin base correspondsabout 6 to 12 million IU of colistimethate.
[◊]For severe hepatic dysfunction: loading dose is the same (100 mg) followed by 25 mg IV every 12 hours.

Table 3.
Dosage of most common prescribed systemic antibiotics in ICU adults with normal renal function.

microorganism at doses above the MIC. Therefore the administration of this type of antibiotic in continuous infusion or in multiple doses is preferred. On the other hand, dose-dependent antibiotics (eg aminosia, colistin), whose effectiveness depends on the peak concentration reached, their administration at a single or twice dose is preferred.

Dosing of the most common prescribed antimicrobials in ICU patients with normal renal function is summarized in the **Table 3.** When renal function impair, antibiotic's doses should be adjusted according to the creatinine clearance.

The follow up of infection's indices is mandatory, including complete blood count and additional cultures. Results should prompt modification of antibiotic choice if a better and safer regimen can be substituted and/or investigations directed towards source control.

3.5 Eradication of septic focus

It should be undertaken in timely manner when they feasible since undrained foci of infection may not respond to antibiotics alone. Typical examples are: infected catheter which must be removed (obviously after the establishment of another vascular access), plumonary abscess and chest wall, obstructive pyelonephritis which indicates percutaneous nephrostomy, cholecystectomy, peritonitis to be cleaned in the operative room, dermo-hypoderma which require debridement or amputation of soft tissues, etc.

Expert opinions recommend not exceeding 6 to 12 hours since the identification of septic focus and its eradication in order to facilitate access to antibiotics and thus improve survival.

3.6 De-escalation and duration of antibiotics

Antibiotics started for sepsis should be reassessed daily for potential discontinuing if sepsis is ruled out or narrowing if more data becomes available [54]. While there is no consensus on de-escalation criteria, most experts use follow-up clinical (improved vital signs), laboratory and imaging data, and a fixed course of broad-spectrum therapy (eg, 3 to 5 days). After culture and susceptibility results return and/or after patients clinically improve, antimicrobial therapy may be narrowed to a few days. When possible, antimicrobial therapy should also be pathogen/susceptibility-directed. However, since no pathogen is identified (almost in 50% of patients), de-escalation of empiric therapy requires a component of clinical judgment. For example, vancomycin is typically discontinued, if no *Staphylococcus* is cultured.

Concerning the duration of antibiotic therapy, it must be reasoned and reassessed on a case-by-case basis. Often duration of 7 to 10 days is sufficient [55]. For certain cases, this duration must be prolonged up to even three weeks (mainly septicaemic presentations with metastatic locations (endocarditis, osteomyelitis, large abscess), a lack of clinical improvement within the usual timeframes, deep infections with *Candida* or *aspergillus,* some viral infections (Herpes or cytomegalovirus), isolation of extensively drug resistant (XDR) Gram-negative bacilli, immune disorders [56].

3.7 Role of procalcitonin

PCT appears to be a more relevant marker in diagnostic for bacterial infections. Its serum level increases in case of severe bacterial or parasitic infection with a sensitivity comparable to that of PCR but with better specificity. The importance

of its serum level at the time of initial treatment would be also correlated with a subsequent poor prognosis of patients.

Although many institutions and guidelines support the use of procalcitonin to limit antibiotic (empiric or therapeutic) use in critically ill patients with suspected infection or documented infection, the evidence to support this practice is limited. Other studies suggest that procalcitonin may distinguish infectious from noninfectious conditions and may therefore facilitate the decision to de-escalate empiric therapy [57, 58].

In addition, studies of the kinetics of PCT were more interesting and useful than studies of a static value of unadjusted PCT. MDT is a favorable marker to assess changes in clinical symptoms and patient prognosis. MDT may improve the judgment of disease severity in patients with sepsis or septic shock, thereby improving the ability of clinicians to accurately assess disease prognosis [59]. Hence, we suggest that PCT be assessed daily or at default every 48 hours for critical septic patients.

4. Conclusions

For patients with sepsis, we opt to an optimal doses of empiric broad spectrum intravenous therapy with one or more antimicrobials be administered, in a prompt fashion (eg, within one hour) of clinical presentation. For patients with septic shock with likely gram negative sepsis we suggest combination therapy (at least two) from different classes given with the intent of covering a known or suspected pathogen with more than one antibiotic. It is the only guarantor for sufficient activity to cover a broad range of gram negative and positive organisms and, if suspected, against fungi and viruses. Agent selection depends upon patient's history, co morbidities, immune defects, clinical context, suspected site of infection, presence of invasive devices, and local prevalence and resistance patterns.

The advent of new technologies (multiplex-PCR) with the ability to type and characterize microorganisms without the need for conventional culture techniques may negate the requirement for highly specialized microbiology staff and facilities. These methods could eventually contribute significantly to improved management of patients with sepsis and septic shock as well as antibiotic stewardship programs.

Conflict of interest

The authors declare no conflict of interest.

Acronyms and abbreviations

APACHE	Acute Physiology and Chronic Health
ABG	Arterial blood gas
CVC	Central venous catheter
CVP	Central venous pressure
$ScvO_2$	Central venous saturation
CMS	Colimesthate sodium
CAP	Community Acquired Pneumonia
CSF	Cerebrospinal fluid
EAT	Empiric Antimicrobial Therapy
EIAD	Extended Interval Aminoglycoside Dosing

ESBL	Extended spectrum betalactamases
GNB	Gram negative bacilli
HCAP	Healthcare acquired pneumonia
HAP	Hospital acquired pneumonia
ICU	intensive care unit
IDSA	Infectious Diseases society of America
MAP	Mean arterial pressure
MV	Mechanical ventilation
MRSA	Methicillin-resistant *Staphylococcus aureus*
MIC	Minimum inhibitory concentration
MRI	magnetic resonance imaging
CPE	Carbapenemase-producing *Enterobacteriaceae*
MDR	Multi drug resistant
OR	Odds ratio
PCR	polymerase chain reaction
PD	peritoneal dialysis
PPV	Pulsed pression variation
RCT	Randomized controlled trial
SARS CoV2	severe acute respiratory syndrome coronavirus 2
VAP	Ventilator acquired pneumonia

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