The Patient with Septic Shock

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16.1 Definition of Sepsis

Sepsis is defined as "life-threatening organ dysfunction caused by a deregulated host response to infection." Septic shock is a "subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality." The patients with septic shock require vasopressors to maintain mean arterial pressure above 65 mmHg and have a lactate level above 2 mmol/L, despite adequate volume resuscitation [1]. The term "severe sepsis" disappeared from definitions.

16.2 Pathophysiology of Septic Shock

Sepsis is an inflammatory process due to the interaction of microbial components and the constituents of the host, resulting in a pro-inflammatory response attributable to the production of interleukin-1 and tumor necrosis factor. In parallel, there is a development of an anti-inflammatory response mediated by several mediators like interleukin-10, associated with an apoptotic process [2]. A close monitoring of the immune status of patients, based on the expression of HLA-DR on the monocytes, should facilitate the determination of the immune status of each patient.

All in one, the cytokine "storm" results in a reduced vascular reactivity to vasoconstrictors and loss of fluid by decreased permeability of the vascular wall. The vasodilation is mediated by the production of nitric oxide, a potent vasodilator. The production of inflammatory mediators reduces cardiac performance. Right and left ventricles are

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dilated and ejection fraction diminishes. Due to the intense vasodilation, resulting in a reduced afterload, the impairment of heart function is a clinically silent injury in most cases. This cardiac impairment is reversible within 7–10 days.

Microcirculation is deeply affected during septic shock, due to local clots, shunts, and tissue edema. As there is a misuse of oxygen, central venous saturation does not adequately reflect the oxygen use, as in hemorrhagic shock or cardiogenic shock. The relation between the level of mean arterial pressure and the microcirculation remains unclear, at least for levels between 65 and 85 mmHg.

16.3 Anesthetic Drugs and Septic Shock

16.3.1 Hypnotics for Induction

General anesthesia of a septic patient is almost exclusively practiced for urgent procedures. Rapid-sequence induction is the gold standard in this setting. Its hemodynamic impact is greater in septic patients. Few hypnotics are commonly used in this indication: hypnomidate, thiopental, propofol, and ketamine.

16.3.1.1 Hypnomidate

Hypnomidate was widely used due to its hemodynamic properties. However, its metabolic effects (blockade of the 11beta-hydroxylase and adrenal insufficiency) with potential harm in the critically ill patient made its use controversial [3]. A meta-analysis including about 1000 patients concluded that its administration for rapid sequence intubation was associated with higher rates of adrenal insufficiency and mortality in patients with sepsis (RR 1.33; 95% CI 1.22–1.46 and RR 1.20; 95% CI 1.02–1.42, respectively) [4]. However, the conclusion of this meta-analysis has been discussed because of the data heterogeneity.

The metabolic effect of this drug was confirmed. Retrospective study of a large electronic intensive care unit (ICU) database [5] in 2013 shows no difference in ICU and hospital mortality, ICU and hospital length of stay, and vasopressor use and duration of mechanical ventilation. However, more patients in the hypnomidate group received steroids before and after intubation (52.9% vs. 44.5%, $p < 0.001$). A multicenter, retrospective, propensity-matched cohort study [6] found that the use of hypnomidate for intubation of septic patients did not increase vasopressor requirements within 72 h after intubation (primary outcome), ICU length of stay, and in-hospital mortality (secondary outcomes). A prospective controlled double blind study [7] found no benefit on ICU length of stay and mortality of a moderate-dose hydrocortisone therapy throughout the period of hypnomidate-related adrenal insufficiency in critically ill patients without septic shock. These findings are consistent with a meta-analysis compelling 5000 patients. This study concluded that hypnomidate administration was associated with an adrenal insufficiency (RR 1.42; 95% CI, 1.22–1.64; p 0.00001) but not with a higher rate of mortality (RR 1.20; 95% CI 0.84–1.72) [8]. However, these findings largely rely on data from observational studies with a potential selection bias.

Current data do not allow to decide for or against hypnomidate for septic shock patients. However, its pharmacodynamic profile is potentially harmful, and other anesthetic drugs with identical or better hemodynamic properties are available.

16.3.1.2 Propofol

Due to its excellent safety features, propofol is the most widely used drug in elective anesthesia. Propofol contains a phenolic hydroxyl group that donates electrons to the free radicals, thus acts as an antioxidant. Many studies highlighted the effects of propofol on the inflammatory pathways. Pretreatment with propofol reduced the mortality rate of rats and attenuated the pro-inflammatory cytokine responses (interleukin-6 and tumor necrosis factor-α) in an endotoxin shock model [9] through an inhibiting induction of high mobility group box 1 protein. In a porcine endotoxemia model [10], propofol reduced enzymatic and nonenzymatic endotoxin-induced lipid peroxidation, improving arterial oxygen tension.

At concentrations used during clinical anesthesia, propofol protects human umbilical vein endothelial cells against arachidonylethanolamine-induced injury, in part by suppressing apoptosis [11]. Propofol also downregulates macrophage nitrous oxide biosynthesis via inhibiting iNOS gene expression [12].

Nevertheless, propofol has significant hemodynamic effects. It suppresses the sympathetic response, decreasing systemic vascular resistance, cardiac contractility, and preload. Hence, it may lead to adverse effects if used in septic patients, in which the sympathetic response is already impaired.

An analysis of anesthesia records of 4096 patients reported predictors of hypotension after anesthetic induction [13]: ASA III–V, baseline mean arterial pressure <70 mmHg, age >50 years, use of propofol for induction, and increasing induction dosage of fentanyl. The authors recommended avoiding propofol induction in patients with baseline mean arterial pressure <70 mmHg. An animal study showed that propofol is the anesthetic drug with the most pronounced direct cardiac effect during sepsis, with a significant decrease in contractility of −38%, a reduction in lusitropy of −44%, and a direct vasodilator effect by increasing coronary flow by +29 [14].

Compared with midazolam, propofol increases preload dependency in septic shock patients [15]. Compared with dexmedetomidine, propofol increases preload dependency in endotoxemic rabbit model with fluid nonresponsiveness and norepinephrine infusion [16]. Despite its anti-inflammatory properties, who are yet to be confirmed by human studies, the hemodynamic effects of propofol make it unsuitable for the anesthesia of patients with septic shock.

16.3.1.3 Thiopental

Thiopental remains the gold standard for rapid-sequence induction thanks to its rapid onset. Nevertheless, its negative hemodynamic [17] and inflammatory properties [18] (elevation of IL-10 from peripheral blood mononuclear cells in the presence of lipopolysaccharide) make it unsuitable for anesthesia of the patient with septic shock.

16.3.1.4 Ketamine

Ketamine seems to be the most valuable choice for the anesthesia of patients with septic shock. Unfortunately, there is a lack of reliable data on its efficiency and safety. Nevertheless, several studies provided data showing that ketamine is the drug of choice in septic shock. The abolition of sympathetic vascular tone is an effect shared by most hypnotics. Hoka et al. [19] showed the preservation of baroreflex control of vascular resistance when using ketamine in rats. The authors wrote that "ketamine may contribute significantly to the maintenance of blood pressure in the subjects with hemorrhagic hypovolemia, since arterial baroreflex is considered to play an important compensatory role in such condition." In vivo, ketamine acts as a sympathomimetic, increasing heart rate, arterial pressure, and cardiac output [17].

The KETASED Collaborative Study Group produced a randomized, controlled, single-blind trial [20], involving 655 patients who needed sedation for emergency intubation. They compared the administration of 0.3 mg/kg of hypnomidate or 2 mg/kg of ketamine for tracheal intubation. The investigators found no difference in the maximum severity score during the first 3 days in the ICU, concluding that ketamine is a safe and valuable alternative to hypnomidate for endotracheal intubation in critically ill patients. Ketamine induces cardiovascular stability over a wide range of concentration in an isolated septic rat heart model, as compared with propofol, hypnomidate, and midazolam [14]. No data is available about the clinical use of ketamine for septic patients, but several studies strongly advocate its use for hemodynamically unstable patients and in emergency settings [21].

Another point of interest is the immunologic effects of ketamine. These effects have been summarized in a review article [22]. In brief, the mechanism is based on a ketamine-involved regulation of pro-inflammatory gene expression. Thus, ketamine suppressed the production of TNF-α, IL-1, and IL-6. Due to its hemodynamic and immunologic properties, and despite the lack of large-scale prospective randomized trials, ketamine seems to be the drug of choice for induction of general anesthesia for patients in septic shock.

16.3.2 Hypnotics for Maintenance

16.3.2.1 Intravenous Anesthetics

Due to its pharmacokinetic properties (short duration of action, hemodynamic stability), midazolam is widely used for the sedation of ICU patients. Propofol may also be used but because of its cumulative toxicity (PRIS syndrome), its use is reserved for limited duration sedation.

Dexmedetomidine, an α-2 agonist, is more and more commonly used in ICU for cooperative sedation. Dexmedetomidine seems to have intrinsic anti-inflammatory properties, suppressing pro-inflammatory mediators. In a murine endotoxemia model, it reduced mortality rate with an inhibitory effect on inflammatory response [23]. In another model, the shift of sedation regimen from propofol to midazolam was associated with an improvement in sublingual microcirculatory perfusion [24].

16.3.2.2 Volatile Anesthetics

In the operating room, volatile anesthetics are a valid choice for maintenance of general anesthesia in the critically ill patients, due to their pharmacologic properties. They are easily titrated to obtain a satisfactory level of sedation with little hemodynamic repercussion. Their short half-life allows a rapid reversal. However, no data from large-scale studies are available to confirm those assertions.

Volatile anesthetics as sevoflurane are used in cardiac surgery in a preconditioning strategy, since this drug decreases ischemia-reperfusion injuries in those patients thanks to its inhibitory action on the inflammatory pathway [25]. Studies have been performed in septic conditions to assess the protective effect of volatile anesthetics. Due to an attenuated inflammatory response, lipid peroxidation, and oxidative stress, sevoflurane, desflurane, and isoflurane significantly improved survival rate in murine models of cecal ligation-puncture-induced sepsis [26]. Those findings are consistent with those in the cardiac surgery preconditioning setting. Even if there is a lack of data regarding hemodynamic safety of volatile anesthetics, the profile of volatile anesthetics seems beneficial.

16.4 Hemodynamics of Patients with Septic Shock

16.4.1 Monitoring

16.4.1.1 Depth of Anesthesia Monitoring of a Patient in Septic Shock

Identifying the best dosage of drugs remains challenging due to the cardiovascular effects of anesthetics, the change in pharmacokinetics due to fluid therapy, and the alterations of pharmacodynamics due to hypermetabolism. In routine, the dosages are lowered to prevent adverse effects although they must be sufficient to maintain an adequate level of sedation and analgesia.

Bispectral index monitoring with a goal between 40 and 60 is efficient to prevent awareness during surgery and to improve sedative drug delivery and postoperative delivery [27]. There is no study evaluating the effect of bispectral index monitoring specifically for septic patient. However, bispectral index monitoring was associated with a decrease of sedative drug doses, recall, and time to wake-up [28]. Furthermore, it could detect inadequate sedation during therapeutic or preoperative paralysis [29].

Guidelines on neuromuscular blockade stress on the train-of-four monitoring to prevent excessive dose infusion leading to prolonged skeletal muscle weakness or remaining blockade leading to respiratory failure after extubation [29]. In septic patients, cisatracurium pharmacokinetics is deeply altered due to both body fluid distribution and organ dysfunction leading to change in volume of distribution, elimination, and effect of neural transmission. These alterations result in a slower response with reduced effect, strengthening the need of paralysis monitoring [30].

16.4.1.2 Hemodynamic Monitoring

Shock is defined as an acute circulatory failure associated with inadequate oxygen utilization by the cells. Circulation remains unable to deliver sufficient oxygen to meet demands of the tissues. Clinical examination and standard monitoring fail to assess fluid responsiveness during circulatory shock. Invasive monitoring of cardiac output is the cornerstone of an efficient hemodynamic optimization. Biomarkers such as blood lactates or central venous oxygen saturation ($ScvO_2$) should be used to detect inadequate tissue perfusion even without hypotension. A close monitoring is mandatory in the septic shock patient in the operating room, since fluid loss due to bleeding, inflammation related to surgical insult, and hemodynamic impairment due to deep anesthesia make her or his management challenging.

Fluid resuscitation is the first intervention for the management of a patient with shock. Preload is an important determinant of cardiac output (such as afterload and contractility). Preload can be optimized with fluid resuscitation to improve cardiac output, but excess of fluid results in adverse effects [31]. Fluid responsiveness can be defined by improvement of 15% of cardiac output after a 500 mL fluid infusion [32]. During shock, clinician should be able to predict fluid responsiveness before fluid administration. Static index such as central venous pressure (CVP) or pulmonary artery occlusion pressure (PAPO) is not reliable enough to guide a fluid resuscitation [33]. Dynamic index is a more reliable criterion than static index. These are based on changes in the relation between heart function and intrathoracic pressure during mechanical ventilation cycles. Pulse pressure variation (PPV) and stroke volume variation (SVV) are classically assessed via an arterial line. In a seminal study, the area under receiver operating characteristic curve was 0.89 (95% CI: 0.86–0.92) for PPV, compared with 0.57 (95% CI: 0.54–0.59) for central venous pressure. The authors defined a gray zone of PPV ranging from 9 to 13% for which fluid responsiveness could not be predicted reliably [34].

The assessment of aortic blood flow variation using a transesophageal Doppler is probably the method with the highest level of evidence. The use of noninvasive inflatable finger cuffs and variation of vena cava (inferior or superior) with echocardiography are other options. This strategy may prevent fluid overload [35]. Dynamic measures have several limitations because they require a sedated, mechanically ventilated patient in sinus rhythm.

Cardiac output monitoring is critical. However, a single value of cardiac output cannot be used to assess the global hemodynamic state. The cardiac output must be integrated with data about tissue perfusion (lactate clearance, $ScvO_2$, and clinical signs of shock). The best level of cardiac output is not a quantitative value but a confrontation between the patient needs and her or his cardiovascular performance. One should always keep in mind that supramaximal cardiac output using inotropic medication leads to complications and increased mortality [36].

Industry proposes several devices to measure cardiac output. All devices based on pulse contour analysis are considered as inaccurate in patients with septic shock. Their use can be discussed in emergent situations to follow the variations rather than absolute values. Similarly, volume clamp system using inflatable cuff wrapped around the finger to generate a real-time pulse contour analysis is not reliable in those patients due to the spontaneous vasoconstriction of finger arteries [37].

In our opinion, thermodilution is the gold standard for hemodynamic assessment. Continuous monitoring of cardiac output is available with new types of pulmonary artery catheter. This device provides information on other hemodynamic variables (CVP, PAPO) and tissue perfusion (SVO_2, oxygen utilization, oxygen delivery). However, this system did not demonstrate a positive effect on the outcome of patients [38].

Thermodilution provides intermittent measurements of cardiac output after infusion of cold bolus through the superior vena cava central line and its detection in the femoral artery by a dedicated catheter. This device measures global end-diastolic volume (volumetric marker of cardiac preload), cardiac function index, and extravascular lung water (quantitative index of pulmonary edema). Those variables are useful to conduct an adequate resuscitation with fluid, vasopressors, and inotropes. Thermodilution is coupled to a pulse contour analysis system. Hence, a real-time calculation of cardiac output is feasible. Potential drift over time makes regular calibration mandatory.

Echocardiography cannot provide continuous hemodynamic data. Performing transthoracic echocardiography in the operating room is challenging due to surgical field. However, it can help physician to characterize the hemodynamic state, to choose the best treatment options, and finally to assess the therapy response. Nevertheless, transesophageal echocardiography (TEE) provides reliable data, as cardiac output, left ventricular ejection fraction (mainly depending of contractility and afterload), left ventricular filing pressure (by analysis of transmitral flow), and preload responsiveness (respiratory variation of VTI or after fluid challenge, superior vena cava variation). All measurements are described in guidelines and require an adequate training [39]. Lung ultrasound also provides interesting variables. For instance, the observation of B-lines may suggest pulmonary edema.

Biological monitoring is critical to assess microcirculation during shock. It helps for shock diagnosis, therapeutic adjustment, and outcome determination. Plasma lactate levels increase in the cases of inadequate oxygen delivery, with 2 mmol/L as a cut-off. This is now part of the definition of septic shock [36]. A decrease in plasma lactate levels (10%/h) is associated with decreased mortality rate. Serial measurements of plasma lactate level are recommended to guide therapy in the critically ill patient [40].

In the septic shock patient, $ScvO_2$ (measured from superior venous cava catheter) provides information on the adequacy of oxygen transport. It reflects hemoglobin, oxygen consumption, arterial oxygen saturation, and cardiac output. A low level of $ScvO_2$ values (<70%) in the context of circulatory failure is a relevant marker for the need of fluid (if fluid responsiveness is found) or positive inotrope (if fluid responsiveness is not found). A supranormal $ScvO_2$ value is associated with impaired outcome in the patient with septic shock [41]. It probably reflects a deep microcirculatory failure. Venoarterial carbon dioxide difference (pCO_2 gap) (measurement of the difference in carbon dioxide between central venous blood and arterial blood) can be used. Values >6 mmHg suggest insufficient blood flow even for $ScvO_2$ values >70% [42].

16.4.1.3 Clinical Management

The management of patients with septic shock should follow the Surviving Sepsis Guidelines [36]. In the operating room, the monitoring of preload should rely on dynamic index rather than on CVP, although the level of evidence is weak. One should keep in mind that it is critical to exclude the source of infection within the 6 h after diagnosis. Then, surgery should be performed even if the patient remains hemodynamically unstable, after a short period of resuscitation.

The management during surgery does not differ from that of a standard patient. The goal of mean arterial pressure ranges from 65 to 85 mmHg. In the normotensive patient, there is no interest to increase mean arterial pressure above the range 65–75 mmHg. In the hypertensive patient, data suggest targeting mean arterial pressure around 85 mmHg may prevent acute renal failure. However, the degree of organ perfusion seems more critical than the level of mean arterial pressure [43].

Fluid is the first intervention required in most situations. Balanced crystalloids are the best choice for these patients [36]. The use of normal saline should be probably avoided to prevent renal dysfunction due to metabolic acidosis, even if a randomized clinical trial did not confirm the beneficial effect of balanced crystalloids [44]. Hydroxyethyl starch should not be used in septic patients, due to their renal effects [45]. The use of albumin can be discussed in the patients requiring vasopressors with low albumin concentration.

Vasopressors are used if the response to fluid is negative and in unstable patients. They can be used early in the patients with severe hypotension or those with diastolic arterial pressure below 45 mmHg. Norepinephrine is the first choice. This agent should be used via a central venous line, but, if required, this drug may be used on a peripheral line (without any concomitant drug) for few minutes. There is no indication for dopamine. Epinephrine should be avoided for preventing arrhythmia. Phenylephrine is widely used for treating hypotension in the surgical theater. This practice can be highly deleterious due to the properties of this drug, and it should be definitively banned in the septic patient [36]. The role of vasopressin and its agonist terlipressin is unclear [46]. To date, there is no data showing a benefit to use these agents instead of norepinephrine. As they have only vasopressive effects, one should avoid using them in the patients without cardiac output monitoring.

Positive inotropes are used in less than 20% of patients, after fluid administration and onset of vasopressor. Their use is based on a level of $ScvO_2$ below 70%, after preload optimization, transfusion if required (Hb >8–9 g/dL), and sedation. The use of cardiac ultrasound may facilitate the diagnosis of myocardial dysfunction. However, one should keep in mind that increasing oxygen delivery to supranormal level was associated with increased mortality in critically ill patients. Thus, in our opinion, the administration of positive inotrope like dobutamine based only on ultrasound imaging can be unsafe. Monitoring of oxygen delivery should be strongly encouraged [36].

16.4.2 Antibiotic

Antibiotics and source control are the cornerstones of the management of the patient with septic shock. The initiation of an antibiotic treatment is considered as emergent, urgent, and delayed. Emergent is defined by the need for starting antibiotics

within 1 h after diagnosis has been made. Many studies report that delays in the initiation of appropriate antibiotic therapy in patients with severe infection are associated with increased mortality [47]. Each hour of delay in antibiotic administration is associated with a decrease in survival. Thus, guidelines recommend prompt introduction of antimicrobial therapy in patients with hemodynamic impairment and suspected infection [36]. In routine, it is suggested to start an empirical antibiotic treatment within the first hour after the diagnosis of septic shock.

Guidelines underline the need to provide antibiotics active against the potential bacteria responsible for the infective episode. Inappropriate initial antimicrobial therapy for septic shock occurs in approximately 20% of patients, resulting in a fivefold reduction of survival [48]. Blood samples for cultures and rapid diagnosis test are systematically required before the onset of treatment. However, the collection of samples during surgery should not delay the administration of antibiotics. In the patients with septic shock, antibiotics are required before the onset of the surgical procedure.

16.4.2.1 Empirical Antimicrobial Treatment

Many patients with septic shock are potential candidates for emergent surgery. Various sources of infections include the abdomen, soft tissue, bone, and others. The use of broad-spectrum antibiotics leads to the emergence of multidrug-resistant pathogens, whose growing prevalence over the last years has become a significant public health threat. The presence of multidrug-resistant bacteria can lead to inadequate antimicrobial therapy, associated with poorer outcomes [49].

Since initial antimicrobial therapy for septic shock patients is empirical, the choice of the drug should be based on the host characteristics, site of infection, severity of infection, and local ecology. The risk factors for multidrug-resistant pathogens are commonly the use of antibiotic within 3 months, a length of stay longer than 5 days, a previous hospitalization (for at least 2 days) within 3 months, and immunosuppression.

With respect to intra-abdominal infection, 60% of spontaneous bacterial peritonitis episodes are produced by Gram-negative enteric bacilli—*Escherichia coli* and *Klebsiella* sp. being the most frequently isolated microorganisms. In approximately 25% of the cases, streptococci (frequently pneumococcus) and enterococci are involved. Secondary peritonitis is polymicrobial including Gram-negative bacteria (*E. coli*, *Enterobacter* sp., and *Klebsiella* spp.), Gram-positive bacteria (enterococci in ~20% of the cases), and anaerobes (*Bacteroides* sp. in ~80% of the cases). For patients with identified risk factors, multidrug-resistant pathogens (including *P. aeruginosa*, *Acinetobacter*, and methicillin-resistant *S. aureus* (MRSA)) and yeasts should be considered [50]. An international multidisciplinary task force called AGORA (Antimicrobials: A Global Alliance for Optimizing their Rational Use in Intra-Abdominal Infections) released a complete and comprehensive review of the management of complicated intra-abdominal infections (cIAI) to actively raise the awareness of the rational and judicious use of antimicrobial medications in the treatment of these infections, in modern health care [51]. Their conclusions are as follows: the choice of empiric antibiotics in patients with community-acquired intra-abdominal infection should be based on the severity of the infection, the individual risk for infection by resistant pathogens, and the local resistance epidemiology. Amoxicillin/clavulanate or

cephalosporins in combination with metronidazole are still good options for the treatment of non-severe IAIs, with piperacillin/tazobactam being a better choice if *P. aeruginosa* coverage is needed. The use of carbapenems should be limited to preserve the activity of this class of antibiotics because of the concern of emerging carbapenem resistance. Ciprofloxacin and levofloxacin are no longer appropriate first-line choices for empiric treatment in many regions because of the prevalence of fluoroquinolone resistance. Other options include aminoglycosides, particularly for suspected infections by Gram-negative bacteria, and tigecycline especially when multidrug-resistant pathogens are suspected. In most case, the addition of aminoglycosides to the pivotal beta-lactam makes it possible to have an efficient coverage of enterobacteriaceae producing extended spectrum beta-lactamases, which is a real challenge in those patients. For the management of multidrug-resistant Gram-negative infections, especially in critically ill patients, the use of "old" antibiotics, such as polymyxins and fosfomycin, should be first considered. Ceftolozane/tazobactam and ceftazidime/avibactam are new antibiotics that have been approved for treatment of intra-abdominal infections (in combination with metronidazole) including infection by enterobacteriaceae producing extended spectrum beta-lactamases and *P. aeruginosa*. As isolation of *Candida* species is an independent risk factor of mortality, the addition of an antifungal, echinocandins in those patients, is suggested for patients with documented or suspected fungal infection [52]. Controversies are still unresolved concerning the right selection of patient who may benefit from antifungal therapy. Two clinical scores are currently used: the *Candida* score (score ≥2.5: Se 81%, Sp 74%) and the peritonitis score (score ≥3: Se 84%, Sp 50). Recent guidelines recommend the discontinuation of those drugs if clinical samples are negatives for fungal infection [53].

Skin infections are frequently polymicrobial. Suspected bacteria should be *Streptococcus* sp. (40%), *S. aureus* (30%), anaerobes (30%), and Gram-negative bacteria (10–20%). The Infectious Diseases Society of America published guidelines about those infections [54]. In septic shock, an emergent surgical inspection and debridement are mandatory, in addition to an empirical antimicrobial therapy. It should include agents effective against both aerobes (including meticillin-resistant *S. aureus* according to local ecology and individual risk factors) and anaerobes. Piperacillin/tazobactam seems the best first option in many cases.

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