

## Literature Review

# Updates in management of abdominal sepsis

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## Abstract

Sepsis is an organ dysfunction caused by a disproportionate host response to infection. The condition is responsible for 1 in every 3 admissions to an intensive care unit (ICU) and about 6 million deaths worldwide. As a result of the imbalance in the inflammatory response, immune dysfunction, mitochondrial damage and other pathophysiological processes, sepsis progresses extremely. This research aimed to search the literature for updates inherent to the therapeutic approach of patients with diseases secondary to intra-abdominal sepsis. The present work is a narrative review with a bibliographical survey carried out in the PUBMED and Virtual Health Library (VHL) research bases, through the search strategy using the following descriptors, in both virtual libraries: "sepsis OR surviving sepsis" AND "intra abdominal infection" AND "therapeutic". At the end of reading the articles in full, ten papers were selected, from which it was observed that new recommendations regarding volume operative source control, and use of additional therapies therapy. The open abdomen technique is being further explored, as well as more in-depth studies on new drugs for this condition, such as acetylcholinesterase inhibitors, and the use of glucocorticoids became contraindicated, due to low scientific evidence. Therefore, it is concluded that, as it is a medical emergency with high mortality, it is relevant to develop scientific research aimed at the effectiveness, feasibility and safety of new forms of management.

## Introduction

Sepsis is characterized as an organic deregulation capable of leading the patient to death and has as a causal factor a deregulated host response to infection. Septic shock is a subset of sepsis where circulatory, cellular and metabolic abnormalities are responsible for increased mortality. Treatment should be started as soon as possible, which is a crucial factor for a good prognosis [1-3].

Worldwide, sepsis is estimated to affect more than 30 million people each year, potentially leading to 6 million deaths. Being responsible for the admissions of 1 in 3 patients to the intensive care unit [4-6]. In the Latin American scenario, the mortality rate due to sepsis, in Brazilian private and public hospitals, ranges from 30% to 70%, respectively [7].

In general, erythrocytes attract and maintain bacteria by

an electrical charge on their surface. Such friction stimulates the immediate release of oxygen from the oxyhemoglobin to the surface and finally, the released oxygen oxidizes and kills the bacteria. This is the common mechanism of host innate immunity for bacteria to be killed when they reach the bloodstream, however, some species have developed numerous virulence factors that corroborate their survival to oxidation [8-10].

Among these, the main ones are the formation of Capsular Polysaccharides (CPS), loss of the cell wall (L-shapes) and the production of biofilms, which represent a highly resistant defense against antibiotic treatment. Thus, the main bacteria that cause sepsis have some of these mechanisms, they are: *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Neisseria meningitidis*, *Klebsiella pneumoniae*, *Escherichia coli*, group B streptococci [11-13].

In cases of sepsis due to complicated Intra-Abdominal Infections (IAIc), the etiology is typically polymicrobial. Among gram-negative pathogens, enterobacteria are the most prevalent. In relation to gram-positives, *enterococci* represent approximately half of the isolates [8].

Because of this complexity, the clinical presentation of sepsis is diverse, given that patients with IAIc usually present with rapid onset abdominal pain and signs of local and systemic inflammation (pain, tenderness, fever, increased white blood cell count, tachycardia and /or tachypnea). Hypotension and signs of hypoperfusion such as oliguria, acute altered mental status and lactic acidosis are indicative of ongoing organ failure [14].

In this scenario, factors related to mortality include time to start antibiotic therapy, infection control, and fluid infusion, in addition to factors intrinsic to patients, such as age and comorbidities [6,15].

The therapeutic approach to bacterial infections in hospital environments is one of the greatest challenges for health professionals, due to the increasing prevalence of multidrug-resistant bacteria. Microorganisms that are resistant to antibiotic therapy increase morbidity, mortality, length of hospital stay and medical costs. Delays in initiation of appropriate antimicrobial therapy tend to increase morbidity and mortality among infected patients, as well as extend hospitalization time [15-18].

In this sense, despite advances in diagnosis, surgery and antimicrobial therapy, the rates of mortality and progression to septic shock associated with complicated intra-abdominal sepsis have remained extremely high [19]. Thus, the objective of the present study is to search the literature for updates inherent to the therapeutic approach of patients with diseases secondary to sepsis with an intra-abdominal focus, characterizing the study as a narrative review on the aforementioned theme.

## Materials and methods

### Research characterization

The present study is a narrative review of the literature, qualitative and descriptive-exploratory type. This review sought to gather and analyze scientific publications about updates in the treatment of intra-abdominal sepsis.

### Conducting the Investigation

The keywords defined for the bibliographic research in question were chosen based on the Health Sciences Descriptors (DeCS), which are "sepsis", "intra-abdominal infection" and "therapeutic". To achieve the desired results, the descriptors were organized according to Boolean logic, using the AND and OR connectors. The organization of descriptors was as follows: "sepsis" OR "surviving sepsis" AND "intra abdominal infection" AND "therapeutic". The databases consulted were PUBMED/MEDLINE and the Virtual Health Library (VHL).

Searches were carried out by two researchers using the same search strategies in the following databases: PUBMED/MEDLINE and the Virtual Health Library (VHL). Based on inclusion and exclusion criteria, described below, the articles resulting from the search were selected in order to prioritize those that were more relevant to the theme of the present study. In this way, the researchers evaluated all the resulting articles from the title, abstract and even reading in full, to better qualify the choice of including or not in the study.

### Selection criteria

During the search process in the bibliographic base, the following inclusion criteria were applied: direct relationship with the central theme of the research (treatment of sepsis with an abdominal focus); and scientific articles with full text available published in the last 5 years (2018-2023) in the languages: Portuguese, English and Spanish. Those that were duplicated and not available in their free full version, which addressed fungal sepsis and reviews articles, with the exception of guidelines and international guidelines, were discarded.

### Presentation of findings and synthesis of information

From this, the results and discussions available on the subject that met the objective of the proposed work were compiled, as well as the main updates on the management of intra-abdominal sepsis. It is reiterated that, according to the methodology adopted, submission to the research ethics committee was not necessary.

## Results and discussions

In all, 3308 articles were listed in the PUBMED/MEDLINE and VHL database results after applying the descriptors without any filter. Then, the filter of publications in the last 5 years was first applied, then the language filter (English, Portuguese, and Spanish) and finally, the full-text filter was available free of charge, obtaining 300 articles for analysis. After reading the titles and abstracts and some articles in full - due to the researchers' doubts as to whether they should be included in the study -, 10 publications were eligible to be used in the composition of this review, with a more accurate reading and analysis.

A Surviving Sepsis Campaign (CSS) 2021 was one of the works selected, as it deals with international guidelines on the management of sepsis and septic shock. It is worth mentioning that some studies that do not deal exclusively with sepsis with an abdominal focus were included, as they are randomized clinical studies, with high scientific relevance [20].

In view of this, it was reiterated that the principles for the treatment of sepsis are adequate resuscitation, early administration of medications, control of the operative source and frequent reassessments, considering that sepsis is a medical emergency [21,22].

However, the absence of a specific test, the various tools and biomarkers used, and the initial care of sepsis in pre-

hospital situations are clearly critical, the diagnosis and, consequently, the treatment are impaired. No sepsis scoring system behaves perfectly, and all seem to be largely dominated by organ dysfunction [19,23].

The Sequential Sepsis-related Organ Failure Assessment (SOFA) score and the Sepsis Severity Score (WSES) were better predictors of poor outcomes, while the SOFA score appeared to be the best tool to identify patients at high risk of death and organ dysfunction induced by sepsis [19]. In another study, the WSES was very accurate in predicting mortality among our patients, allowing its generalization to all patient populations worldwide [23].

Furthermore, in intensive care units, the most common limitation is identifying patients with sepsis, especially in the elderly and immunocompromised, due to concomitant medical and surgical conditions that confuse the diagnosis. Another factor that compromises the treatment is the choice of the ideal moment for the administration of antibiotics [24].

A recent study evaluated 4792 patients receiving antimicrobial treatment in German hospitals, in which the primary outcome was 28-day mortality. There were no significant differences comparing treatment within 1h versus 1-3h, or 1h versus 3-6h. Delays greater than 6h significantly increased mortality. In addition, delay in antimicrobials also increased the risk of progression from severe sepsis to septic shock [25].

Furthermore, culture studies have failed to prove any source of infection in a large number of patients suspected of having sepsis. Approximately 30% - 89% of patients with sepsis have negative culture results. This fact is due to previous treatment with antibiotics, insufficient blood sampling, transport problems, and insufficient technique [26-29].

### Volume resuscitation

Initial resuscitation should be done with at least 30 ml/kg of intravenous crystalloid fluid in the first 3 hours. If it is necessary to maintain resuscitation, the criteria used to guide the introduction of fluids are the hemodynamic evaluation, the decrease in serum lactate, in cases where it is increased and, when not available, using the capillary refill time [20].

The ANDROMEDA-SHOCK study evaluated whether peripheral perfusion normalization-guided resuscitation (PPTR) was more effective than lactate-directed resuscitation (CRT), aiming to normalize lactate or decrease it at a rate of more than 20% per 2 hours during the 8-hour study period. At the end of the study period, 34.4% of patients in the PPTR group and 43.4% in the lactate group had died. However, this difference was not statistically significant (HR: 0,75; 95% CI, 0,55 to 1,02) [30].

Ultrasound measurement of the Inferior Vena Cava (IVC) diameter is a technique used to adapt fluid therapy in patients with shock and is widely used to help physicians predict responsiveness to fluid in patients with shock [31].

When comparing the 30-day mortality of patients with sepsis: a group treated with usual therapy and another by ultrasound-guided resuscitation of the IVC diameter, it was seen that there were no differences in survival between the two groups, only a lower amount of fluid used during the process in patients who used IVC diameter ultrasonography. However, the study addressed cases of sepsis induced by tissue hypoperfusion and septic shock [31].

### Antibiotic therapy

Early administration of antibiotics is one of the most effective interventions to reduce mortality in patients with sepsis. The recommendation is that: for patients with septic shock, antimicrobials should be administered immediately, ideally within 1 hour of recognition; in the presence of suspected sepsis and absence of shock, antimicrobials should be administered within 3 hours if concern about infection persists [20,32].

In addition, the empirical use of broad-spectrum antibiotics and the combination of two antimicrobials for gram-negative coverage in patients at high risk for Multidrug-Resistant Organisms (MDR) is recommended.

To combat MDR organisms in cases of IAIC and complicated soft tissue infections, a new antibiotic is being analyzed: tigecycline. A cohort study evaluated the best dosage of the drug, from 68 patients with different body weights. It was observed that patients who received high doses (100 mg every 12 hours) had a lower mortality rate compared to patients who received normal doses. However, the study was unable to eliminate some confounding factors, such as the fact that monotherapy with tigecycline was only possible in a few patients [33].

Regarding the duration of antibiotic therapy after surgical control, the DURAPOP study included 21 French hospitals and ICU patients with intra-abdominal infection, in whom focus control had been achieved and who had received adequate antibiotic coverage. A total of 249 patients were randomized to either short-term (8 days) or long-term (15 days) regimens, with no differences in mortality or need for surgical reintervention between the two arms, so that short-term regimens were considered more effective [34,35].

### Operative source control

Source control can be achieved by surgical (laparotomy or laparoscopy) or non-surgical (percutaneous drainage) means. The primary goals of these interventions are to identify the source of peritonitis, drain fluid collections and control the cause of abdominal sepsis [36].

It is currently rare to perform urgent surgery for intra-abdominal abscess alone. Data showed that the number of percutaneous drainage for abdominal abscesses has doubled in the last ten years [37]. Surgery still remains essential for abscesses that cannot be accessed radiologically and infections associated with a source that requires excision [37].

The recent novelty lies in the potential benefits and complications of open abdomen (OA) therapy. Indications

for OA therapy would include severe IAI or abdominal sepsis, intra-abdominal hypertension or abdominal compartment syndrome, dehiscence and ongoing intra-abdominal bleeding. The goal of OA in patients with IAI is to achieve early source control [37].

Regarding open abdomen surgery, fifty acute patients in the context of damage control surgery for sepsis for abdominal disease, non-traumatized, were treated with the open abdomen technique and temporary abdominal closure by active negative partial pressure therapy (NPWT). Of these, two-thirds survived, despite the high morbidity, with a high rate of overall complications (58.8%). It has been demonstrated that the OA and DDC technique are valuable tools, but that they demand multiple reoperations and long ICU stays [38].

When assessing outcomes after DDS in patients with perforated colonic diverticulitis secondary to Hinchey III Acute Diverticulitis (ACD), it was found that the most common method of Temporary Abdominal Closure (TAC) was NPWT therapy and that a mean of 35 % of patients developed septic shock [39,40].

In the case of patients who suffered penetrating trauma and underwent laparotomy, the main factors related to the development of abdominal sepsis and abdominal infections were precisely the need for surgery to monitor damage or management with an open abdomen, as well as the prolonged hospitalization time [41].

A retrospective study analyzed 111 patients affected by abdominal sepsis and treated with an open abdomen over nine years. It has been reported that early source control of patients with severe IAI using an open abdomen could significantly improve outcome [42].

In a study conducted in a tertiary hospital in Somalia, source control was achieved by laparotomy in 81%, while the 19% were managed in a percutaneous approach. In a country with few resources, percutaneous drainage is considered more appropriate, as it provides a shorter hospital stay and procedure and can be performed at the bedside for patients admitted to the ICU without the risk of anesthesia, leading to lower morbidity [43].

### Acetylcholinesterase inhibitors

The parasympathetic autonomic nervous system has been the focus of studies for the treatment of sepsis due to the Cholinergic Anti-Inflammatory Pathway (CAP). The mechanism is based on an inflammatory reflex of the vagus nerve, by which the parasympathetic nervous system can suppress systemic inflammation and thus protect against cytokine-mediated diseases [44].

From this, neostigmine, when used as adjuvant therapy in patients with sepsis compared to placebo, showed better results with regard to significant improvements in the change of SOFA score (Sequential Organ Failure Assessment) in 5 days of treatment. Furthermore, regarding secondary outcomes, mortality, and survival did not present significant differences

and the length of stay in the ICU was reduced in patients who used neostigmine [44].

Another drug, physostigmine, also showed promise when randomized to 20 patients with perioperative septic shock due to intra-abdominal infection. The primary result was based on mean SOFA scores during treatment and up to 14 days, noting that physostigmine salicylate was well tolerated, presenting itself as a viable and safe option, although it needs further studies [45].

### Glucocorticoids

Despite having an unknown role in sepsis, recent work has suggested that low-dose glucocorticoids do not reduce mortality, but are associated with a shorter duration of artificial organ support in the treatment of sepsis. Currently, intravenous hydrocortisone is no longer recommended to treat adult patients with septic shock [9,46,47].

Treatment with hydrocortisone, evaluated in a prospective observational study, demonstrated a potential anti-inflammatory, hemodynamic reversal, and stability effect when compared to the non-hydrocortisone group [48]. However, among mechanically ventilated patients with septic shock, a continuous infusion of hydrocortisone did not result in lower 90-day mortality than a placebo [49].

When associated with vitamin C and thiamine, in the VICTAS study, the hypothesis was tested that the association of these substances would improve the clinical outcome in patients with respiratory and/or circulatory failure induced by sepsis. It was found that there was no significant improvement for these individuals [50].

A similar analysis was performed in the VITAMINS trial, where the combination of drugs was compared with the use of hydrocortisone alone, which did not show more efficacy in reducing the time alive and free of vasopressors over 7 days [51].

### Conclusion

The present study demonstrated that there were updates on the management of sepsis, mainly in relation to volume resuscitation, the use of new antibiotics for antibiotic therapy, the exploration of new surgical techniques and the use of acetylcholinesterase inhibitors. However, that research found as limiting factors in its execution, the lack of protocol standards that guarantee a fast and correct diagnosis, especially when it comes to immunosuppressed and elderly patients. Thus, as this is a condition with high mortality, research into the efficacy, feasibility and safety of new forms of treatment should be encouraged.

Therefore, this study will be useful for future research that seeks updated information on the main surgical and therapeutic approaches for the management of patients affected by sepsis with an abdominal focus, as it brings well-established techniques and protocols in the current literature.



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