Archives of Medical Research 52 (2021) 808–816

REVIEW ARTICLE

Sepsis in Trauma: A Deadly Complication

Fernanda Mas-Celis,[a] Jimena Olea-López,[a] and Javier Alberto Parroquin-Maldonado[b]

[a] *Departamento de Ortopedia y Traumatología, Hospital Angeles del Pedregal, Ciudad de México, México*
[b] *Departamento de Ortopedia y Traumatología, Hospital Angeles Lomas, Estado de México, México*

Received for publication July 12, 2021; accepted October 15, 2021 (ARCMED-D-21-00853).

Sepsis is a major cause of death following a traumatic injury. As a life-threatening medical emergency, it is defined as the body's extreme response to an infection. Without timely treatment, sepsis can rapidly lead to tissue damage, and organ failure The capacity to limit tissue damage through metabolic adaptation and repair processes is associated with an excessive immune response of the host. It is important to make an early prediction of sepsis, based on the quick Sepsis associated Organ Failure Assessment Score (qSOFA), so an accurate treatment can be initiated reducing the morbidity and mortality at the emergency and UCI services. Many factors increase the rate of complications and the development of sepsis in a trauma patient, representing a challenge to orthopedic surgeons. Several early biomarkers that help to identify and predict the inflammatory and immune responses of the host going through polytrauma and sepsis have been studied; procalcitonin (PCT), C-reactive protein (CRP), glycosylated hemoglobin (HbA1c), the Neutrophil/lymphocyte ratio (NLR), Interleukin-17 (IL-17), Caspase-1, Vanin-1, High-density lipoproteins (HDL), and the Thrombin-activable fibrinolysis inhibitor (TAFI). Once sepsis is diagnosed, treatment must be immediately initiated with an appropriate empiric antimicrobial, an all-purpose supporting treatment, and metabolic control, followed by the specific antibiotic therapy based on blood culture. Since the participation of sepsis in polytrauma has been recognized as a key event in the outcome of patients at the ICU, the ability of the specialist to early recognize a septic process has become a key feature to reduce mortality and improve clinical prognosis.

Key Words: Sepsis, Polytrauma, Orthopedics, Trauma surgery, Early prediction.

Introduction

Trauma and sepsis are important medical problems of the 21st century that demand renewed attention. Sepsis develops occasionally in trauma patients where 10% of trauma deaths are due to sepsis. According to the United States Centers for Disease Control and Prevention (CDC), trauma is the leading cause of death among people under the age of 45, where sepsis is a major cause of these deaths following traumatic injuries and infection, with an estimated annual incidence of over 750,000 hospitalized patients showing a mortality rate close to 30% (1,2).

Sixty percent of trauma patients die before reaching the hospital, while 60% of mortality occurs within the first few hours after hospital admission. Injury-related causes of death account for 10% of infectious diseases, accounting for 54% mortality after 48 h, and 76% after 7 d of admission. Traumatic infections are usually associated with dysfunction of several organs and usually appear early within the first 4 d. While a group of trauma patients suffers from systemic inflammatory response syndrome (SIRS), another group of patients might present the opposite compensatory anti-inflammatory response syndrome (CARS), showing a markedly reduced inflammatory response (3).

Address reprint requests to: Fernanda Mas-Celis, Camino Sta. Teresa 1055-S, Consultorio 645. Héroes de Padierna, La Magdalena Contreras, 10700, Ciudad de México, México; Phone: (+52) (55) 5135-0167; Mobile: (+52) (55) 14734579; E-mail: dra.fernanda.mas@gmail.com

https://doi.org/10.1016/j.arcmed.2021.10.007

The risk of infection in trauma patients is the destruction of mechanical barriers, exogenous bacterial contamination, local wound factors, and invasive diagnostic and therapeutic interventions. Also, risk factors associated with infection include the host defense state that might be associated with a severe weakening of the patient's immunity, impairing both humoral and cell-mediated responses (4). The opportunistic infections in trauma are carried out by any microorganism (bacteria, fungus, or virus) that presents the capacity to multiply, despite the activation of the hostś initial defense mechanisms followed by rapid inflammatory response and immunosuppression. Examples of these microorganisms associated with trauma are Clostridium difficile, Candida albicans, and Cytomegalovirus (CVM) (4).

On the other hand, orthopedic device-associated infections and sepsis continue to be a diagnostic challenge and a therapeutic test (4). These types of infections occur because of intraoperative or post-surgical contamination that might involve the identification of the microorganism associated with an orthopedic device, based on the culture of synovial fluid and samples obtained from the periimplant tissue (4). The treatment of choice depends on the clinical type of infection, and the potential involvement of bone and/or soft tissue (5). Direct contamination that occurs during the perioperative period might be associated with primary bacteremia or an infection from a site distant from the surgery known as secondary bacteremia. The specific microbiology of an orthopedic device affects the severity form of onset to the prognosis of infection. Most infections are associated with Gram-positive microorganisms that are part of the normal biota of the skin, including Staphylococcus epidermidis and Staphylococcus aureus. Nevertheless, other microorganisms like Enterococcus and Gram-negative bacteria, including Pseudomonas aeruginosa, Enterobacter cloacae, and Klebsiella spp., are also frequently isolated in orthopedic infections (5).

The presence of biofilms also plays a significant role in the pathogenesis of orthopedic infections. Once the microorganism makes contact and adheres to the device or bone, it can develop a biofilm (6). A biofilm can be defined as a layer-like aggregation of cells and cellular products attached to a solid surface or substratum. Bacterial growth and division then lead to the colonization of the surrounding area and the formation of the biofilm (7). Although macroscopically an idealized biofilm corresponds to a thin homogeneous layer, microscopically it is a nonuniform structure characterized by variable thickness and densities. This dense extracellular matrix protects the bacteria from antibiotics and host defense mechanisms, such as phagocytosis by leukocytes (7,8). The goal for prevention and treatment aimed to eradicate the infection in orthopedia is supported using orthopedic fixation devices and implants that present bactericidal activity against slow-growing and biofilm-producing microorganisms (9). Moreover, early identification and supplemental monitoring of patients with an increased propensity for sepsis may aid the specialist in maintaining lower overall complication rates, thereby improving the clinical outcome in high-risk groups (2,10).

Therefore, since the participation of sepsis has been recognized as a key event in the outcome of ICU patients who had suffered polytrauma, or had gone through orthopedic surgery, the main objective of this review is to put into perspective the importance of the specialist's ability to early recognize a septic process to improve clinical prognosis and reduce mortality.

Defining Sepsis and Polytrauma

For many years, sepsis has been defined as a sort of blood poisoning, so the treatment (theoretically), implies a blood de-poisoning. For many years, sepsis has been defined as suspected or proven infection, associated to the criteria of the systemic inflammatory response syndrome (SIRS). However, during the last decade, clinical characteristics that serve to define sepsis changed due to an improved understanding of the underlying pathobiology. This situation remarks the importance of having accurate and specific definitions for complex concepts, such as sepsis and septic shock (11,12).

In 2016 a new definition was proposed by the European Society of Intensive Care Medicine and the Society of Critical Care Medicine: Sepsis-3 as a life-threatening organ dysfunction that is caused by a dysregulated host response to infection (11,12). Based on the observation that sepsis cannot be explained only by an increased SIRS; rather, the course of the disease is determined significantly by the body's capacity to limit tissue damage through metabolic adaptation and repair processes. This new definition represents a paradigm shift, from the excessive inflammatory response to the failure of adaptation mechanisms, with resulting tissue damage and multiple organ dysfunction, introducing the quick Sepsis associated Organ Failure Assessment Score (qSOFA). Ever since, this score has been used as a screening tool to facilitate rapid diagnosis of sepsis in emergency departments, allowing the initiation of further diagnostic and therapeutic steps (Table 1) (11,12).

Pape H-C, et al. proposed a definition of polytrauma based on several consensus meetings and a database analysis as: the injuries of three or more points in two or more different anatomic regions in conjunction with one or more additional variables from five physiologic parameters: hypotension (systolic blood pressure $\leq$90 mm Hg); level of consciousness (Glasgow Coma Scale [GCS] score $\leq$8); acidosis (base excess ≤ -6.0); coagulopathy (international normalized ratio $\geq$1.4/partial thromboplastin time $\geq$40 s); and age ($\geq$70 years) (Figure 1) (13).

Lakomkin N, et al. in 2017 made the first study to assess the incidence of postoperative septicemia for a large cohort of orthopedic trauma patients and demonstrated the

Table 1. SIRS: Systemic Inflammatory Response Score; qSOFA: Quick Sepsis associated Organ Failure Assessment Score.

SIRS criteria (two or more)	qSOFA citeria (two or more)
<36°C Temperature >38°C	Systolic blood pressure <100 mmHg
Respiratory rate >22/min	Resiratory rate >20/min
Heart rate >90 bpm	Glasgow Coma Scale ≤14
<4000 White cell count >12,000	

*The presence of two or more of these criteria indicates increased risk of poor outcome.

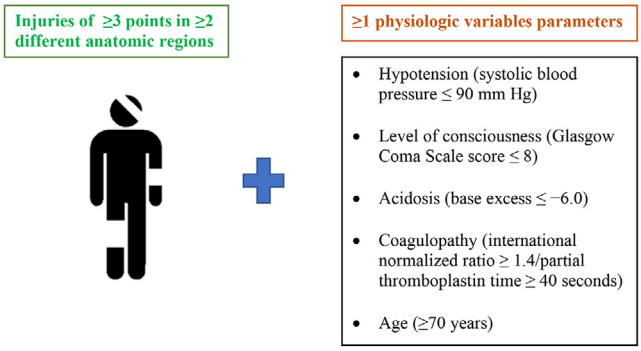

Figure 1. Pape's definition proposal of polytrauma.

frequency of postoperative sepsis at significantly greater rates than those undergoing non-traumatic events (10).

Over the past four decades, there has been a significant increase in the incidence of sepsis mainly attributed to the aging population, whereas traumatic injuries are the major cause of death in the productive age group. Polytrauma patients often have severe soft tissue injuries as well as other conditions that make infection and wound healing a major problem (14,15). Despite modern treatment protocols, sepsis-related mortality remains highly associated with delays inadequate treatment (1,16).

Although trauma-associated deaths typically occur within 48 h of a traumatic event, the occurrence of sepsis is a major concern in trauma patients who have survived initial resuscitation. A retrospective study analyzed by Chung S, et al. with a total of 422 patients, demonstrated that sepsis occurred in 11.8% ($n = 50$) of the study patients. The sepsis group presented higher mortality rates (28.0%), and a longer intensive care unit stay (23 d) than the non-sepsis group. Male patients with high ISS and a high lactate level, that presented the need for a RBC transfusion, were also associated with sepsis. Nevertheless, unlike other associated factors, a transfusion was considered a modifiable risk factor (17). Moreover, since many factors increase an uncontrolled response, such as tissue damage by the trauma itself, the presence of immune defenses to eliminate affected tissues, activation of metabolic responses to trauma, and the presence of SIRS, it is paramount for the patient to recover balanced homeostasis in their adaptive physiological responses, to achieve full recovery (11).

The Physiopathology Behind Sepsis in Polytrauma

An accident or a violent event causes inflammatory and immunological reactions proportional to the severity of the trauma. Called the first hit, this event is characterized by the local and systemic proliferation of various pro-inflammatory mediators. Further inflammation and an immunological reaction, called the second hit, potentiates the effect of the first one. This second hit can be caused, for instance, by a prolonged surgery associated with profuse bleeding. If contamination by bacteria, viruses, or fungi is present, the case is aggravated with the onset of infection and sepsis. Although for years it was believed that the pathogen invasion itself was the only event responsible for the clinical signs of sepsis, nowadays it is recognized that it is also associated with an uncontrolled and excessive host immune response that leads to an inflammatory imbalance, and eventually a lethal outcome (11,12,18).

The most important factors in sepsis originate from de insufficiency of non-adaptive hosts factors as well as hosts defense mechanisms which include anatomic barriers, cellular immunity, and specific and nonspecific humoral defenses (11,18). This immune-metabolic disturbance strongly influences the patient's clinical outcome (1). The perturbations in several metabolic pathways associated with a hypoxic response of the host, and the exacerbated immune system activation, are considered hallmarks of trauma associated with sepsis at the molecular level (1). These factors have helped to understand the molecular events of this association while providing important information in terms of diagnosis, and follow-up treatment of patients (18).

Innate Immunity

Pattern-recognition receptors (PRR) have been recognized as key components of the innate immune system that get activated after recognition of hazard signals, such as the presence of invading bacteria in the bloodstream. These PRR's recognize conserved motifs expressed by bacteria, named pathogen-associated molecular patterns (PAMPS), and damage-associated molecular patterns (DAMPS). An important example of these motifs is lipopolysaccharides (LPS), present in the outer membrane of Gram-negative bacteria. Other motifs, for instance, are constituted by lipoteichoic acid (a cell wall component of Gram-positive

bacteria), peptidoglycans, and bacterial DNA. PRRs can also recognize molecules considered endogenous stress signals, such as the ones associated with the presence of trauma, tissue necrosis, or burns (18).

Coagulation Abnormalities

The function of coagulation in infection is to surround microorganisms and keep the inflammatory response local with cytokines that stimulate thrombin formation. However, its excessive activation leads to negative effects such as fibrin thrombi occurring in the microvascular bed that eventually contributes to organ failure. During the inflammatory response of a septic patient, coagulation proteins are consumed leading to bleeding, and at the same time thrombus formation (18).

Anti-inflammatory Mechanisms and Immunosuppression

During sepsis, the innate immune system activated by PAMPS and DAMPS, releases a series of pro-inflammatory cytokines, a phenomenon recognized as the "cytokine storm," which maintains a severe inflammatory condition. Mediated by PAMPS and DAMPS developed by bacteria, the initial immune recognition response is carried out by PPR's of innate immune cells. The activation of PPR's produces a series of pro-inflammatory cytokines, such as interferon-γ (IFN-γ), interleukin-6 (IL-6), and tumor necrosis factor (TNF). Nevertheless, new data coming from genomic analyses, proposes that during the activation of PPR's, a simultaneous anti-inflammatory state may be also present, defined as CARS (compensatory anti-inflammatory response syndrome). Since the most important effect of trauma on immune function is inhibitory, immunosuppression promotes infection and sepsis (18).

Organ Dysfunction

During the last phase of sepsis leading to septic shock, multiple organ failure (MOF) occurs. The death risk increases by 15–20% for each organ failure; with four or more organ failures the death rate increases above 90%. Although organ failure pathogenesis is still under intense study, the main factors associated with its appearance are microvascular occlusion caused by fibrin accumulation, platelet-activating factor, disruption of the microvascular homeostasis by vasoactive substances (histamine and prostanoids), and disruption of tissue oxygen transport. Finally, an excess in nitric oxide (NO) promotes vascular instability and myocardial depression, leading to death (18).

Prediction of Sepsis in Trauma Patients

The ability to identify the onset of sepsis has been recognized as a critical point to improve the outcome of patients. The possibility to recognize on an early stage the source of infection and the ability to initiate antibiotic treatment, with no doubt is considered crucial steps to reduce septic shock and mortality in trauma patients (19). Although important advances in the early diagnosis of sepsis have been nowadays achieved, a uniform criterion is still a matter of debate. Therefore, multiple efforts including the identification of novel biomarkers for this syndrome, have been made to establish the criteria for early diagnosis based on scientific evidence.

The description of an ideal biomarker able to recognize early septic complications in trauma patients is still a challenge for researchers. Scientific evidence has been sought to identify effective and early biomarkers to predict which patients are at high risk of morbidity and mortality. A biomarker can be considered ideal when it has high sensitivity, high specificity and presents clinical relevance. Less-specific or less-sensible tests can introduce false-positive or false-negative results and further complicate an already intricate clinical picture. This is important since trauma patients going through a state of hyper-inflammation frequently camouflage a septic event causing a delayed initiation of the correct treatment (20,21).

Several biomarkers have been identified to be involved in the acute phase of the systemic inflammation cascade caused by trauma and directly related to the severity of the injury (22), examples are: Interleukin-17 (IL-17), Caspase-1, Vanin-1, High-density lipoproteins (HDL), Procalcitonin (PCT), C-Reactive Protein (CRP), Thrombin-activatable fibrinolysis inhibitor (TAFI), Glycosylated hemoglobin (HbA1c) (23), and the Neutrophil/lymphocyte (NLR) ratio (24). It is important to mention that, in general, these inflammatory mediators can be maintained in the plasma of patients even though the infection has been already eradicated (22).

Biomarkers

Interleukin 17 (IL-17)

IL-17 is a glycoprotein that releases pro-inflammatory cytokines and makes synergism with IL-1, IL-6, and TNF-α. Together they activate tissue infiltrating neutrophils and function as a defense mechanism against bacteria and fungi (15).

Following a six-month study made by Ahmed A-M, et al. studying 100 ICU patients, they observed in septic plasma samples after 3 h of admission, a significant increment of IL-17 in comparison with samples of the non-septic patients. The levels of IL-17 were found to be almost 2 fold in those patients with a greater risk of sepsis, and higher in patients who died within 28 d after ICU admission (15).

Caspase-1

Caspase-1 dependent pyroptosis of peripheral blood mononuclear cells (PBMCs), is considered a type of programmed cell death that contributes to the development of sepsis and posterior septic shock. Pyroptosis is mediated by different caspases (caspase-1, -11, -12, -20) and induces an extensive inflammatory response in the host playing an important role in lethality during the cytokine storm (25).

In a prospective study of 60 trauma patients, Wang Y-C, et al. compared blood samples of two groups. While the control group had major trauma and samples obtained in less than 24 h, for the second group blood samples were taken 24 h after the sepsis diagnosis was made. They found significant correlations: patients who develop sepsis had a higher level of pyroptotic PBMCs within 24 h of the injury. So far, PBMCs pyroptosis is considered an important biomarker indicator associated with the development of sepsis (25).

Vanin-1

Vanin-1 (Vascular non-inflammatory molecule 1; VNN1) is a pantetheine that hydrolyzes pantetheine to pantothenic acid (vitamin B5) and cysteamine. This molecule has an important role in oxidative stress and the inflammatory response.

In a cohort study involving 426 patients with severe trauma injuries, Lu H, et al. demonstrated that most of the patients developed sepsis 3–5 d after polytrauma, and Gram-negative bacteria were the most common pathogenic microorganism present. They observed the significant elevation of vanin-1 levels during the first days after admission, comparing septic and non-septic patients. Nevertheless, after 5 d post-admission, no differences were observed (26). Therefore, a high level of vanin-1 has been proposed exclusively as an early predictive biomarker for sepsis in trauma patients (26).

High-density Lipoproteins (HDL)

HDL particles display pleiotropic properties, including anti-inflammatory, anti-apoptotic, and antioxidant functions. Tanaka S, et al. studied 75 ICU patients (50 sepsis and 25 trauma) and demonstrated HDL levels were low in septic patients, whereas the HDL concentration was not altered in trauma patients (27).

Procalcitonin (PCT)

PCT is a precursor of the hormone calcitonin and is normally produced by C-cells in the thyroid gland. In the case of a systemic bacterial infection, or by stimulation with endotoxin or pro-inflammatory cytokines (TNF-α, IL-1β), the levels of PCT dramatically increase up to 1000 fold. PCT shows rapid kinetics, with levels peaking at 24–48 h after trauma, showing a rapid decrease in non-complicated patients. Persistent high levels or secondary increases are adequate predictors of sepsis and multiple organ failure (28). Procalcitonin can be used also as a marker of the resolution of sepsis, and to judge the adequacy of drainage, debridement, or the need for a further surgical revision (28). The use of procalcitonin to guide the initiation and duration of antibiotic treatment results in lower risks of mortality, lower antibiotic consumption, and lower risk for antibiotic-related side effects (29). The strongest evidence currently available indicates PCT as an efficient biomarker helping in the early recognition of sepsis in trauma patients (20).

C-reactive Protein (CRP)

CRP is an acute-phase protein, predominantly produced by hepatocytes where its transcription is induced by several cytokines (IL-6, TNF-α, IL-1β) in response to inflammation, infection, and tissue damage. CRP peaks within the first 3 d, but the period of recovery is long and does not allow discrimination between septic and non-septic conditions (20).

Thrombin-activable Fibrinolysis Inhibitor (TAFI)

TAFI plays a dual role as an anti-fibrinolytic and anti-inflammatory factor by downregulating complement anaphylatoxin C5a. Vollrath J.T, et al. studied a cohort of 48 patients and found that 14 of them developed sepsis after major trauma, when associated with decreased TAFI and increased C5a levels. TAFI and C5a are also early biomarkers to detect patients at risk for developing sepsis (30).

Glycosylated Hemoglobin (HbA1c)

Guo and Shenś retrospective study, conducted at Shengjing Hospital in China, included 397 patients admitted to the ICU due to trauma. They observed that the most common underlying comorbidities were hypertension (26.4%), alcohol abuse (16.4%), and diabetes (15.9%). A glycosylated hemoglobin (HbA1c) level of 6.5% above normal, was used as an independent risk factor for both, sepsis, and septic shock development in trauma patients. The results of this study emphasize the importance of proper blood glucose management, and the regular measurement of HbA1c in trauma patients (23). Most findings also stress the fact that diabetics, especially those with poor blood glucose control, are more likely to develop associated with a trauma event, an infection complicated with sepsis than those non-diabetic patients (23).

Neutrophil/lymphocyte Ratio (NLR)

Although it is well known that a positive microbiological culture is fundamental to confirm bacteremia, there is a pressing need for biomarkers showing good sensitivity and specificity without the need for time-consuming procedures. In this sense, several groups looking for simple and easily measurable parameters for defining bacteremia and patient prognosis, have demonstrated that the ratio between the lymphocyte and neutrophil count (NLR) can be a very useful parameter to measure in the ICU setting. Kaushik R, et al. studying a total of 56 cases of newly diagnosed cases of sepsis, and 20 healthy adults taken as controls where daily NLR was calculated, reported that NLR seems to present a promising role as a diagnostic and prognostic marker (24).

Management

There are several scores commonly use to assess disease severity and predict events following trauma. These are based on physiological changes, such as the one that presents RTS (Revised Trauma Score). Another score is based on anatomical changes known as NISS (New Injury Severity Score), and a third one combining both, physiological and anatomical findings, known as TRISS (The Trauma and Injury Severity Score) (31).

Recently, an update regarding the concepts of sepsis and septic shock has been introduced, defining sepsis as a life-threatening state caused by an uncontrolled response to an infection. Therefore, a system for assessing the multi-organ failure was acquired and named Sequential Organ Failure Assessment (SOFA), in which a change in the score of 2 or more was associated with an in-hospital mortality greater than 10% (32). Nevertheless, from the clinical point of view, this assessment system was found not to be as accurate as needed due to the recently introduced concept of Multiple Organ Failure. Therefore, a study was carried out studying patients showing signs of infection with a high probability to develop sepsis. Through a multivariate regression study, it was evidenced that 2 of 3 variables offered predictive validity like that obtained in the complete SOFA score for patients with suspected sepsis showing an unfavorable prognosis (32). This new assessment system was called Quick Sequential Organ Failure Assessment (qSOFA), including a Glasgow Coma Scale value (33). The presence of a qSOFA score equal to or greater than 2, is associated with a high risk of death or prolonged stay in the ICU (12,34).

In trauma, the term damage control (DC), although not a medical concept, was developed to manage trauma showing massive bleeding, shorten the surgical time, and avoid the lethal triad of hypothermia, coagulopathy, and acidosis. Since polytrauma that includes soft tissue damage and multiple fractures can happen in many forms, mostly because of an accident, or a violent event, frequently these incidents take place in septic conditions, and therefore patients must be considered as contaminated (35,36).

In the emergency clinical setting, the purpose of any fracture classification system is to allow simplicity to help define fracture morphology and treatment parameters. The Gustilo-Anderson classification has been the most widely used system, and it is generally accepted as the primary classification system for open fractures (Table 2). On the other hand, the Winquist and Hansen classification considers fracture comminution and the grading system to evaluate bone loss (Table 3) (35). A new approach based on minimizing the impact of the second hit by shortening the operating time and avoiding a delay for definitive treatment was adapted and defined as damage control in orthopedics (DCO) (35).

Therefore, when receiving a polytrauma patient, the specialist DCO protocol should include:

a) The history information regarding the mechanism, location, and timing of the injury.
b) The physical exam including inspection of soft-tissue damage. The size and nature of the external wound may not reflect the damage to deeper structures. If possible neurovascular damage is suspected, seek consultation from the vascular surgery department ASAP.
c) The indication to administer IV antibiotics and tetanus prophylaxis.
d) The indication to obtain radiographs and/or CT scans of the injured extremities.
e) The urgent thorough surgical irrigation with a balanced salt solution, such as Ringer lactate, to reduce bacterial growth.
f) Debridement according to the degree of injury employing the Gustilo-Anderson Classification (Table 2).
g) Fracture fixation.

Since patients undergoing polytrauma are predisposed to a septic event, protection against the onset of sepsis is the most important way of reducing the morbidity and mortality rates in ICU patients (35). Nevertheless, patient prognosis also depends on early diagnosis, appropriate treatment, and recognition of other underlying disorders (18). It is the physician's responsibility to control the patient's overall response, always trying to avoid immune system activation (11).

According to a cohort study, septic patients can develop a chronic illness with a 63% survival rate at 6 months and continue to have the presence of cytokines for chronic inflammation as well as biomarkers distinctive of persistent immunosuppression (36). Failure to Rescue (FTR) is defined as death after any recorded complication, separated into infectious and non-infectious causes and directly associated with deficient initial management of complications which include pneumonia, respiratory failure, arrhythmia,

Table 2. Gustilo Anderson Classification.

Type	Description	Surgical Irrigation	Empiric Antibicrobial Therapy
I	≤1 cm wound (minimal energy trauma, soft tissue damage, contamination, or comminution)	3 L saline solution	1st generation cephalosporin
II	≥2 cm wound (moderate energy trauma, soft tissue injury, contamination, or comminution)	6 L saline solution	
III	≥10 cm wound (Severe/extensive energy trauma, soft tissue injury, contamination or comminution or segmental fractures)	9 L saline solution	1st generation cephalosporin + aminoglycoside (Add Penicillin for anaerobic coverage if heavy contamination)

Table 3. Winquist and Hansen Classification

Classification	Description
0	No comminution
1	Small butterfly fragment
2	Larger butterfly fragment, but >50% cortical contact between major proximal and distal fragments
3	Large butterfly fragment with <50% cortical contact between major proximal and distal fragments
4	Segmental comminution with no direct contact between major proximal and distal fragments

Winquist RA, and Hansen, ST, Jr. Comminuted fractures of the femoral shaft treated by intramedullary nailing. Orthop Clin North Am 1980;11:633–648.

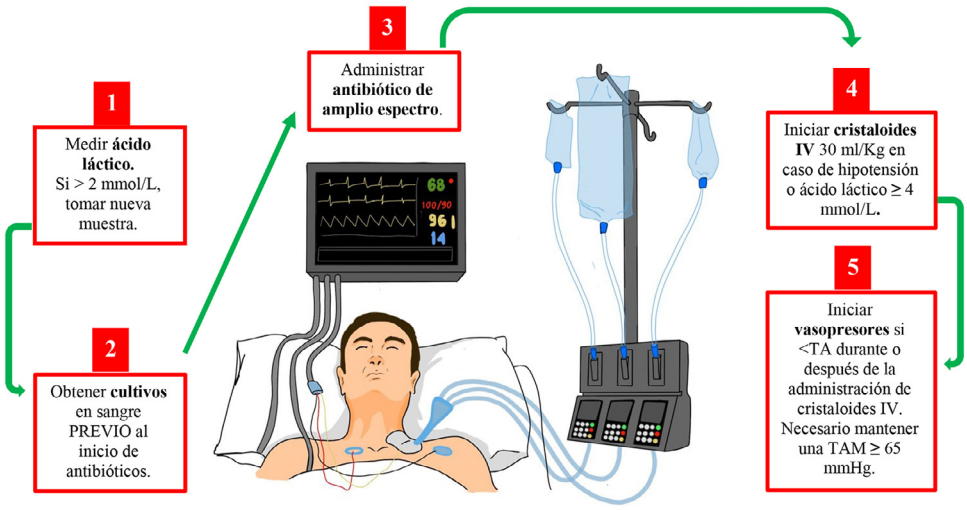

Figure 2. SSC (Surviving Sepsis Campaign) initial resuscitation protocol for sepsis and septic shock.

and stroke. In most trauma centers, FTR corresponds to an important set of variables representing the institutional skill necessary to rescue a patient that develops complications secondary to the initial injury. In this kind of setting, the multidisciplinary approach plays an important role in trauma care by reducing misdiagnosis, and delays of treatment, therefore rescuing patients from developing further critical complications (37,38).

The treatment of sepsis always must be examined under two main headings: appropriate antimicrobial treatment, and all-purpose supporting treatment. Since during the first 6 h after any trauma event, treatment is extremely important in terms of prognosis, during this time, antibiotics are mostly given empirically, until the specific identification of the active microorganism is achieved (29). A late administration of antibiotics is significantly associated with an increased mortality rate, especially when associated with hypotension (19,20). González del Castillo J, et al. describe a standardized series of steps to implement within the first 3 h after the major incident, which include: a) lactate measurement, b) the collection of blood cultures before the administration of antibiotics, c) initiation of a broad-spectrum empiric antibiotic treatment, d) administration of 30mL/kg crystalloid IV fluid or lactate >4mmol/L, e) administration of vasopressors if hypotension persists (Figure 2) (39).

Since the participation of sepsis in polytrauma has been recognized as a key event in the outcome of ICU patients, the specialist's ability to early recognize a septic process has become a key feature to reduce mortality and improve clinical prognosis. Considering that prediction of sepsis in patients that have suffered severe trauma is still a challenge, the need for new biomarkers that might help to perceive the presence of this syndrome,

and the establishment of early treatment strategies, must be dramatically improved. Although important alterations of several immune-metabolic pathways associated with sepsis have been identified, the need to further study the molecular basis of the immune reactivity associated with the inflammatory process will undoubtedly help to better predict and treat a septic process in polytrauma patients.

Conflict of Interest

All authors declare that they have no competing interests. All authors read and approved the final manuscript.

Acknowledgments

The authors thank Dr. Isaac Shueke-Hop for his participation in the investigation of information and writing of the article.

References

1. Raju R. Immune and metabolic alterations following trauma and sepsis – an overview. Biochimica et Biophysica Acta (BBA) Biochim Biophys Acta Mol Basis Dis 2017;1863:2523–2525. doi:10.1016/j.bbadis.2017.08.008.
2. Mayr F-B, Yende S, Angus D-C. Epidemiology of severe sepsis. Virulence 2014;5:4–11. doi:10.4161/viru.27372.
3. Cavaillon J-M, Adib-Conquy M. Compensatory anti-inflammatory response syndrome. Thromb Haemost 2009;101:36–47.
4. Stengel D, Bauwens K, Sehouli J, et al. Systematic Review and meta-analysis of antibiotic therapy for bone and joint infections. Lancet Infect Dis 2001;1:175–188. doi:10.1016/S1473-3099(01)00094-9.
5. Zimmerli W. Prosthetic-joint-associated infections. Best Pract Res Clin Rheumatol Dec 2006;20:1045–1063. doi:10.1016/j.berh.2006.08.003.
6. McConoughey S-J, Howlin R, Granger J-F, et al. Biofilms in periprosthetic orthopedic infections. Future Microbiol 2014;9:987–1007. doi:10.2217/fmb.14.64.
7. Zoubos A-B, Galanakos S-P, Soucacos P-N. Orthopaedic and biofilm. what we know? A review. Med Sci Monit 2012;18:RA89–RA96. doi:10.12659/msm.882893.
8. van Gennip M, Christensen L-D, Alhede M, et al. Interactions between polymorphonuclear leukocytes and pseudomonas aeruginosa biofilms on silicone implants in vivo. Infect Immun 2012;80:2601–2607. doi:10.1128/IAI.06215.
9. Cataldo M-A, Petrosillo N, Cipriani M, et al. Prosthetic joint infection: Recent developments in diagnosis and management. J Infect 2010;61:443–448. doi:10.1016/j.jinf.2010.09.033.
10. Lakomkin N, Sathiyakumar V, Wick B, et al. Incidence and predictive risk factors of postoperative sepsis in orthopedic trauma patients. J Orthop Traumatol 2017;18:151–158. doi:10.1007/s10195-016-0437-4.
11. Dickmann P, Bauer M. Sepsis 2019 – new trends and their implications for multiple trauma patients. Z Orthop Unfall 2020;158:81–89 English, German. doi:10.1055/a-0853-2054.
12. Koch C, Edinger F, Fischer T, et al. Comparison of qSOFA score, SOFA Score, and SIRS criteria for the prediction of infection and mortality among surgical intermediate and Intensive Care Patients. World J Emerg Surg 2020;15:63. doi:10.1186/s13017-020-00343-y.
13. Pape H-C, Lefering R, Butcher N, et al. The definition of Polytrauma revisited. J Trauma Acute Care Surg 2014;77:780–786. doi:10.1097/TA.0000000000000453.
14. Lee C, Rasmussen T-E, Pape H-C, et al. The polytrauma patient: Current concepts and evolving care. OTA International. OTA International 2021;4:e108. doi:10.1097/oi9.0000000000000108.
15. Ahmed A-M, Mikhael E-S, Abdelkader A, et al. Interleukin-17 as a predictor of sepsis in polytrauma patients: A prospective cohort study. Eur J Trauma Emerg Surg 2018;44:621–626. doi:10.1007/s00068-017-0841-3.
16. Pruinelli L, Westra B-L, Yadav P, et al. Delay within the 3-hour surviving sepsis campaign guideline on mortality for patients with severe sepsis and septic shock. Crit Care Med 2018;46:500–505. doi:10.1097/CCM.0000000000002949.
17. Chung S, Choi D, Cho J, et al. Timing and associated factors for sepsis-3 in severe trauma patients: A 3-year Single Trauma Center experience. Acute Crit Care 2018;33:130–134. doi:10.4266/acc.2018.00122.
18. Polat G, Ugan R-A, Cadirci E, et al. Sepsis and septic shock: Current treatment strategies and new approaches. Eurasian J Med 2017;49:53–58. doi:10.5152/eurasianjmed.2017.17062.
19. Dellinger R-P, Levy M-M, Rhodes A, et al. Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock, 2012. Intensive Care Med 2013;39:165–228. doi:10.1007/s00134-012-2769-8.
20. Ciriello V, Gudipati S, Stavrou P-Z, et al. Biomarkers predicting sepsis in polytrauma patients: Current evidence. Injury 2013;44:1680–1692. doi:10.1016/j.injury.2013.09.024.
21. Wang J, Wen D, Sun J, et al. Cytokine biomarker phenotype for early prediction and triage of sepsis in blunt trauma patients. 02 October 2020, PREPRINT (Version 1) available at Research Square. doi:10.21203/rs.3.rs-84088/v1
22. van Engelen T-S-R, Wiersinga W-J, Scicluna B-P, et al. Biomarkers in sepsis. Crit Care Clin 2018;34:139–152. doi:10.1016/j.ccc.2017.08.010.
23. Guo F, Shen H. Glycosylated hemoglobin as a predictor of sepsis and all-cause mortality in trauma patients. Infect Drug Resist 2021;14:2517–2526. doi:10.2147/IDR.S307868.
24. Kaushik R, Gupta M, Sharma M, et al. Diagnostic and prognostic role of Neutrophil-to-lymphocyte ratio in early and late phase of sepsis. Indian J Crit Care Med Sep 2018;22:660–663. doi:10.4103/ijccm.IJCCM_59_18.
25. Wang Y-C, Liu Q-X, Liu T, et al. Caspase-1-dependent pyroptosis of peripheral blood mononuclear cells predicts the development of sepsis in severe trauma patients. Medicine (Baltimore) 2018;97:e9859. doi:10.1097/MD.0000000000009859.
26. Lu H, Zhang A, Wen D, et al. Plasma vanin-1 as a novel biomarker of sepsis for trauma patients: A prospective multicenter cohort study. Infect Dis Ther 2021;10:739–751. doi:10.1007/s40121-021-00414-w.
27. Tanaka S, Labreuche J, Drumez E, et al. Low HDL levels in sepsis versus trauma patients in intensive care unit. Ann Intensive Care 2017;7:60. doi:10.1186/s13613-017-0284-3.
28. Hoshino K, Irie Y, Mizunuma M, et al. Incidence of elevated procalcitonin and presepsin levels after severe trauma: A pilot cohort study. Anaesth Intensive Care 2017;45:600–604. doi:10.1177/0310057X1704500510.
29. Ho V-P, Kaafarani H, Rattan R, et al. Sepsis 2019: What surgeons need to know. Surg Infect (Larchmt) 2020;21:195–204. doi:10.1089/sur.2019.126.
30. Vollrath J-T, Marzi I, Herminghaus A, et al. Post-traumatic sepsis is associated with increased C5A and decreased TAFI levels. J Clin Med 2020;9:1230. doi:10.3390/jcm9041230.
31. Ringdal K-G, Skaga N-O, Steen P-A, et al. Classification of comorbidity in trauma: The reliability of pre-injury ASA physical status classification. Injury 2013;44:29–35. doi:10.1016/j.injury.2011.12.024.

32. Singer M, Deutschman C-S, Seymour C-W, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315:801–810. doi:10.1001/jama.2016.0287.
33. Reith F-C, Van den Brande R, Synnot A, et al. The reliability of the Glasgow Coma Scale: A systematic review. Intensive Care Med 2016;42:3–15. doi:10.1007/s00134-015-4124-3.
34. Raith E-P, Udy A-A, Bailey M, et al. Prognostic Accuracy of the SOFA Score, SIRS Criteria, and qSOFA Score for In-Hospital Mortality Among Adults With Suspected Infection Admitted to the Intensive Care Unit. JAMA 2017;317:290–300. doi:10.1001/jama.2016.20328.
35. Akdemir M, Erbay A, Turan A-C, et al. P22 Treatment of bone and soft tissue infections and sepsis due to war injuries including polytrauma. Injury 2016;46(Supplement 5):S32. doi:10.1016/S0020-1383(16)30573-3.
36. Bergmann C-B, Beckmann N, Salyer C-E, et al. Potential targets to mitigate trauma- or sepsis-induced immune suppression. Front Immunol 2021;12:622601. doi:10.3389/fimmu.2021.622601.
37. Kaufman E-J, Earl-Royal E, Barie P-S, et al. Failure to Rescue after Infectious Complications in a Statewide Trauma System. Surg Infect (Larchmt) 2017;18:89–98. doi:10.1089/sur.2016.112.
38. Abe T, Komori A, Shiraishi A, et al. Trauma complications and in-hospital mortality: Failure-to-rescue. Crit Care 2020;24:223. doi:10.1186/s13054-020-02951-1.
39. González del Castillo J, Candel F-J, Núñez Orantos M-J, et al. La Adecuación del Tratamiento antibiótico. Med Intensiva 2016;40:391–393. doi:10.1016/j.medin.2015.11.004.