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RESEARCH ARTICLE

SEPSIS AND ANTIMICROBIAL THERAPY IN TRAUMA PATIENTS

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ABSTRACT

Sepsis is body's systemic inflammatory response to infection. Sepsis physiopathogenesis is characterized by an inflammatory cascade. The cascade has humoral, cellular, complement and cytokine components. Sepsis in trauma patients is common. Multisystem trauma patients have a reduced capacity to fight infections as there immune system is compromised. Following a major trauma there is a catabolic phase secondary to tissue injury and surgical intervention. Sepsis in trauma essentially has the same physiopathogenesis. Trauma, inflammation, or infection leads to the activation of the inflammatory cascade. The host response is perhaps as important as the site of infection or type of microorganism in the cause of sepsis. Sepsis should be identified as early as possible. Sepsis patients should be rendered a comprehensive therapy. Multi organ support therapy is essential. The high morbidity and mortality of severe sepsis and septic shock fosters a continuous search for novel therapies that go beyond pure correction of oxygenation and hemodynamics. Before the advent of antibiotics, sepsis was considered almost inevitable after severe trauma. This adage was the basis of judicious antibiotic use and was seed for the concept of "Antibiotic Stewardship". The concept of antibiotic usage in trauma has always drawn controversy. There are diverse schools of thoughts on necessity, duration and choice of antibiotics. Judicious antibiotic selection in required for various trauma scenarios.

INTRODUCTION

Sepsis is body's systemic inflammatory response to infection. [1] Sepsis is the result of inappropriate and global activation or deactivation of innate immune, inflammatory, thrombotic, and metabolic pathways. [2] Sepsis is a dynamic disease which often progresses to severe form manifested by multiorgan failure. [3] Systemic inflammatory responses seen in septic patients is not specific and localized. The response may also result from insults other than infection, such as pancreatitis or trauma. The clinical course of a trauma patient is often complicated by late onset sepsis. [4] Judicious antibiotic prescription is must for improving outcomes in trauma related infections and sepsis. [5]

Objectives

- To understand the importance of Sepsis in patients with trauma
- To recognize the risk factors for development of sepsis in trauma patients
- Understand Trauma related sepsis
- General concepts of antibiotic stewardship
- Judicious antibiotic use in trauma scenarios

Pathophysiology

Sepsis physiopathogenesis is characterized by an inflammatory cascade. The cascade has humoral, cellular, complement and cytokine components. [6] The endothelial cell is the focal point of interactions between the inflammatory events and disordered hemostasis. Vascular bed-specific factors and endothelial cell injury can shift the balance between antithrombotic or prothrombotic state. The mediators ultimately lead to microvascular plugging and vasoconstriction. [7] The resultant hypo perfusion /ischemia leads to acute organ dysfunction. Uninterrupted, a vicious cycle ensues that can end in death. Organ failure is linked to mortality in sepsis. Sepsis is a dynamic disease with progress to severe sepsis or a septic shock.8 Disease progression in sepsis is highly heterogeneous and unpredictable. Disease course is dependent on several innate, immunological and external factors.

Sepsis in Trauma

Multisystem trauma patients have a reduced capacity to fight infections as there immune system is compromised. Following a major trauma there is a catabolic phase secondary to tissue injury and surgical intervention. [10] Patients with severe trauma already have a stressed metabolic state, one where proinflammatory mediators are abundant. Severe trauma is characterized by a distinct immunological response with both pro inflammatory and anti inflammatory traits. Sepsis itself causes major immunosupression, which initiates, augments and propagates a vicious cycle leading inexorably to severe sepsis and organ dysfunction. [11] Breach of body's defense further makes the patient susceptible to infections.

This breach could be secondary to skin/mucosal injury catheters/ drains/ devices or blood transfusions. The integumentary breach is a potential source of infection. Dead tissue and poor perfusion makes trauma patients vulnerable to infections. Sepsis is leading cause of late deaths occurring in multisystem trauma. [12] Sepsis is third most common cause of death following multi organ failure and acute lung injury. [13] Patients with limited mobility are at risk to develop atelectasis and bed sores. [14] Open fractures and compound injuries potentates the risk. Emergency invasive procedures add to risk of infection.

Sepsis in trauma essentially has the same physio pathogenesis. [15]However, there are intricate differences in etiology, microbiology and pattern of disease. Sepsis following major trauma is related to type of injury, together with extent of injury and anatomical location. [16] Additionally, increased severity of trauma heightens the risk of developing sepsis.[17] the clinical presentation of sepsis is often blurred in trauma patients. We need to have low index of suspicion and utilize surrogates, microbiology services and biomarkers judiciously. [18-19]

However, most patients admitted after injury or a major trauma, do not have any infection at the onset. The consequence of injury and hospital stay renders the patient susceptible to infections particularly health care associated infections. [20] Although our ability to treat sepsis has improved considerably, still prevention always have a great impact on survival. Infection control practices need to be standardized and followed stringently. Sepsis could be triggered by multitude of stimuli. There is often an overlap among the trigger factors in trauma related sepsis. Trauma, inflammation, or infection leads to the activation of the inflammatory cascade. [21-22]

Table 1 Dynamics of Sepsis Severity [9]

Systemic Inflammatory Response Syndrome (SIRS): The systemic inflammatory response to a variety of severe clinical insults
Sepsis: Systemic manifestations of infection
Severe sepsis: Sepsis with organ dysfunction, hypoperfusion, or hypotension
Septic shock: Sepsis with arterial hypotension, despite fluid resuscitation, with organ dysfunction

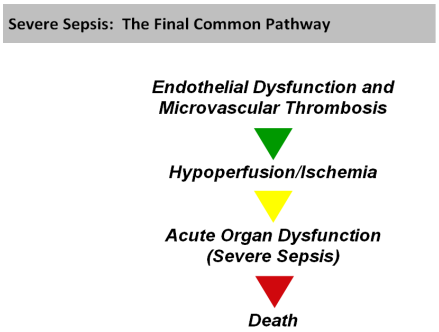

Figure 1 Severe Sepsis - The Final Common Pathway [8]

Infection Site and Microbiologic Considerations

The host response is perhaps as important as the site of infection or type of microorganism in the cause of sepsis. [27] The lung is the most common site of infection, followed by the abdomen and urinary tract. In 20 to 30 percent of patients, a definite site of infection is not determined, and even among patients in whom a site is strongly suspected, a similar proportion have sterile cultures or questionable microbiologic isolates. [28] Pleural, peritoneal, and paranasal-sinus infections can easily be overlooked, even with the use of computed tomography.[29] No imaging study can definitively rule out infection. Penetration of skin and soft tissues, especially dirty impalement can result in infection. A good surgical technique with thorough debridement lowers the risk. Infection in patients with multi system trauma carries high morbidity and mortality. Prophylactic antibiotics are thus indicated in multisystem trauma. [30]

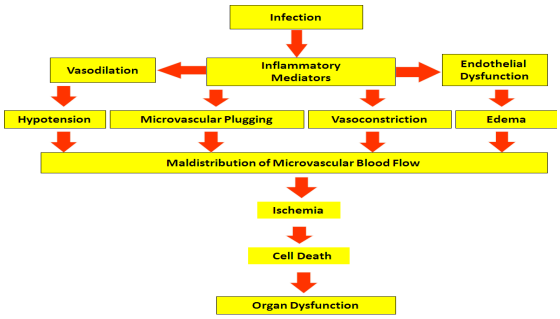

Figure 2 Pathophysiology of Sepsis [6]

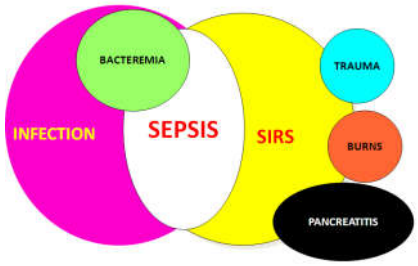

Figure 3 Relationships between Sepsis and SIRS [3]

Table 2 Factors influencing Sepsis in Trauma[23-26]

Injury Factor	Host Resistance	Iatrogenic factor	Triggers
Tissue Damage Debris/Dead tissue Impaired perfusion Inoculum Virulence	Primary Defenses Reticuloendothelial system Accessory cells T cells B cells	Antibiotic prophylaxis Steroids Other drugs Unresolved shock Inadequate Debridement Nutrition	Infection Inflammation-including traumatic pancreatitis Trauma –major injuries, burns and electrocution Surgery Hemorrhage Uncorrected shock Bacterial translocation

Table 3 Ten Commandments of Judicious Antibiotic use[55]

Drug	Dilution
Dose and dosing frequency	Drug resistant
Duration	Drug toxicity
Data-microbiology	Descalation
Drug penetration	Drug interaction

Pneumonia in Trauma patients

In patients with chest injury pulmonary contusion, emergency intubation, shock, blood transfusion and extra pulmonary

injury further increases the risk of nosocomial pneumonia. [14] Early onset pneumonia is secondary to aspiration at the time of injury, especially in head injury patients. Common pathogens implicated in early onset pneumonia are H *Influenzae*, Pneumococcus and anaerobes. Late onset pneumonia is usually caused by aerobic gram negative bacilli and S.*aureus*. Diagnosis is based on new or progressive infiltrate and worsening of respiratory parameters. Infiltrates can however be also due to atelectasis, hemothorax, pleural collection, aspiration or pulmonary edema. Microbiological sampling with endotracheal aspirate or bronchoalveolar lavage is must. [31] Antibiotics should be reserved for superimposed pneumonia in patients who has suffered pulmonary contusion.

Table 4 Local wound factors those interfere in host resistance[61]

Necrotic tissue	Suture
Decreased perfusion – Systemic and local	Hematoma
Acidic milieu	Dead space
Tissue hypoxia/ischemia	Poor antibiotic penetration

Sepsis Management

Sepsis should be identified as early as possible. [32] Sepsis patients should be rendered a comprehensive therapy. Multi organ support therapy is essential. [33] Identify source(s) of infection and deliver broad spectrum antibiotics at the earliest. Routine screening of potentially infected seriously ill patients for severe sepsis is must. [34] Severity of sepsis and shock should be analyzed. Hemodynamic resuscitation should be quantitative and should utilize serial lactate values, Central venous pressure, mixed venous saturation and other parameters. [35] Clinical, metabolic and hemodynamic parameters should be closely monitored during resuscitation. [36]Algorithms of care based on lactate clearance appear to work as well or better than other approaches. [37] Volume and physiologic resuscitation should be initiated promptly with objective goals and end points. [38] Crystalloids are favored as the initial fluid. [39]Hydroxyethyl starches are likely harmful. [40] Albumin 5% or plasmanate may have a role, particularly if rapid resuscitation is required [41-42]A lower Hb target (~7) is generally accepted. [43]

Sepsis Bundles

3 hour bundle[44-46]

i. Measure lactate level
ii. Obtain blood cultures prior to administration of antibiotics
iii. Administer broad spectrum antibiotics
iv. Administer 30 ml/kg crystalloid for hypotension or lactate ≥4mmol/L

6 hour bundle[44-46]

v. Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP)≥65 mmHg
vi. In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate≥ 4mmol/L: -Measure central venous pressure (CVP)* -Measure central venous oxygen saturation ($ScvO_2$)*
vii. Remeasure lactate if initial lactate was elevated*

Targets for quantitative resuscitation included in the guidelines are CVP of ≥8 mm Hg; $ScvO_2$ of ≥70%, and normalization of lactate.

Source control is essential in management of sepsis. Source of infection should be identified and controlled at the earliest. [28] Establish institutional goals for physiologic resuscitation. Multidisciplinary chronic phase of care is must to ensure compliance and improve outcomes. System based approach should be followed for improving outcomes. [47]

Adjuvant Therapies

Adjuvant therapy, also called adjuvant care, is treatment that is given in addition to the primary, main or initial treatment. [48] The high morbidity and mortality of severe sepsis and septic shock fosters a continuous search for novel therapies that go beyond pure correction of oxygenation and hemodynamics. Adjuvant therapies commercially available are ulinastatin and extracorporeal techniques. [49] Toraymyxin, Cytocorb and oXiris are commercially available in India. The adjuvant therapies works on principle of immunohomeostsis. Ulinastatin is effective agents for immune modulations which prevents organ dysfunction and promote homeostasis. [50]

Antibiotic Stewardship

Before the advent of antibiotics, sepsis was considered almost inevitable after severe trauma. This adage was the basis of judicious antibiotic use and was seed for the concept of "Antibiotic Stewardship".[51] the concept has been there for decades and with huge strides in pharmacokinetics and pharmacodynamics the concept is evolving with each passing day. [52] Antibiotics are the only class of therapeutic agent which apart from influencing the patient also influences the society at large.[53] Definition and understanding on adequate antibiotic therapy has evolved in last two decades. The widely accepted definition of "Adequate" Antibiotic Therapy is "Correct matching of sensitivity of the etiologic organism to the therapeutic agent an organism's susceptibility to the antibiotic chosen, optimal dose, administration by the route to ensure penetration at the site of infection, and use of combination therapy if necessary."Antibiotic Care Bundles is a group of evidence based interventions in antibiotic therapy which leads to better outcome then when each intervention is followed alone. The antibiotic care bundle involves grouping together key elements of care such as site of infection, risk stratification for MDRs, local microbiology data, de-escalation and the management of specific diagnosis in order to provide an "evidence based" antibiotic protocol that can improve and monitor the delivery of clinical care processes. [54]

Use the correct drug active against possible pathogen and achieving adequate concentration at the site of infection. We should be using the highest dose in life threatening infection. Dose should consider severity and organ dysfunction. Dosing schedule should be adjusted based on PK-PD principles. [55] Duration of therapy should neither be too short nor too long. However, it should be adequate enough to prevent metastatic seeding and relapse. For severe life threatening infection we should "Hit hard and Hit early". Start with antibiotics having maximum killing power at maximum doses and later streamline the therapy. [55]Adequate institutionalized retrospective and prospective microbiological data, which should be periodically updated, is a must for judicious

antibiotic therapy. We should take patient's data in terms of antibiotic history and do risk stratification for each patient. Relevant cultures and other surrogate makers for infection should be utilized. The agent being used should have good penetration at the site of infection. The antibiotics should be diluted in appropriate IV fluids. Reconstitution and dilution are different processes for few drugs. Some organisms like Pseudomonas may develop resistance while on antibiotic therapy. [56] This must be kept in mind if we face treatment failure. The common adverse effects should be known to clinicians and should be actively looked for especially in critically ill trauma patients. De-escalation of antibiotic is as necessary as escalation. De-escalation is based on antibiogram, clinical conditions and surrogates for infection markers. [57] Clinicians are often hesitant to change the winning combinations but studies have shown that prolonged course or overuse of antibiotic is associated with poor outcome. [58] Drug interactions should be actively looked for patients receiving polypharmacy and should be specially screen for interaction by clinical pharmacist or clinicians and we should utilize software program for studying drug interaction. There are often interactions among stake holders to arrive at an appropriate antibiotic prescription. The clinical pharmacist, physician and clinical microbiologist should all act as a team while deciding an appropriate antibiotic therapy. Antibiotic selection is a precarious affair especially in critically ill trauma patients. [31]

Antibiotic Prescription in Trauma

The concept of antibiotic usage in trauma has always drawn controversy. There are diverse school of thoughts on necessity, duration and choice of antibiotics. [30] Guidelines and practice are highly variable. Antibiotic prophylaxis is an adjunct to good clinical practices for preventing infections. The need for antibiotic stewardship is pivotal. Trauma deaths follow a tri modal pattern. The third peak is largely attributed to infectious complications, MODS and sepsis. Antibiotics early in course of trauma are generally used for prophylaxis as against later phase where the usage is either empirical or culture driven. The duration of antibiotic therapy is often ambiguous in trauma settings. There is no benefit with therapy longer than two days for prophylaxis. [58]

Continued contamination is the primary reason for antibiotic failure. Patient should be monitored for new infections and therapy should accordingly be modified. Antibiotics should only be used as adjunct to good decontamination. Empiric antibiotics should be initiated after relevant microbiology samples have been collected. However, broad spectrum antibiotics should be instituted at the earliest in patients getting unstable secondary to infectious complications. [5] We should follow a source directed therapy in a trauma patient. De escalation to culture guided therapy should be done when appropriate. The microbiology of warfare injury is complex and often multi drug resistant bugs are the cause of infections. [59]

It is essential to cover gram positive, gram negative as well as anaerobes. [60] Further escalation or preemptive use depends on clinical scenario. Microbiological guidance with antimicrobial susceptibility testing is must in later phase. [19] Specific infections occurring during hospital stay have to be treated as any other hospital acquired infection. [31]

Antibiotics in Trauma Scenarios Open Fractures

A short course of first generation cephalosporin commenced at the earliest after injury. Hand fractures do not require routine prophylaxis. Gram negative coverage need to be augmented in Gustillo type III fractures. [62]For Type I/II open fractures first generation cephalosporin is adequate. For Gustillo type II/III aminoglycoside is added. For grossly contaminated wounds consider cover for Clostridium with metronidazole. [63]

Abdominal Injury

Antibiotic should generally be used for 24 hours to reduce infections. Single pre operative dose of prophylactic antibiotic with broad spectrum aerobic and anaerobic coverage should be administered to patients with penetrating abdominal trauma. [64-65]

Craniocerebral Injuries

In penetrating head injury there is no evidence to support the use of prophylactic antibiotic. There is no evidence to support routine antibiotic prophylaxis in post traumatic cases without meningitis. This applies irrespective of CSF leak. [66] Current evidence suggests that prophylactic antibiotic does not reduce the risk of meningitis. However, perioperative antibiotic are indicated for surgical repair of CSF leaks, and in some special circumstances like active bacterial infection or gross contamination of tract leading to cranium. [67] Current practices support antibiotic prophylaxis when there is fracture involving paranasal sinuses.

Soft Tissue Penetrating Trauma

Short course, single agent regimen using cephalosporin in order to prevent adverse outcomes is advocated. Antibiotics are not favored in burn trauma or superficial laceration. Bite wounds to hand carries a high risk of infection. [68] Prophylaxis is variable depending on many factors including characteristics of bite wound. Prophylactic antibiotic is indicated for amputation, crush or degloving injury. Dead tissue with debris is a good medium for bacterial growth. Battle wounds often harbingers resistant organism. Antibiotic cover need to be tailored according to local epidemiology. [69-70] Acute compartment syndromes is characterized by increase tissue pressures, decreased blood flow with local hypoxia and necrosis making the patient susceptible to infection. Prophylactic antibiotic for a short duration is advocated. [70]

Thoracic Trauma

Use prophylactic perioperative short course antibiotics when there is contamination of the sterile cavities of the thorax. Some guidelines support the use of 24 hours of a first generation cephalosporin in the management of tube thoracostomy for traumatic hemopneumothorax. [71]

CONCLUSIONS

Sepsis and infective complications often complicate the clinical course of trauma patients. Sepsis management has to be comprehensive for optimal outcomes. The basic concepts of sepsis management are similar for trauma related sepsis. Judicious antibiotic selection in required for various trauma scenarios.

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