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Optimizing Antimicrobial Therapy in Sepsis and Septic Shock

Essay

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مقال

توطئة للحصول على درجة الماجستير في الرعاية المركزة

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List of abbreviations

AE	Adverse events
AKI	Acute kidney injury
AKIN	Acute Kidney Injury Network
AKIN	The Acute Kidney Injury Network
ALI	Acute lung injury
ALT	Alanine transaminase
AP	Activator protein
APACHE	Acute Physiologic and Chronic Health Evaluation
APTT	Activated partial thromboplastin time
ARDS	Acute respiratory distress syndrome
AST	Aspartate transaminase
ATIII	Antithrombin III
AUC	Area under curve
BAL	Bronchoalveolar lavage
BASES	Brazilian Sepsis Epidemiological Study
BSI	Bloodstream infection
CARS	Compensatory anti-inflammatory response syndrome
CD	Cluster of differentiation
CDC	The Centers for Disease Control
Cl	Clearance
CNS	Central nervous system
CPIS	Clinical Pulmonary Infection Score
Cr	Creatinine
CRP	C-reactive protein
CRRT	Continuous renal replacement therapy
CSF	Cerebrospinal fluid
CT	Computed tomography
DIC	Disseminated intravascular coagulation
DO_2	Oxygen delivery
ECMO	Extracorporeal membrane oxygenation
EDD	Extended daily dialysis
EPCR	Endothelial protein C receptor
ESBL	Extended-spectrum beta-lactamase
FDA	Food and drug administrations

GI	Gastrointestinal
HLA	Human leucocytic antigen
HMGB1	High mobility group B1
IAIs	Intra-abdominal infections
ICU	Intensive care unit
IDSA	Infectious Diseases Society of America
IDSA	The Infectious Diseases Society of America
IFI	Invasive fungal infections
IHD	Intermittent hemodialysis
IIR	Inflammatory immune response
IL	Interleukin
KPC	Klebsiella pneumoniae carbapenemase
LBP	LPS-binding protein
LOS	Length of stay
MAP	Mean arterial pressure
MCP-1	Monocyte chemoattractant protein-1
MDL-1	Myeloid DAP12-associating lectin
MDR	Multidrug resistant
MIC	Minimal inhibitory concentration
MIF	Migration inhibitory factor
MOF	Multiple organ failure
MRSA	Methicillin Resistant *Staph. Aureus*
MSSA	Methicillin-susceptible S. aureus
NF-κB	Nuclear factor-κB
NO	Nitric oxide
OR	Odds ratio
PAF	Platelet-activating factor
PAFE	Post antifungal effect
PAI-1	Plasminogen activator inhibitor 1
PAR1	Protease activated receptor 1
PCT	Procalcitonin
PCT	Procalcitonin
PD	Pharmacodynamics
PGRPs	Peptidoglycan-recognition proteins
PIRO	Predisposition, infection, response, organ dysfunction
PK	Pharmacokinetic
PRR	Pattern-recognition receptor
rAPC	Recombinant activated protein C
RBCs	Red blood cells
RCTs	Randomized controlled trials

RIFLE	Risk/Injury/Failure/Loss/End-Stage Renal Disease
ROS	Reactive oxygen species
RR	Relative risk
RRT	Renal replacement therapy
SBP	Systolic blood pressure
SIRS	Systemic Inflammatory Response Syndrome
SIRS	Systemic inflammatory response syndrome
SMART	Study for Monitoring Antimicrobial Resistance Trends
SOAP	Sepsis Occurrence in Acutely Ill Patients
SOFA	Sequential Organ Failure Assessment
SSTI	Skin and soft-tissue infection
SVR	Systemic vascular resistance
TAFI	Thrombin activatable fibrinolysis inhibitor
TFPI	Tissue factor pathway inhibitor
TLRs	Toll-like receptors
TNF	Tumour necrosis factor
TREM-1	The triggering receptor expressed on myeloid cells
TSST	Toxic shock syndrome toxin
US	United States
VAP	Ventilator-associated pneumonia
Vd	Volume of distribution
VISA	Vancomycin-intermediate S. aureus
VRE	Vancomycin-resistant enterococci
VRSA	Vancomycin-resistant S. aureus
VSE	Vancomycin-susceptible enterococci
WBC	White blood cell count

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Introduction

Nomenclature is important when it helps us understand the pathophysiology of a disease. Sepsis is defined as suspected or proven infection plus a systemic inflammatory response syndrome (e.g., fever, tachycardia, tachypnea, and leukocytosis). Severe sepsis is defined as sepsis with organ dysfunction (hypotension, hypoxemia, oliguria, metabolic acidosis, and thrombocytopenia). Septic shock is defined as severe sepsis with hypotension, despite adequate fluid resuscitation (Bone et al., 2000).

The mortality rates associated with severe sepsis and septic shock are 25 to 30%and 40% to 70% respectively (Bernard et al., 2001).

There are approximately 750,000 cases of sepsis a year in the United States, and the frequency is increasing, given an aging population with increasing numbers of patients infected with treatment-resistant organisms and patients with compromised immune systems (Martin et al., 2003).

The pathophysiology of Sepsis is complex interactions between the infecting microorganism and the host immune, inflammatory, and coagulation responses (Hotchkiss and Karl, 2003).

The cornerstone of emergency management of sepsis is early goal-directed therapy, plus lung-protective ventilation, broad-spectrum antibiotics, and possibly activated protein C (Leibovici et al., 2000).

Appropriate antimicrobial therapy depends on adequate coverage of the resident flora of the organ system presumed to be the source of the septic process (Cunha, 2006).

Selection of antibiotic agents is empirically based on an assessment of the patient's underlying host defenses, the potential source of infection, and the most likely responsible organisms. Antibiotic choice must be broad spectrum, covering gram-positive, gram-negative, and anaerobic bacteria when the source is unknown. In addition, consideration must be given to pathogens with antibiotic resistance, such as Methicillin Resistant *Staph. Aureus* (MRSA), *Pseudomonas* species and gram-negative organisms with extended-spectrum beta-lactamase (ESBL) activity (Kumar et al., 2006).

Optimal use of antibiotic regimens is the critical determinant of survival in sepsis and septic shock. Beyond the issues related to the infecting organisms and their sensitivity profile, optimal antimicrobial therapy includes assessment of host

factors (e.g., immune status, organ function, site of infection), pharmacokinetics (e.g., drug absorption, distribution, elimination), and pharmacodynamics (e.g., mode of action, bacteriocidal vs bacteriostatic characteristics, rate of killing) (Pinder et al., 2002).

Candida and *Aspergillus* are the most common causes of invasive fungal infections, accounting for 70–90% and 10–20% of all invasive mycoses, respectively(Lamagni et al., 2001).

Invasive candidiasis and aspergillosis are associated with substantial morbidity, high Mortality (40–60% and 60–90%, respectively), prolonged hospital stay and increased health care costs. Early diagnosis and prompt initiation of antifungal therapy are thus essential to reduce morbidity and mortality (Gudlaugsson et al., 2003).

Aim of the Work

The goal of this activity is to review the current medical literature to provide a strategy to optimize antibiotic use, including defining epidemiology, of sepsis and septic shock and the role of newer antibiotic options in treating serious infections in intensive care unit.

Sepsis

The word sepsis is derived from the Greek term for rotten or "to make putrid". Sepsis, defined as the systemic host response to microorganisms in previously sterile tissues, is a syndrome related to severe infections and is characterized by end-organ dysfunction away from the primary site of infection. To meet the definition of sepsis, patients need to satisfy at least two of the Systemic Inflammatory Response Syndrome (SIRS) criteria in association with having a suspected or confirmed infection (Levy et al., 2003).

The term "shock" comes from the French word choquer meaning "to collide with," and aptly describes the body's response to invading microbes and, to a large extent, its disruptive effect on normal physiology. Initially used in the medical literature in the 1700s, its earliest uses connoted a sudden jolt that often led to death (the initial physical injury). This definition evolved to describe widespread circulatory dysfunction following injury (Nduka & Parrillo, 2011).

The severity and mortality increase when this condition is complicated by predefined organ dysfunction (severe sepsis) and cardiovascular collapse (septic shock). The syndrome currently known as sepsis has had many definitions over the years. In 1991, a consensus conference organized by the American College of Chest Physicians and the Society of Critical Care Medicine clinically defined the terms SIRS, sepsis, severe sepsis and septic shock (Balk, 2004; Rivers et al., 2005).

Even though the definition has high sensitivity and low specificity, it has been helpful in improving patient care, enrollment in clinical trials and communication between ICUs (Silva et al., 2008).

A second conference held in 2001 attempted to refine the definitions, increase specificity by emphasizing prompt recognition and add a list of common symptoms and signs of sepsis (Rivers et al., 2005; Levy et al., 2003).

The current definitions are as follows:

- Infection: pathologic process caused by invasion of normally sterile tissue, fluid or body cavity by pathogenic or potentially pathogenic microorganisms.
- Sepsis: documented or suspected infection associated with any of the systemic inflammatory syndrome signs.
- Severe Sepsis: sepsis complicated by pre-defined organ

dysfunction.

- Septic Shock: sepsis-induced acute circulatory failure characterized by persistent arterial hypotension despite adequate volume administration and not explained by causes other than sepsis(Silva et al., 2008)

Table (1): Sepsis definitions (Silva et al., 2008)

1. Systemic Inflammatory Response Syndrome (SIRS). Two or more of the following: a) temperature (core) > 38.3ºC or < 36ºC; b) heart rate > 90 beats/min; c) respiratory rate > 20 breaths/min, PaCO2 < 32 mm Hg or need for mechanical ventilation; d) WBC count > 12.000/mm3 or < 4.000/ mm3 or > 10% immature forms (bands).
2. Sepsis is defined as SIRS associated with suspected or confirmed infection. Positive blood cultures are not necessary.
3. Severe sepsis is sepsis complicated by a predefined organ dysfunction.
4. Septic shock is cardiovascular collapse related to severe sepsis despite adequate fluid resuscitation. Hypotension is: systolic blood pressure (SBP) < 90 mm Hg, mean arterial pressure (MAP) < 65 mm Hg or a reduction of > 40 mm Hg on baseline SBP.
5. Organ dysfunction criteria are a) hypoxemia (PaO2/FiO2 ratio < 300); b) acute oliguria (urine output < 0.5 ml/kg/h for 2 h) or creatinine > 2.0 mg/dL; c) coagulopathy (platelet count < 100.000, INR > 1.5 or pTTa > 60 s); d) ileus; e) plasma bilirubin > 4 mg/dL).

Besides refining the diagnostic definitions, the 2001 consensus conference brought new insight into sepsis staging, with the aim of better characterizing disease severity. The PIRO concept was then introduced with the idea that these factors would have relevant impact on sepsis development and outcome (Balk, 2004; Vincent and Abraham, 2006).

Table (2): PIRO concept

	Clinical	Other tests
P (predisposition	Age, alcohol abuse, steroid or immunosuppressive therapy	Immunologic monitoring, genetic factors,
I (infection)	Site-specific (e.g., pneumonia, periotonitis)	x-ray, CT scan, bacteriology
R (response)	Malaise, temperature, heart rate, respiratory rate	WBC, CRP, PCT, modified APTT
O(organ dysfunction)	Arterial pressure, urine output, Glasgow coma score	PaO2/FiO2, creatinine, bilirubin, platelets

APTT: Activated partial thromboplastin time; CRP: C-reactive protein; CT: Computed tomography; PCT: Procalcitonin; WBC: White blood cell count (Vincent JL, Abraham, 2006).

Epidemiology

Sepsis has been recognized as a major public health problem in population-based and ICU-based epidemiological studies. Two studies have reported the sepsis incidence in the United States (Annane et al., 2003; Silva et al., 2004).

Martin et al. (2003) estimated the incidence of sepsis in the US as 240 cases per 100,000 people, and Angus et al. (2001) reported 300 cases of severe sepsis per 100,000 people. The incidence was projected to increase by 1.5% per annum. The mortality rate reported in these studies was also similar, ranging from 17.9% for sepsis to 28.6% for severe sepsis.

These numbers translate into approximately 750,000 new episodes of severe sepsis, with an annual mortality rate of 220,000 (29%) in the US. It is the tenth most common cause of death in the US, more so even than Acquired Immune Deficiency Syndrome, breast cancer, colon cancer and a first episode of acute myocardium infarction (Martin et al., 2003; Angus et al., 2001).

A French study found that septic shock was the reason for ICU admission in 8.4% of cases, with a mortality rate of 60% (Annane et al., 2003).

Recently, "Sepsis Occurrence in Acutely Ill Patients (SOAP)" in Europe reported more than 35% of ICU patients meet sepsis criteria during their ICU stay, with a mortality rate of 27% (Vincent et al., 2006).

The recent microbiological patterns of infections that cause septic shock and severe sepsis have changed significantly. Gram-negative bacteria used to be the most frequent germs involved in the pathogenesis of these syndromes. However, Gram-positive bacteria are currently as common as Gram-negative, and fungi are also responsible for a large portion of infections. It is not possible to isolate a pathogen in about a third of sepsis episodes; in some patients, it is difficult to obtain material for culture. Cultures are often not positive after the initiation of antibiotics (Angus et al., 2006).

Large epidemiologic studies report an incidence of 1 to 3 cases per 1000 population per year resulting in approximately 750,000 cases annually in the United States (Martins et al., 2003).

The average sepsis survivor requires 7 to 14 days of intensive care unit (ICU) support with much of this time spent on a ventilator. After ICU discharge, an additional 10- to 14- day hospital stay is typical. Thus, the average hospital length of stay for survivors is 3 to 5 weeks. Hospital charges in excess of tens of

thousands of dollars are common for individual patients, resulting in annual US expenditures of nearly $17 billion (Neilson et al., 2003).

Septic patients present typically in their sixth or seventh decade of life (Bernard et al., 2004), and the average age of afflicted patients has increased consistently over time (Martin et al., 2006). For unclear reasons, males are affected more commonly (Angus et al., 2001).

Although the condition can occur in previously healthy individuals, it is more common in patients with chronic diseases, particularly the immunocompromised. Occurrence rates are higher in those with diabetes mellitus, malignancy, chronic immune suppressive therapy, or human immunodeficiency virus infection. Patients with disrupted skin, especially trauma victims or surgical patients, are also more likely to develop severe sepsis. In the United States, African Americans have higher rates of hospitalization and mortality from sepsis as compared with whites, but the rates of case fatality are similar between the two groups (Neilson et al., 2003).

Despite these observations, sepsis has no definitive age, gender, racial, or geographic boundaries. Today hospital mortality rates remain unacceptably high; 30% to 40% of patients die despite prompt, comprehensive treatment. Predictors of worse outcomes include advanced age, cancer, and a hypothermic presentation (Vandijck et al., 2008). Historically, it was believed specific characteristics of the invading pathogen determined prognosis, but recent investigations have undermined this long-held belief (Kinasewitz et al., 2004).

The identity of the infecting organism is of lesser consequence than physiologic derangements provided appropriate, prompt antimicrobial therapy is administered. At the bedside, the best practical predictor of outcome is simply the number of organ systems with sepsis-induced dysfunction () Brun-Buisson, 2000).

Each new organ system failure adds roughly 15% to 20% risk of death to the baseline 10% to 15% mortality rate seen among ICU patients (Martins et al., 2003). On average, patients have two or three failing organ systems at the time of diagnosis (Levy et al., 2005). In addition to the number of malfunctioning organs, the severity of organ dysfunction also correlates with outcome (Dhainaut et al., 2005). For example, the need for higher or escalating vasoactive medication doses is associated with a worse prognosis than lower dose requirements or no requirement at all (Levy et al., 2005).

Likewise, increasing levels of renal dysfunction, as measured by either the Risk/Injury/Failure/Loss/End-Stage Renal Disease (RIFLE) or Acute Kidney Injury Network (AKIN) criteria, are also prognostic, including degrees of creatinine elevation heretofore thought to be unimportant (Ricci et al., 2008)

Pathophysiology of sepsis

Historically, sepsis was considered primarily-or perhaps solely-a disease of unbridled inflammation. One legacy of this view is the widely accepted consensus definition that highlights signs of inflammation as prerequisites to the diagnosis. This paradigm envisioned a multistage inflammatory cascade triggered by microbial invasion into a typically sterile body compartment or fluid. The subsequent proinflammatory state, while considered important to control the spread of local infection or injury, became dysregulated, and inflammation became destructive (Martin and Wheeler, 2009).

It is now clear that inflammation is just one of many contributors to septic physiology; other factors include enhanced coagulation and impaired fibrinolysis (Amaral et al., 2004).

The complex interplay between these pathways is fueled both by endogenous and exogenous factors. Exogenous sepsis triggers are typically protein, lipid, or carbohydrate microbial constituents. The most notorious exogenous microbial component is endotoxin, the integral cell wall component of gram-negative bacteria. Other well-recognized toxins are staphylococcal toxic shock syndrome toxin (TSST-1) and group B streptococcal toxin. Endogenous triggers - such as activated complement proteins, clotting cascade components, or dead host tissue - can also incite the pathophysiologic pathways of sepsis. Neither bacteremia nor endovascular infection is required for the development of sepsis; humoral release of toxic products from localized sites (such as an abscess) or the colon (as with gut translocation) can trigger a septic event. Abnormal coagulation is nearly universal in severe sepsis. The hematologic dysfunction of sepsis is detectable by widely available laboratory assays. Although routine clotting tests (prothrombin and activated partial thromboplastin times) may be near normal, most patients will have elevated fibrin degradation products (fibrin split products and D-dimers) and depleted levels of specific clotting factors (namely, fibrinogen) and anticlotting proteins(Aird, 2003).

Early in the syndrome, tissue factor expressed by leukocytes and damaged endothelium, together with proinflammatory mediators; stimulate clotting factors V and VII, resulting in the production of thrombin. Initially, the accelerated thrombosis is attenuated by the host's natural anticlotting proteins, namely protein C, protein S, and antithrombin. Over time, clot formation consumes clotting proteins, and anticlotting proteins are depleted as well. Sepsis also selectively impairs host conversion of inactive anticlotting precursors to active anticlotting proteins, and this impairment favors unabated thrombosis. As a second line of defense, fibrinolysis (primarily via plasminogen activation) is normally stimulated to dissolve the clots