Infectious Diseases
Lesson 2

SEPSIS SYNDROME

Bernardino Roca Villanueva
Servicio de Medicina Interna, Hospital General de Castellón
Departamento de Medicina, Universidad Jaume I
broca@uji.es
Objectives and learning goal
Objectives

• To know the definitions of sepsis and related conditions
• To review all clinically relevant concepts on sepsis and related conditions
Learning goal

To promptly recognize and to know how to manage a patient with sepsis
Contents

- **Definitions**
- **Epidemiology**
- **Etiology**
- **Pathogenies**
- **Clinical manifestations**
- **Analysis abnormalities**
- **Diagnosis**
- **Treatment**
- **Prognosis**
- **Prevention**
- **Key messages**
- **Further reading**
Definitions
Infection

- Pathological process caused by the invasion of normally sterile tissue or fluid or body cavity by pathogenic or potentially pathogenic microorganisms.
- Invasion and multiplication of microorganisms such as bacteria, viruses, and parasites that are not normally present within the body.
Systemic inflammatory response syndrome (SIRS)

At least two of the following conditions:

- Fever (oral temperature > 38 °C) or hypothermia (oral temperature < 36 °C)
- Heart rate > 90 beats per minute
- Tachypnea (> 24 respirations per minute), or hyperventilation (arterial Pa CO₂ < 32 mm Hg) or invasive or noninvasive ventilation needed
- Leukocytosis (> 12,000/mm³), or leukopenia (< 4,000/mm³), or > 10 % bands in white blood cell count
Sepsis

- Systemic inflammatory response syndrome (SIRS), and
- Infection, confirmed or suspected

\[
\text{Infection} + \text{SIRS} = \text{Sepsis}
\]
Causes of SIRS, partial list

- Infections
- Pulmonary embolism
- Myocardial infarction
- Dissection of the aorta
- Cardiac tamponade
- Acute pancreatitis
- Acute adrenal failure
- Burns
- Traumatisms
- Surgery
- Shock of any etiology
- Substance overdose
Severe sepsis

Sepsis + dysfunction of at least one organ or system different to the site of infection. For example:

- Cardiovascular: systolic blood pressure ≤ 90 mmHg, that responds to intravenous fluids
- Renal: urine output < 0.5 ml/kg per hour despite adequate fluid
- Respiratory: arterial PaO₂/FiO₂ ≤ 250
- Hematologic: platelet count < 80,000/mm³, or 50% decrease over the previous 3 days
- Metabolic acidosis: pH ≤ 7.30 and plasma lactate level > 1.5 times upper limit of normal
Septic shock

**Sepsis + at least one of the two following conditions:**

- Hypotension (systolic blood pressure < 90 mmHg, or 40 mmHg lower than patient’s normal) for at least 1 hour despite adequate fluid resuscitation

- Need for vasopressors to maintain systolic blood pressure ≥ 90 mm Hg or mean arterial pressure ≥ 70 mmHg

Sepsis + Maintained hypotension = Shock septic
SIRS

Infection + SIRS = Sepsis

Sepsis + Maintained hypotension = Septic shock
Refractory septic shock

Septic shock that ... 

- Lasts for >1 h, and
- Does not respond to
  - Fluid or
  - Vasopressor drug administration
Multiple-organ dysfunction syndrome

Dysfunction of more than one organ, requiring intervention to maintain homeostasis
In brief …

- Infection
  - Sepsis
    - Severe sepsis
      - Septic shock
        - Refractory septic shock
          - Multiple-organ dysfunction syndrome
Epidemiology
Impact of sepsis syndrome

- Incidence of severe sepsis or septic shock: 3 cases per 1,000 inhabitants and year
- 2/3 of sepsis cases in patients with significant underlying illnesses
- Occurs in 2% of all hospitalizations, in 10% of intensive care unit admissions
- Increase over last years due to:
  - Older population
  - Increased prevalence of chronic disease
  - Use of immunosuppressive drugs
  - Use of medical invasive procedures
Etiology
Causative microorganisms

- **Bacteriae:**
  - Gram-positive cocci
  - Gram-negative bacilli
  - Other
- Fungi
- Parasites
- Virus
Source of infection leading to sepsis

- Lungs
- Abdomen
- Genitourinary tract
- Wounds, including surgical
- Catheters
- Other
Pathogenesis
Factors influencing the pathogenesis of sepsis - I

- Microorganisms
  - Endotoxins (bacterial wall)
  - Exotoxins
- Host cells
  - Macrophages
  - Neutrophils
  - Endothelial cells
  - Dendritic cells
  - Lymphocytes
Factors influencing the pathogenesis of sepsis - II

• **Cytokines**
  • Tumor necrosis factor alpha
  • Interleukin-1
  • Interleukin-10
    
• **Other substances**
  • Oxygen derivatives
  • Nitric oxide
  • Lipid mediators

Proinflammatory
Antiinflammatory
Factors influencing the pathogenesis of sepsis - III

- Body systems activation
  - Coagulation and fibrinolysis
  - Complement
  - Neuroendocrine
- Organ dysfunction
  - Liver
  - Digestive tract
Factors influencing the pathogenesis of sepsis - IV

- Diverse cell receptor dysregulation
- Acceleration of apoptosis
- Genetic factors
- Iatrogenic effects
Infection, sepsis and inflammatory response

Infection → Immune system activation → Mediators

- Adequate response
  - Control and resolution of infection
- Hyperreactivity (SIRS)
  - Sepsis
- Hiporeactivity (immune paralysis)
  - Uncontrolled infection
Pathogenesis of sepsis

- Microorganisms
- Toxins
- Macrophages
  - TNF-α, IL-1
    - TNF-α, IL-1, IL-6, IL-8, IL-10, free radicals, proteases, bradikinin, platelet activator factor, prostaglandins, leukotrienes
    - Neutrophils
      - Adhesion to endothelium
        - Cell aggregation, microthrombi formation
    - Microvascular injury
  - Organic dysfunction
    - Ischemia
    - Extravasation

Detoxification: 
- TNF-α, IL-1, IL-6, IL-8, IL-10, free radicals, proteases, bradikinin, platelet activator factor, prostaglandins, leukotrienes
Endotoxins = lipopolisacarids (LPS) of bacterial wall

LPS binding protein (LPS-BP)

LPS + PC-LPS

CD14

Toll-like receptors

Macrophage

Proinflammatory cytokines
- Tumor necrosis factor - α
- Interleukins 1, 6, 8, etc.
- Interferon - γ
- Etc.
Pathogenesis of septic shock

• **Decreased systemic vascular resistance**, caused by:
  • Nitric oxide
  • Bradykinin
  • Prostacyclin

• Circulatory volume depletions caused by increased vascular permeability, etc.

• Abnormal distribution of blood among different organs
Clinical manifestations
Clinical manifestations come from ...

- ... concomitant illnesses
- ... the infection causing sepsis
- ... sepsis itself
  - General symptoms
  - Symptoms from different affected organs

Complex and varied clinical presentation
General manifestations

- Fever
- Hypothermia, alcohol abusers or old patients
- Hyperventilation
- Hypotension
- Signs of de DIC
  - Ischemia
  - Bleeding

Sepsis and DIC due to *Neisseria meningitidis*
Purpura and edema due to *N. Meningitidis* sepsis and DIC
Heart and lung manifestations

- Myocardiopathy
- Lung ventilation – perfusion mismatch → hypoxia
- Increased alveolar capillary permeability → adult respiratory distress syndrome → hypoxia
Adult respiratory distress syndrome
Adult respiratory distress syndrome
Neurologic manifestations

- Encephalopathy: obtundation and disorientation
- Worsening of previously present symptoms
- Polyneuropathy:
  - Axonal
  - Motor → weakness and muscular atrophy
  - Distal
  - Frequently impedes ventilator weaning
Skin manifestations

- Microorganisms and toxins → macules, papules, pustules, bullae, cellulitis, bruising, etc.
- DIC → petechiae and purpura
- Peripheral hypoperfusion → slow capillary filling, distal cyanosis and necrosis
Macules and bullae
Morbilliform rash
Hand gangrene due to sepsis and DIC
Gastrointestinal manifestations

- Nonspecific gastrointestinal symptoms such as nausea, diarrhea, etc.
- Mild cholestasis
- Paralytic ileus
- Other conditions:
  - Stress ulcers in the stomach
  - Acute hepatocellular necrosis
  - Acute intestinal ischemia
Paralytic ileus

Normal

Paralytic ileus
Kidney manifestations

- Decreased urine output
- Renal failure
- Renal hypoperfusion → acute tubular necrosis
Analysis abnormalities
Frequent alterations - I

- Leukocytosis with left shift
- Thrombocytopenia
- Increased bilirubin and liver enzymes
- Respiratory alkalosis $\rightarrow$ metabolic acidosis
- Increased lactic acid
- Hyperglycemia
- Hypoalbuminemia
- Hypoxia
Toxic granulation and Döhle body (arrow)
Frequent alterations - II

- Increased creatinine and blood urea nitrogen
- Proteinuria
- DIC:
  - Prolonged prothrombin time, or increased international normalized ratio
  - Prolonged activated partial thromboplastin time
  - Decreases fibrinogen
  - Presence of D dimer or other fibrin degradation products
Diagnosis
Relevance and difficulties

- Sepsis, essentially a clinical diagnosis
- Must be diagnosis “asap”
- Differential diagnosis is extensive:
  - That of SIRS
  - That of shock
Helpful diagnostic procedures

- Microbiology studies:
  - Gram stain and culture of body specimens
  - Molecular techniques
  - Serologies and other tests
- Procalcitonin serum level:
  - ↑ in bacterial infections
  - Useful for diagnosis, prognosis and control of response to treatment
- Image studies
Pneumonia
Acute cholecystitis
Treatment
Principles of treatment

• Start treatment “asap”
• In an Intensive Car Unit (ICU) (or in an Emergency Room [ER])
• At the same time:
  • Control of infection
  • Supportive measures
Control of infection

- Drainage if needed:
  - Percutaneous needle aspiration
  - Surgery

- Antimicrobials:
  - After obtaining specimens for gram and culture
  - Individualize the election
  - Broad-spectrum → narrow-spectrum when possible
Supportive measures

Main objective: to maintain the provision of **oxygen** and other **vital substrates** to the distinct organs

If hypotension: intravenous perfusions → inotropic agents → corticosteroids → (vasopressin)

If hypoxia: noninvasive or invasive ventilation with low volumes

Other commonly needed treatments:
- Dialysis
- Transfusions
- Bicarbonate, if lactic acidosis
- Rehabilitation if clinical improvement
Antagonists of mediators of SIRS

- Drotrecogin-α (recombinant activated C-reactive protein)
  - Antiinflammatory
  - Antithrombotic
  - Anticoagulant
- Endotoxin antagonists
- Etc.
Prognosis
Sepsis, a condition with a grim prognosis

- **Death at 30 days:**
  - > 25% of those with severe sepsis
  - > 50% of those with septic shock

- **Factors that increase the risk of death:**
  - Advanced age
  - Preexistent comorbidity
  - Sepsis caused by hospital acquired pneumonia
  - Sepsis due to...
    - *Pseudomonas aeruginosa*
    - *Candida albicans*
    - Multiresistant *Enterococcus faecium*

- Sepsis is an independent predictor of death
Prevention
General measures

- Treatment of infections “asap”
- Any measures that prevent infections:
  - Adequate use of vaccines
  - Use of antibiotic prophylaxis when needed, as for example in advanced HIV-infection
  - Treatment of immunodeficiencies when feasible
  - Judicious use of immunosuppressants and invasive diagnostic procedures
  - Avoid the unjustified use of antibiotics
  - Etc.
Key messages
To remember...

- Sepsis is a very common condition that may adopt many clinical presentations
- Prompt diagnosis and treatment of sepsis is key to reduce mortality of the disease
Further reading
Used references


Preparing the exam


- These slides