LECTURE 9

SEPSIS. EXTRACORPOREAL TECHNIQUES FOR BLOOD PURIFICATION. DETOXICATION AND IMMUNOTHERAPY. SURGICAL ASPECTS OF AIDS AND DRUG ABUSE.

I. Actuality of theme.

Sepsis is the leading cause of death in noncoronary ICUs and the 13th leading cause of death in the United States overall. 751,000 cases of severe sepsis occur annually in the United States. More than 55% of these patients have underlying comorbidity, and more than one half of the cases occur in those aged 65 years and older. The incidence of sepsis is expected to rise during the next decade owing to the aging population, a growing immunosuppressed population, the increased use of invasive catheters and prosthetic materials, and the growing problem of antimicrobial resistance. In the year 2010, it is estimated that there will be 934,000 new sepsis cases in the United States and in 2020, 1,100,000.

II. Aims of lecture :

Educational:

- To describe the history of study of the sepsis (β=I);
- To elucidate the pathophysiology the inflammatory cascade and target therapy for septic patient (β=III);
- To expound the modern classification of sepsis (β=II);
- To characterize the main items in diagnosis and treatment of sepsis (β=II);
- To describe the methods of blood purification as a treatment for septic shock (β=III);
- To elucidate the immunotherapy for septic patients(β=III);
- To descride the surgical aspects of AIDS and drug abuse(β=III);
- To study the students the main principles of evidence-based medicine according the subject of lecture (β= IV).

Educative:

1. To educate for students sense of responsibility for every prescription, research, procedure, manipulation or surgery, for a health and renewal of capacity of patient, for the rightness of adequate estimation of the common state of patients and grant of timely effective treatment.
2. To develop deontological notion in the students, to study the students carry our deontological approach to drug abuse patients, patients with HIV infection.

III. Plan and organization of structure of lecture

№	Basic stages of lecture and their maintenance	Aims are in the levels of abstraction	Type of lecture, methods and facilities of activation of students, equipment	Division of time
1	Preliminary stage. Determination of educational aims and motivation.		Items I, II	5%
2	**Basic stage. Teaching of lecture's material** • The history of study of sepsis; • Pathophysiology the inflammatory cascade and the main goals of target therapy; • Classification of sepsis; • Diagnosis and treatment of sepsis; • Blood purification as a treatment for septic shock; • Immunotherapy for septic patients • Surgical aspects of AIDS and drug abuse	I III II II III III III	Type of lecture – thematic (with controversial elements – critical analysis of results of meta-analyses, randomized controlled, trials, guidlines which are devoted for the problem sepsis and blood purification). Facilities of activation of students are a questions, controversial situations, illustrative material	85%
3	Final stage (resume of lecture, general conclusions, answers to the possible questions, task for students for preparation for practical classes)		List of literature, question, task for students	10%

IV. Subject of a lecture

Sepsis is systemic infection accompanied by a reaction that has been termed the systemic inflammatory response syndrome (SIRS). SIRS represents an acute inflammatory reaction with systemic manifestations caused by release into the bloodstream of numerous endogenous mediators of inflammation. SIRS can also be caused by acute pancreatitis and major trauma, including burns. It has previously been defined by 2 or more of the following:

- Temperature > 38° C or < 36° C
- Heart rate > 90 beats/min
- Respiratory rate > 20 breaths/min or $Paco_2$ < 32 mm Hg
- WBC count > 12,000 cells/µL or < 4000 cells/µL, or > 10% immature forms

The term SIRS was coined in 1992 by a panel comprised of American College of Chest Physicians and Society of Critical Care Medicine members. They convened to develop consensus definitions of critical illness for the purposes of clinical trial design.
SIRS describes the host response to critical illness of either infectious or noninfectious etiology, such as burns, trauma, and pancreatitis. More specifically

- ***Sepsis* is SIRS** due to a presumed or known site of infection.
- ***Severe sepsis*** is sepsis with an acute associated organ failure.
- ***Septic shock*,** a subset of severe sepsis, is defined as a persistently low mean arterial blood pressure despite adequate fluid resuscitation.
- ***Refractory septic shock*** is a persistently low mean arterial blood pressure despite vasopressor therapy and adequate fluid resuscitation.

The History of Sepsis

As long ago as 2735 B.C., the Chinese Emperor, Sheng Nung, wrote about the use of herbal medicines to treat fever brought on by sepsis. In more recent history, many infections that cause sepsis have changed the course of history. There is the "Black Death" of the bubonic plague epidemic in medieval Europe, the deaths of New World natives exposed to Old World contagions imported by European colonists and the uncountable deaths of wounded war veterans in the American Civil War and many other armed conflicts.

The concept of anti-sepsis (an organized, rational effort to prevent and treat sepsis) was originated by John Pringle, Surgeon General of the British army in the 18th century. A century later, Ignaz Semmelweis introduced antiseptic techniques for the care of women during childbirth. Semmelweis's advances brought the death rate from puerperal fever down from 13.6% of all women who were giving birth to 1.5%. In 1879, the French physician Louis Pasteur identified the streptococcus

bacteria as the cause of puerperal sepsis. Thirteen years later, Richard Pfeiffer discovered that bacteria released poisonous endotoxins in the body of a person afflicted with sepsis. The recognition by Sir Alexander Fleming that a certain mold could be toxic to bacteria resulted in the discovery of penicillin and ushered in the modern era of antibiotic treatments.

Toward the end of the twentieth century, it became clear that sepsis causes the release of what are known as inflammatory mediators, (for example, tumor necrosis factor-alpha and interleukin-1(IL-I)). These and other mediators can cause hypotension (low blood pressure), damage to the cardiovascular system, and, ultimately, fatal damage to bodily organs and stroke.

Pathophysiology the inflammatory cascade

Severe sepsis can occur as a result of infection at any body site, including the lung, abdomen, skin or soft tissue, or urinary tract and as a result of a primary blood stream infection, such as meningococcemia. Bacteria are the pathogens most commonly associated with the development of sepsis, although fungi, viruses, and parasites do cause sepsis. The pathophysiology of sepsis is initiated by the outer membrane components of both gram-negative organisms (lipopolysaccharide [LPS], lipid A, endotoxin) and gram-positive organisms (lipoteichoic acid, peptidoglycan). These outer membrane components are able to bind to the CD14 receptor on the surface of monocytes. By virtue of the recently described toll-like receptors, a signal is then transmitted to the cell, leading to the eventual production of the proinflammatory cytokines tumor necrosis factor-alpha (TNF-alpha) and IL-I. These cytokines have a direct toxic effect on tissues; they also activate phospholipase A2. These and other effects lead to increased concentrations of platelet-activating factor, promotion of nitric oxide synthase activity, promotion of tissue infiltration by neutrophils, and promotion of neutrophil activity. Interleukin-1 and TNF-alpha also have direct effects on the endothelial surface. As a result of these inflammatory cytokines, tissue factor, the first step in the extrinsic pathway of coagulation, is expressed on the surfaces of the endothelium and of monocytes. Tissue factor leads to the production of thrombin, which is a proinflammatory substance itself. Thrombin results in fibrin clots in the microvasculature, a sequela most easily recognized in meningococcal septic shock with purpura fulminans. Fibrinolysis is also impaired during the septic process. IL-1 and TNF-alpha lead to the production of plasminogen activator inhibitor-1, a potent inhibitor of fibrinolysis. Proinflammatory cytokines also disrupt the body's naturally occurring modulators of coagulation and inflammation, activated protein C (APC) and antithrombin. Protein C circulates as an inactive zymogen, but in the presence of thrombin and the endothelial surface-bound protein thrombomodulin, is converted to the enzyme-activated protein C. Proinflammatory cytokines can shear thrombomodulin from the endothelial surface as well as lead to downregulation of

this molecule and, thus, prevent the activation of protein C. APC with its cofactor protein S turn off thrombin production by cleaving factor Va and VIIIa. APC also restores fibrinolytic potential by inhibiting plasminogen activator inhibitor-1. In vitro studies reveal that APC has direct anti-inflammatory properties, including inhibiting the production of proinflammatory cytokines by LPS-stimulated monocytes, inhibiting leukocyte adhesion and rolling, and inhibiting neutrophil accumulation.Antithrombin is the second naturally occurring endothelial regulator affected during sepsis. Antithrombin inhibits thrombin production at multiple steps in the coagulation cascade as well as by directly binding and inhibiting thrombin. Antithrombin, when bound to endothelial cell surface glycosaminoglycans (GAGs), leads to the production of the anti-inflammatory molecule prostacyclin (PGI_2). Evidence exists that neutrophil elastase cleaves GAGs off the surface of the endothelial lining, thus limiting the anti-inflammatory properties of antithrombin.
As a result of the viscious cycle of inflammation and coagulation, cardiovascular insufficiency and multiple organ failure occur and often lead to death. Cardiovascular insufficiency can occur at the level of the myocardium as a result of the myocardial-depressant effects of TNF or at the level of the vessel, due to vasodilation and capillary leak.

Signs and symptoms

Clinical signs that may lead the physician to consider sepsis in the differential diagnosis include fever or hypothermia, unexplained tachycardia, unexplained tachypnea, signs of peripheral vasodilation, unexplained shock, and unexplained mental status changes. Laboratory or invasive hemodynamic measurements that suggest sepsis include increased cardiac output with a low systemic vascular resistance, increased oxygen consumption, leukocytosis or leukopenia, unexplained lactic acidosis, unexplained impairment in renal or liver function, a prolonged prothrombin time, thrombocytopenia, unexplained hypophosphatemia, and an increased C-reactive protein.

Conditions other than sepsis can produce a systemic inflammatory response and organ dysfunction. Noninfectious illnesses that should be considered in the differential diagnosis include tissue injury due to trauma, hematoma, venous thrombosis, myocardial or pulmonary infarcts, transplant rejection, pancreatitis, hyperthyroidism, addisonian crisis, drug or blood product reaction, malignancies, and central nervous system hemorrhages.

Diagnosis

The diagnosis of severe sepsis requires the presence of a presumed or known site of infection, evidence of a systemic inflammatory response, and an acute sepsis-associated organ dysfunction. Below is a description of the specific diagnostic criteria used in past clinical trials to define patients with severe sepsis.

1) A presumed or known site of infection is indicated by one of the following:

- Purulent sputum or respiratory sample, or a chest radiograph with new infiltrates not explained by a noninfectious process;
- Spillage of bowel contents noted during an operation;
- Radiographic or physical examination evidence of an infected collection;
- White blood cells in a normally sterile body fluid;
- Positive blood culture ;
- Evidence of infected mechanical hardware by physical or radiographic examination.

2) Evidence of a systemic inflammatory response is indicated by at least two of the following:

- *Fever or hypothermia*—Core body temperature of greater than or equal to 38ºC or less than or equal to 36ºC
- *Tachypnea*—greater than or equal to 20 breaths per minute or need for mechanical ventilation for an acute process
- *Tachycardia*—heart rate greater than or equal to 90 beats per minute, unless the patient has a preexisting tachycardia
- *White blood cell count*—greater than or equal to 12,000 cells/mm^3 or less than or equal to 4,000 cells/mm^3, or greater than 10% bands on differential

3) A sepsis-induced organ failure is indicated by one of the following criteria:

- *Cardiovascular dysfunction*—mean arterial pressure less than or equal to 60 mm Hg, the need for vasopressors to maintain this blood pressure in the face of adequate intravascular volume (central venous pressure greater than 8 or pulmonary artery occlusion pressure greater than 12), or after an adequate fluid challenge has been given
- *Respiratory organ failure*—an arterial oxygen pressure/fraction of inspired oxygen ratio less than 250 in the absence of pneumonia or less than 200 in the presence of pneumonia
- *Renal dysfunction*—urine output less than 0.5 mL/kg/hr for 1 hour in the face of adequate intravascular volume or after an adequate fluid challenge
- *Hematologic dysfunction*—thrombocytopenia with 80,000 platelets/mm^3, a 50% drop in the previous 3 days, or a prothrombin-INR greater than 1.2 that cannot be explained by liver disease or concomitant warfarin usage
- *Unexplained metabolic acidosis*—a pH less than 7.30 and a plasma lactate greater than 1.5 times the upper limit of normal for the laboratory

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are inflammatory disorders of the lung most commonly caused by sepsis, pneumonia, trauma, and/or aspiration. ALI and ARDS are characterized by hypoxemia and diffuse infiltrates on chest x-ray in the absence of elevated left atrial pressure. ALI

and ARDS differ only in the degree of hypoxemia. Diagnosis is by clinical presentation, ABGs, and imaging studies. Treatment is with lung-protective, low tidal volume mechanical ventilation, supportive therapy, and treatment of underlying causes. Mortality is still high (30 to 40%) and worsens with age and comorbidities, although overall mortality rates have declined in the past decade.

Treatment of sepsis

The International Sepsis Forum, a group of experts in the field of critical care and infectious diseases, has developed guidelines on the management of severe sepsis and septic shock.. Below is an evidenced-based summary of the treatment recommendations for the management of severe sepsis, with updates based on recent literature. Management of the infection responsible for severe sepsis should focus on two critical issues: the use of appropriate antimicrobial therapy and adequate source control of infection.

Appropriate Antimicrobial Therapy

When the clinician is faced with a patient with severe sepsis, the site of infection and the causative organism or organisms often are not known. Empiric antibiotics must be given in these cases. Appropriate empiric antimicrobial therapy must be guided by the knowledge of the most common site of infection and the most common infecting organisms. A recent clinical trial of patients with severe sepsis revealed that the lung is the most common site of infection followed by the abdomen. In terms of pathogen type, gram-positive organisms and gram-negative organisms cause sepsis with equal frequency; fungal organisms account for fewer cases. The most common gram-positive organisms are *Staphylococcus aureus* and *Streptococcus pneumoniae*, and the most common gram-negative organisms are *Escherichia coli*, *Klebsiella* species, *Pseudomonas* species, and *Enterobacter* species.

The following guidelines should be considered in providing appropriate empiric antimicrobial therapy to patients with severe sepsis:

- **Community-acquired pneumonia**
  Patients should receive a macrolide agent and a third-generation cephalosporin, or a respiratory quinolone alone.
- **Nosocomial pneumonia**
  If *P aeruginosa* is suspected, patients should receive a beta-lactam agent active against nosocomial pathogens with an aminoglycoside. The use of a carbapenem or quinolone should be considered when an extended-spectrum beta-lactamase-producing *Enterobacter* or *Klebsiella* is suspected based on knowledge of the ICU microbiology, in patients with a prolonged or multiple hospital stay, or in patients who had received multiple antibiotics in the past. Vancomycin can be added if a high rate of methicillin-resistant S aureus (MRSA) infection occurs in one's institution.

- **Intra-abdominal sepsis**
  Antibiotics should be given that treat enteric gram-negative rods and anaerobes.
- **Intravascular catheter infections or prosthetic device infections**
  Empiric coverage for gram-negative and gram-positive organisms should be given while awaiting microbiology data. Vancomycin should be given for MRSA if the incidence is high at the institution.

Empiric antifungal therapy should be given in patients at high risk for fungemia. High-risk patients include those who have had prior colonization with *Candida* at two or more sites, those being treated with more than two different antibiotics, those who have taken antibiotics for more than 14 days, those who have had prior placement of a Hickman catheter, and those who have undergone prior hemodialysis.

Source Control of Infection

Adequate source control of infection is as important as appropriate antimicrobial therapy in the treatment of a patient with severe sepsis. Source control of infection includes removal of infected foreign bodies, such as urinary catheters, intravascular catheters, peritoneal dialysis cannulas, prosthetic joints, vascular grafts, and mechanical valves. Incision and drainage of cutaneous abscesses as well as either open or percutaneous drainage of intra-abdominal abscesses also fall under the principle of adequate source control of infection. Furthermore, one specific clinical scenario requires specific mention. For patients with necrotizing fasciitis, mortality and extent of tissue loss are directly related to the rapidity of surgical intervention.

Hemodynamic Support

The first principle of hemodynamic support in the patient with septic shock is to provide adequate fluid resuscitation. Fluid resuscitation will produce tissue perfusion as indicated by these clinical endpoints: physical examination, urine output, central venous pressure, or pulmonary artery wedge pressure. The use of packed red blood cells as fluid resuscitation to achieve a hemoglobin of 10.0 mg/dL has not been shown to be more beneficial than transfusing patients to a hemoglobin level of 7.0 mg/dL. With respect to vasopressor therapy, norepinephrine was shown in a randomized study to be superior to dopamine in volume-resuscitated hyperdynamic sepsis syndrome. The use of epinephrine should be avoided in the setting of sepsis because this agent has harmful effects on gastric blood flow and lactate levels. In addition, the use of *renal-dose* dopamine to treat or prevent acute renal failure is not justified. When cardiac output is low in a patient with septic shock, dobutamine remains the inotropic agent of choice.

Therapy for patients with refractory septic shock requires particular attention. As many as 76% of septic shock patients unresponsive to fluid resuscitation and vasopressor therapy are adrenally hyporesponsive as defined by a less than 9 mg/dL rise in the cortisol level from baseline following an adrenocorticotropic hormone (ACTH) stimulation test. Administration of 50 mg intravenous hydrocortisone every 6 hours with 50 μg oral fludrocortisone every day for 7 days improved survival when compared with placebo in patients with refractory septic shock and adrenal hyporesponsiveness. Therefore, administration of an ACTH stimulation testing followed by treatment with the above regimen in patients with refractory septic shock and adrenal hyporesponsiveness is recommended.

Additional Treatment Components

Three additional components in the care of severe sepsis patients include ensuring adequate nutrition, providing deep venous thrombosis prophylaxis, and providing gastric ulcer prophylaxis. Adequate nutrition is best accomplished enterically to avoid catheter-related bloodstream infections, to maintain gut mucosa integrity, and to prevent the theoretical possibility of translocation of bacteria across the intestinal wall. Enteral feedings containing arginine and omega-3 fatty acids have been shown to decrease the number of ICU and ventilator days as well as the number of infectious complications, but have not yet shown a mortality advantage over standard tube feedings. Deep venous thrombosis prevention can be accomplished with the use of subcutaneous heparin or continuous use of pneumatic compression stockings. Gastric ulcer prophylaxis may be accomplished with sucralafate, an H2 receptor antagonist, or a proton pump inhibitor.

Severe sepsis refers to patients with sepsis and acute organ dysfunction (eg, acute renal failure or respiratory failure); these patients have a mortality rate of approximately 40%. Septic shock refers to sepsis patients with arterial hypotension that is refractory to adequate fluid resuscitation, thus requiring vasopressor administration. These patients often require intensive care, consume substantial healthcare resources, and ultimately die in 50% to 80% of cases.

Septic shock carries the greatest risk of dying for all patients with sepsis. The cornerstone of management for these patients is antibiotic therapy and hemodynamic support. Hemodynamic support is targeted toward restoring tissue perfusion in order to promote aerobic cellular function. This target is achieved by raising the arterial blood pressure through a combination of fluid resuscitation and vasopressor administration. The practical application of these goals has been codified in guidelines published in the form of the Surviving Sepsis Campaign and the Practice Parameters for Hemodynamic Support in Sepsis by the Society of Critical Care Medicine. The general schema for both of these documents is an evidence-based and practical approach to hemodynamic management in sepsis. One of the first goals in managing these patients is to define the goals or endpoints

for hemodynamic support and ensure that there is a (reasonably) objective measurement against which to judge the adequacy of the applied interventions. For example, if hemodynamic support is targeted to restoring a mean arterial pressure of 65 mm Hg, then measurements of arterial blood pressure should be accurate and readily available. A closely related concept for resuscitation is that early restoration of tissue perfusion is important, and delays should not be incurred because of patients being in a temporarily inappropriate environment (for instance, outside the intensive care unit).

Fluid Resuscitation

For sepsis patients who require only limited intervention to restore tissue perfusion, such as small-to-moderate volumes of crystalloid fluid resuscitation, more invasive measures may not be required, and these patients may simply be serially monitored for continued progress or any deterioration. For patients requiring more aggressive measures to correct tissue perfusion or organ dysfunction, additional hemodynamic monitoring may be appropriate. Central venous catheterization, with measurements of central venous pressure and/or $ScvO_2$, is an appropriate next step to guide resuscitation. During the resuscitation period, transfusion of red blood cells should be considered for patients who are significantly anemic or have evidence of deficient tissue oxygen delivery.

Vasopressors

When sufficient intravenous fluids have been administered and hypotension or tissue hypoperfusion remains a problem, then vasopressors should be added. This was an area of particular evolution over the past decade, when dopamine was the vasopressor of first choice in septic shock. It is now considered that norepinephrine (NE) should generally be the vasopressor of first choice for these patients. Substantial interest has grown for arginine vasopressin (AVP) as a second-line agent in treating patients with refractory septic shock. Although AVP is not used as a typical titratable infused vasoconstrictor, low fixed doses of AVP may be an effective addition to NE, particularly given that it works through a different pathway to stimulate vasoconstriction.

Sepsis Immunotherapy (cytokines)

TNF-a is a pro-inflammatory cytokine, which is regarded as an important mediator of sepsis. Serum levels have been shown to correlate with outcome in both animal and human models of sepsis. Therefore, much of the early work in immunotherapy focused on TNF-a, either by producing antibodies to it or blocking its receptors. While this strategy showed much promise in animal studies, TNF targeted immunotherapy has failed to demonstrate a benefit in humans. NORSEPT and INTERSEPT (International Sepsis Trial) were two trials conducted in North America and Europe, respectively, which compared TNF-a monoclonal

antibody with placebo in septic patients. Interim analysis in the NORSEPT trial indicated that there was a higher mortality in patients receiving antibody than those receiving placebo in patients without shock. Thereafter, both trials restricted entry to those patients with septic shock. The primary endpoint measured was 28-day mortality at which no significant difference in outcome was seen between the two groups. However, the NORSEPT study did show a dose-dependant decrease in three-day mortality in the patients receiving the TNF-a antibody. Furthermore, the INTERSEPT study demonstrated more rapid resolution of shock and decreased progression to multi-organ failure, in those who survived 28 days, than in the group receiving the study antibody.
Another strategy to reduce the effects of systemic TNF-a in sepsis has been through the development of a recombinant receptor which competes for circulating TNF-a. The design of this receptor (p75) has been such as to increase its affinity for the circulating cytokine. While it has shown some promise in animal studies, it had deleterious effects in the only human clinical trial conducted using it. It was found to produce a dose-dependant increase in mortality as compared with placebo. This surprising result may have been due to the retention of receptor-TNF-a complexes in the serum with subsequent delayed release of TNF-a.

Extracorporeal techniques in treatment of sepsis and septic shock

Extracorporeal therapies designed to remove substances from the circulation now include hemodialysis, hemofiltration, hemoadsorption, plasma filtration, cell-based therapies and combinations of any of the above.
Hemodialysis is a method for removing waste products such as potassium and urea, as well as free water from the blood when the kidneys are incapable of this (i.e. in renal failure). It is a form of renal dialysis and is therefore a renal replacement therapy.
Hemofiltration is a renal replacement therapy similar to hemodialysis which is used almost exclusively in the intensive care setting. Thus, it is almost always used for acute renal failure. It is a slow continuous therapy in which sessions usually last between 12 to 24 hours and are usually performed daily. During hemofiltration, a patient's blood is passed through a set of tubing (a filtration circuit) via a machine to a semipermeable membrane (the filter) where waste products and water are removed. Replacement fluid is added and the blood is returned to the patient.

Hemofiltration is most commonly used in an intensive care unit setting, where it is either given as 8-12 hours treatments, so called SLEF (slow extended hemofiltration), or as CHF (continuous hemofiltration also sometimes called continuous veno-venous hemofiltration (CVVH)). Hemodiafiltration (SLED-F or

CHDF or CVVHDF) also is widely used in this fashion. In the United States, the substitution fluid used in CHF or CHDF is commercially prepared, prepackaged, and sterile (or sometimes is prepared in the local hospital pharmacy), avoiding regulatory issues of on-line creation of replacement fluid from dialysis solution.
With slow continuous therapies, the blood flow rates are usually in the range of 100-200 ml/min, and access is usually achieved through a central venous catheter placed in one of the large central veins. In such cases a blood pump is used to drive blood flow through the filter. Native access for hemodialysis (eg AV fistulas or grafts) are unsuitable for CHF because the prolonged residence of the access needles required might damage such accesses.
Plasmapheresis is the removal, treatment, and return of components of blood plasma from blood circulation. It is thus an extracorporeal therapy. The method can also be used to collect plasma for further manufacturing into a variety of medications.
An important use of plasmapheresis is in the therapy of autoimmune disorders, where the rapid removal of disease-causing autoantibodies from the circulation is required in addition to slower medical therapy. Other uses are the removal of blood proteins where these are overly abundant and cause hyperviscosity syndrome.
Examples of diseases that can be treated with plasmapheresis:

- Guillain-Barré syndrome
- Chronic inflammatory demyelinating polyneuropathy
- Goodpasture's syndrome
- Hyperviscosity syndromes:
    - Cryoglobulinemia
    - Paraproteinemia
    - Waldenström macroglobulinemia
- Myasthenia gravis
- Thrombotic thrombocytopenic purpura /Hemolytic Uremic Syndrome
- Wegener's granulomatosis

Extracorporeal membrane oxygenation (ECMO) is an extracorporeal technique of providing both cardiac and respiratory support oxygen to patients whose heart and lungs are so severely diseased that they can no longer serve their function.
There are several forms of ECMO, the two most common of which are veno-arterial (VA) and veno-venous (VV). In both modalities, blood drained from the venous system is oxygenated outside of the body. In VA ECMO, this blood is returned to the arterial system and in VV ECMO the blood is returned to the venous system. In VV ECMO, no cardiac support is provided.

More recently, extracorporeal techniques have been employed in both adults and children in treating sepsis. Extracorporeal therapies for sepsis include continuous renal replacement (CRRT), plasma-based removal techniques, and ECMO. These treatments could theoretically 1) provide immunohomeostasis of pro- and anti-

inflammatory cytokines and other sepsis mediators, 2) decrease organ microthrombosis through removal of pro-coagulant factors and modulating the impaired septic coagulation response in sepsis, and 3) provide mechanical support of organ perfusion during the acute septic episode to allow time for response to traditional sepsis therapies and antimicrobials. CRRT is beneficial in managing fluid overload and acute renal failure in sepsis. Removal of sepsis mediators through the technique is variable, and the outcome impact of CRRT on sepsis has not been definitively determined. High-flow CRRT has demonstrated benefit in septic adults. Intriguing early results suggest that plasma exchange could improve outcomes in both adults and children. Based on experience, ECMO is recommended for refractory septic shock in neonates and should be considered for use in children. Ongoing trials may help determine whether the promise of extracorporeal therapies translates into outcome improvement in septic children.

Surgical aspects of AIDS and drug abuse

Drug abuse has a wide range of definitions related to taking a psychoactive drug or performance enhancing drug for a non-therapeutic or non-medical effect. Some of the most commonly abused drugs include alcohol, amphetamines, barbiturates, cocaine, methaqualone, opium alkaloids, and minor tranquilizers. Use of these drugs may lead to criminal penalty in addition to possible physical, social, and psychological harm, both strongly depending on local jurisdiction. Other definitions of drug abuse fall into four main categories: public health definitions, mass communication and vernacular usage, medical definitions, and political and criminal justice definitions.

"Intravenous (IV) drug user" is now the preferred term instead of the previous, broad term of "drug abuser". This term also places the focus on the major common cause of these medical complications—needle use. Although the term intravenous drug user excludes subcutaneous usage and the inhalation route used for "crack" cocaine intoxication, we use it because of its connection with the major infectious disease complications.

Skin infections in IV drug users

Skin and soft tissue bacterial infections are a common complication of intravenous drug use. This high rate is due to:

- Injection of drugs into the fatty layer under the skin (skin popping);
- Leakage of drugs out of veins during the injection (extravasation);
- Tissue death (necrosis) due to toxic materials in drugs;
- Increased numbers of bacteria on the skin surface.

Skin and soft tissue lesions, once the most common reason for emergency room visits by intravenous drug users, result from the nonsterile injections, sharing of equipment, poor personal hygiene, subcutaneous injection into deltoid muscles and thighs in the absence of an available vein, or injection into the veins of the neck or groin. Some active intravenous drug users have stigmata (scars due to old abscesses or "track marks," a darkening of the skin over the antecubital veins, which is literally tattooing with carbon particles and other materials pushed under the skin). It is easy to understand how these repeated injections result in cellulitis, skin abscess, septic thrombophlebitis, necrotizing fasciitis, gas gangrene, pyomyositis, localized Fournier gangrene , lymphedema, or even infected, pulsatile pseudoaneurysms of the neck or groin.

The microorganisms involved in the skin and local vascular infections vary, but Staphylococcus aureus is the main agent, followed by various streptococci, aerobic gram-negative rods, anaerobic cocci, and bacilli. The same range of organisms has been found in the metastatic bone and joint infections and the endocarditis of intravenous drug users.

However, new and unique symptoms continue to be reported; a syndrome of severe dermatitis, eosinophilia, and dermatopathic lymphadenopathy has recently been described in two intravenous drug users with dual infection with HIV-I and human T-lymphotropic virus II.

Clinical Features

Although skin infections usually present as areas of redness, warmth and tenderness (inflammation), the appearance in intravenous drug users is often atypical. This is because the skin, venous and lymphatic systems are damaged by the frequent penetration of the skin and consequent low-grade infection.
The results are:

- Swelling due to blocked lymphatic vessels;
- Swollen lymph glands;
- Darkly pigmented skin of the affected area;
- Scarring.

Fever may or may not be present but bloodstream infection (septicaemia) is uncommon, unless the individual is immune suppressed (e.g. HIV infection). Infections usually affect the arms or legs as these are the sites used most frequently for injection. Unusual sites may be involved (eg. abdomen, back, groin, scrotum and neck) due to injections in the jugular (neck) or femoral (groin) veins.

Types of Infection

Cellulitis

Cellulitis is usually caused by Group A streptococci or Staphylococcus aureus.

Abscess

Abscesses are collections of pus. They are usually caused by infection with Staphylococcus aureus but in drug users they occasionally contain a mixture of aerobic bacteria (that require oxygen) and anaerobic bacteria (that do not require oxygen). These mixed abscesses often result in a foul odour.

Skin ulcers

Skin ulcers are common in intravenous drug users. They are generally shallow but have hardened edges. The ulcers are thought to arise from a combination of inflammation around foreign bodies (ie. material from injected drugs) and infection. They can heal with good wound care and oral antibiotics but occasionally require skin grafting.

Necrotising Fasciitis

Necrotising fasciitis is a rare but life-threatening complication of intravenous drug use. In drug users, it most frequently affects an injection site on the left arm. It presents as an area of cellulitis i.e. red, swollen, tender skin with a fever. However the affected area is exquisitely painful and tender and the patient is much sicker and may collapse in shock. There may be crepitus: this is a crackling, popping sensation under the skin due to gas in the soft tissues.

Necrotising fasciitis in drug users may be caused by a variety of bacteria including Staphylococcus aureus, aerobic and anaerobic streptococci, Gram-negative bacilli from the gut and other anaerobes.

Management involves immediate surgical exploration of the tissue to drain the pus and remove all the dead skin. Broad spectrum antibiotics such as amoxicillin with clavulanic acid or a combination of vancomycin or flucloxacillin and metronidazole and an aminoglycoside are required.

Necrotising fasciitis in intravenous drug users is less likely to result in death or amputation than in non-drug users. The better outcome may be because it affects less dangerous sites (ie. limbs versus buttocks and trunk) or because the patients are generally younger and are less likely to suffer from a predisposing illness such as diabetes.

Septic thrombophlebitis

Septic thrombophlebitis is an infected blood clot in a vein, which may be life-threatening. The effects of septic thrombophlebitis may include:

- Redness, swelling and tenderness of the skin overlying a vein;
- Pus draining from the vein;
- Septic clots in the blood vessels of the lungs (pulmonary emboli);
- Bloodstream infections (septicaemia);

Treatment is with intravenous antibiotics. These should be broad-spectrum until cultures confirm the causative organism(s). If possible, the affected vein should be tied off and removed surgically.
Miscellaneous Infections Much rarer infectious complications of intravenous drug use that have characteristic skin findings include:

- Botulism due to Clostridium botulinum toxin, with progressive cranial nerve paralysis
- Tetanus due to Clostridium tetani, resulting in seizures & muscle spasms
- Widespread candida infection
- Heart valve infection (endocarditis)
- HIV infection and AIDS
- Liver disease (hepatitis).

HIV constitutes one of the most difficult challenges facing the healthcare profession today. It is estimated that HIV infects over 40 million people in the world and 14 million have died from the disease so far.

As the prevalence of the HIV infection continues to rise, healthcare workers in all geographic regions can expect greater clinical exposure to patients with HIV/AIDS. Thus HIV/AIDS infected individuals may present with surgical problems common to the general population. A survey conducted in 2003 by the *Department of Oral and Maxillofacial Surgery, Preventive Dentistry, Surgery of Awolowo University* in Nigeria showed that almost half (41.5%) of the surgeons had operated on a known HIV/AIDS infected individuals; besides, this is probably an underestimate as many HIV-positive individuals have never been tested and are therefore unaware of their status.

When surgery started dealing with the stigma of AIDS some surgeons avoided operating on HIVpositive patients, as they were worried to contract the virus. Moreover, especially in the United States a surgeon who was known to be positive could have his career, practice and reputation severely damaged. Yet many scientific organisations and societies have underlined that it is unethical to screen an individual without consent or to exclude an HIV/AIDS infected from treatment or to refer them to other colleagues and that there is an ethical duty to treat all patients without being influenced by any eventual seropositivity, but adopting the highest measures against cross infection. Furthermore, it has been established that HIV positive surgeons can continue their clinical activity and practice of surgical interventions.

Surgical indication is complex and must come after an evaluation of the stage according to the criteria established by the *Centre for Disease Control (CDC)of Atlanta*, and after an assessment of the performance status and of the possible

therapeutic options.Pre-operative HIV screening of patients is not necessary, as all the patients must be considered as potentially infectious.

Surgical management includes the same standard precautions necessary for cross infection control such as the uses of goggles with side screens and double gloving and anaesthetic procedures are not different from those ones for non-HIV patients. Must be reduced the incidence of any eventual exposition to biological fluids during the intervention and must be adopted an indirect sharp instrument passing technique.

On the contrary mortality is not significantly high in HIV patients; thus there is no increase of mortality during mini-invasive procedures compared to that normally occurring during traditional thoracotomies or laparoscopies. Generalised lymphoadenopathy is a common symptom of HIV infections. Fine needle aspiration usually gives sufficient diagnostic information. Surgical biopsy is requested in case you need to confirm and classify a lymphoma, tuberculosis, lymphoadenitis. Kaposi's sarcoma is a rare cutaneous tumour quite common in AIDS patients. The surgeon is involved in the diagnosis and the control of complications. Thrombocytopenic purpura can appear in asymptomatic HIV patient and AIDS patient as well. Ahtiretroviral therapy has showed an increment in plateletscount. Splenectomy is indicated only to control purpura in those selected cases not responding to therapy.

Emergency Surgery in HIV patient includes different pathologies like internal organs perforations and peritonitis related to Cytomegalovirus , Cryptosporodium, Candida. Obstruction and haemorrhage are possible complications of lymphomas and Kaposi of gastrointestinal tract.

Opportunistic infections can involve gallbladder and biliary tract. Acute cholecystitis demands an urgent cholecystectomy. Biliary tract obstruction caused by sclerosing cholangitis and ampullary stenosis is treated by ERCP. The obstruction can also be caused by hyperplastic portal lymph nodes and commob bile duct lymphoma as well.

The anal rectal pathology is one the most common surgical problem in HIV patient. Anal condylomata, anal squamous cell carcinoma, perianal fistula and abscess are the most frequent cases. Regarding gynaecological diseases PID is the most frequent one very often with severe presentation and Fits-Hughs Curtis Syndrome. HIV patients present very often a variety of thoracic diseases. Kaposi's sarcoma, lymphoma, opportunistic infection like Pneumocystis Jirovecii are common and tuberculosis pleural effusion and empyema as well.

Concerning orhopaedic surgery the earlier studies report increased frequency of infection after open reduction of fractures in HIV patient, although too little is known about the relationship between HIV and implant sepsis. The risk of wound infection increases as the immunity deteriorates. In conclusion surgical procedures in HIV individuals present with indications and characteristics common to non-HIV population. In particular there are no statistically significant differences between the surgical success rate and mortality and morbidity rates.

V. Materials of activation of students

(questions, tasks, controversial situations, illustrative materials and other).

VI. Materials of selftraining of students on the topic of lecture: literature, questions, tasks.

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