Ministry of Health of the Republic of Belarus
Educational Institution
“Gomel State Medical University”

Department of Pathological Anatomy

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METHODICAL GUIDELINES

for conducting a practical class
in the academic discipline “Pathological Anatomy”
for students
of the 3rd year, Faculty of International Students (instruction in English),
enrolled in the specialty
7-07-0911-01 “General Medicine”

Topic: “Infectious pathology: sepsis, high consequence infectious diseases (HCIDs)”

Duration: 3 hours

Approved at the meeting of the Department of Pathological Anatomy
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EDUCATIONAL AND INSTRUCTIONAL GOALS, OBJECTIVES, AND MOTIVATION FOR MASTERING THE TOPIC

Educational Goal:

- To study the definition, classification, etiology, pathogenesis, morphology, complications, and outcomes of sepsis. To define sepsis as life-threatening organ dysfunction caused by a dysregulated host response to infection. To discuss the continuum: infection → bacteremia → systemic inflammatory response syndrome (SIRS) → sepsis → severe sepsis (with acute organ dysfunction) → septic shock (with persistent hypotension) → multiple organ dysfunction syndrome (MODS). To analyze the etiological agents: bacteria (Gram-positive – Staphylococcus, Streptococcus; Gram-negative – E. coli, Klebsiella, Pseudomonas, Neisseria; anaerobes), fungi (Candida), viruses. To describe the pathogenesis: release of pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), activation of inflammatory cascade (cytokines – TNF, IL-1, IL-6, IL-8, chemokines), complement activation, coagulation dysregulation (disseminated intravascular coagulation – DIC), endothelial activation and injury, vasodilation, increased capillary permeability, hypotension, tissue hypoperfusion, multiorgan failure. To examine the morphological findings in sepsis: diffuse alveolar damage (DAD) – shock lung (hyaline membranes, edema, inflammation), acute tubular necrosis (ATN) in kidneys, centrilobular necrosis in liver (hypoxic), DIC (microthrombi in small vessels, hemorrhages), Waterhouse-Friderichsen syndrome (bilateral adrenal hemorrhage in meningococcemia), splenic and lymph node hyperplasia (reactive), lymphoid depletion, formation of microabscesses. To discuss the clinical criteria (qSOFA, SOFA), laboratory markers (procalcitonin, CRP, lactate, blood cultures), and causes of death (refractory shock, MODS, underlying disease).

Instructional Goal:

- Within the framework of the educational process for this academic discipline, the student must acquire not only theoretical knowledge, practical skills and abilities in the specialty but also develop their personal potential. They should cultivate qualities of responsibility and patriotism, be prepared to actively participate in the economic, socio-cultural, and public life of the country, recognize the social significance of their future professional activity, understand the norms of medical ethics and deontology, and learn to observe academic and labor discipline. In the course of studying the educational material, students should realize the importance of maintaining a healthy lifestyle and, as an example in the future, when performing professional duties, set an example for those around them and their patients.

Objectives: Upon completion of the practical session, the student must:

***Know*:**

- The definition and stages of sepsis (SIRS, sepsis, severe sepsis, septic shock, MODS);

- The pathogenesis of sepsis (inflammatory cascade, endothelial injury, DIC);
- The morphological changes in sepsis (diffuse alveolar damage, acute tubular necrosis, centrilobular necrosis, DIC, Waterhouse-Friderichsen syndrome);
- The clinical criteria and laboratory markers for sepsis diagnosis;
- The causes of death in septic patients.

Be able to:

- Recognize the morphological features of DIC (microthrombi, hemorrhages);
- Identify diffuse alveolar damage (hyaline membranes) on lung histology;
- Diagnose pathological processes and diseases based on the description of macroscopic and microscopic changes in organs and tissues of the body.

Master:

- Basic techniques for working with a microscope;
- Skills in clinical-anatomical analysis;
- The fundamentals of synthetic generalization of morphological diagnostic signs of diseases and their correct interpretation in cause-and-effect relationships.

Motivation for Mastering the Topic:

Sepsis is a major cause of morbidity and mortality worldwide, with millions of cases annually and a high case fatality rate, particularly in intensive care units. It is a medical emergency requiring prompt recognition and treatment. Understanding the pathophysiology and morphological changes in sepsis is essential for intensivists, infectious disease specialists, emergency physicians, surgeons, pathologists, and all clinicians involved in the care of critically ill patients. Sepsis can complicate any infection and often occurs in hospitalized patients, making it a critical topic for patient safety and quality improvement.

QUESTIONS

1. Sepsis. Diagnostic criteria. Morphology.
2. SOFA score.
3. Clinical and anatomical forms of sepsis.
4. Anthrax. Definition. Etiopathogenesis. Morphology. Clinical manifestations. Causes of death.
5. Plague. Definition. Etiopathogenesis. Morphology. Clinical manifestations. Causes of death.

COURSE OF THE SESSION

A **1991 consensus conference** developed initial definitions that focused on the then-prevailing view that sepsis resulted from a host's **systemic inflammatory response syndrome** (SIRS) to infection.

Sepsis complicated by organ dysfunction was termed **severe sepsis**, which could progress to **septic shock**, defined as "sepsis-induced hypotension persisting despite adequate fluid resuscitation."

A 2001 task force, recognizing limitations with these definitions, **expanded the list of diagnostic criteria** but did not offer alternatives because of the lack of supporting evidence. In effect, the definitions of sepsis, septic shock, and organ dysfunction have remained largely unchanged for more than 2 decades.

SIRS (Systemic Inflammatory Response Syndrome)

Two or more of:

- Temperature >38°C or <36°C
- Heart rate >90/min
- Respiratory rate >20/min or PaCO2 <32 mm Hg (4.3 kPa)
- White blood cell count >12 000/mm3 or <4000/mm3 or >10% immature bands

Recognizing the need to reexamine the current definitions, the European Society of Intensive Care Medicine and the Society of Critical Care Medicine convened a task force of 19 critical care, infectious disease, surgical, and pulmonary specialists in January 2014.

The task force sought to differentiate sepsis from uncomplicated infection and to update definitions of sepsis and septic shock to be consistent with improved understanding of the pathobiology.

A comparison of definitions of Sepsis

Table 2. Definitions of Sepsis, Severe Sepsis, and Septic Shock

Sepsis Category	Sepsis-3	2001 Sepsis	CMS SEP-1
Sepsis	SOFA score ≥ 2 + suspected infection	2 of 4 SIRS criteria + suspected infection	2 of 4 SIRS criteria + suspected infection
Severe sepsis	Not applicable	Sepsis + organ dysfunction, hypoperfusion, or hypotension	Sepsis + sepsis-induced organ dysfunction*
Septic shock	Vasopressor requirement to maintain MAP ≥ 65 mm Hg + serum lactate level > 2 mmol/L in the absence of hypovolemia	Sepsis-induced hypotension persisting after adequate IV fluid resuscitation + presence of perfusion abnormalities or organ dysfunction	• Lactate > 4 mmol/L • SBP < 90 mm Hg, not responsive to IV fluids **or** • MAP < 70 mm Hg, not responsive to IV fluids

*Organ dysfunction variables according to CMS SEP-1 include: SBP < 90 mm Hg or MAP < 70 mm Hg, or a SBP decrease > 40 mm Hg or < 2 SD below normal for age or known baseline; creatinine > 2.0 mg/dL (176.8 mmol/L) or urine output < 0.5 mL/kg/hr for > 2 hr; bilirubin > 2 mg/dL (34.2 mmol/L); platelet count < 100,000; coagulopathy (INR > 1.5 or aPTT > 60 sec); lactate > 2 mmol/L (18.0 mg/dL).

Abbreviations: aPTT, activated partial thromboplastin time; CMS, Centers for Medicare and Medicaid Services; INR, international normalized ratio; MAP, mean arterial pressure; SBP, systolic blood pressure; SD, standard deviation; SIRS, systemic inflammatory response syndrome; SOFA, sequential organ failure assessment.

Key Concepts of Sepsis

Sepsis is the primary cause of death from infection, especially if not recognized and treated promptly. Its recognition mandates urgent attention.

Sepsis is a syndrome shaped by pathogen factors and host factors (eg, sex, race and other genetic determinants, age, comorbidities, environment) with characteristics that evolve over time. What differentiates sepsis from infection is an aberrant or dysregulated host response and the presence of organ dysfunction.

Sepsis-induced organ dysfunction may be occult; therefore, its presence should be considered in any patient presenting with infection. Conversely, unrecognized infection may be the cause of new-onset organ dysfunction. Any unexplained organ dysfunction should thus raise the possibility of underlying infection.

The clinical and biological phenotype of sepsis can be modified by preexisting acute illness, long-standing comorbidities, medication, and interventions.

Specific infections may result in local organ dysfunction without generating a dysregulated systemic host response.

Definition of Sepsis

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.

Organ dysfunction can be identified as an acute change in total **Sequential Organ Failure Assessment** (SOFA) score ≥2 points consequent to the infection.

The baseline SOFA score can be assumed to be zero in patients not known to have preexisting organ dysfunction.

SOFA score ≥2 reflects an overall mortality risk of approximately 10% in a general hospital population with suspected infection. Even patients presenting with modest dysfunction can deteriorate further, emphasizing the seriousness of this condition and the need for prompt and appropriate intervention, if not already being instituted.

In lay terms, sepsis is a life-threatening condition that arises when the body's response to an infection injures its own tissues and organs.

Patients with suspected infection who are likely to have a prolonged ICU stay or to die in the hospital can be promptly identified at the bedside with qSOFA, ie, alteration in mental status, systolic blood pressure ≥100 mm Hg, or respiratory rate ≥22/min.

Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality.

Patients with septic shock can be identified with a clinical construct of sepsis with persisting hypotension requiring vasopressors to maintain MAP ≥65 mm Hg and having a serum lactate level >2 mmol/L (18mg/dL) despite adequate volume resuscitation. With these criteria, hospital mortality is in excess of 40%.

SOFA score

Table 1. Sequential Organ Failure Assessment Score

Variables	SOFA Score				
	0	1	2	3	4
Respiratory	PaO_2/FiO_2: > 400 SpO_2/FiO_2: > 302	PaO_2/FiO_2: < 400 SpO_2/FiO_2: < 302	PaO_2/FiO_2: < 300 SpO_2/FiO_2: < 221	PaO_2/FiO_2: < 200 SpO_2/FiO_2: < 142	PaO_2/FiO_2: < 100 SpO_2/FiO_2: < 67
Cardiovascular (doses in mcg/kg/min)	MAP ≥ 70 mm Hg	MAP ≥ 70 mm Hg	Dopamine ≤ 5 or ANY dobutamine	Dopamine > 5 Norepinephrine ≤ 0.1 Phenylephrine ≤ 0.8	Dopamine >15 or Norepinephrine > 0.1 Phenylephrine > 0.8
Liver (bilirubin, mg/dL)	< 1.2	1.2-1.9	2.0-5.9	6.0-11.9	> 12
Renal (creatinine, mg/dL)	< 1.2	1.2-1.9	2.0-3.4	3.5-4.9	> 5.0
Coagulation (platelets x $10^3/mm^3$)	≥ 150	< 150	< 100	< 50	< 20
Neurologic (GCS score)	15	13-14	10-12	6-9	< 6

According to Sepsis-3, a new (or presumed new) increase in SOFA score above baseline in the presence of infection makes the diagnosis of sepsis. Increasing SOFA scores are associated with incremental increases in mortality.

Abbreviations: GCS, Glasgow coma scale; FiO_2, fraction of inspired oxygen; MAP, mean arterial pressure; PaO_2, arterial oxygen pressure; SOFA, sequential organ failure assessment (score); SpO_2, oxygen saturation.

qSOFA (quick SOFA) criteria (Two or more)
Respiratory rate ≥22/min
Altered mentation
Systolic blood pressure ≥100 mm Hg

Anthrax

Anthrax is an acute infectious disease caused by **Bacillus anthracis**, a gram-positive, spore-forming, rod-shaped bacterium. It primarily affects herbivorous animals and can be transmitted to humans via **contact with infected animals**, their products (such as wool, hides, or meat), or contaminated environments. In humans, anthrax presents in four clinical forms: **cutaneous**, **inhalational** (pulmonary), **gastrointestinal**, and **meningeal**. Due to the durability of spores and the severity of systemic infection, anthrax is considered both a public health concern and a potential biological weapon.

Etiopathogenesis

B. anthracis can form environmentally resistant spores and produce potent exotoxins. Upon entry into the host, spores germinate into vegetative bacilli that replicate and secrete toxins. The bacterium possesses a poly-D-glutamic acid capsule, which impairs phagocytosis and allows for systemic dissemination. Two exotoxins—**lethal toxin** (LT) and **edema toxin** (ET)—interfere with host immune signaling. LT promotes macrophage lysis and systemic inflammatory responses, while ET increases intracellular cAMP, causing massive edema and disruption of endothelial integrity. The combined effects lead to hemorrhage, tissue necrosis, immune evasion, and progression to septic shock.

Anthrax: morphology

Macroscopically, anthrax is characterized by severe **hemorrhagic** and **edematous** changes.

Cutaneous lesions evolve from **papules to vesicles** and then to **necrotic ulcers** with a black eschar, often surrounded by extensive non-pitting edema.

Inhalational anthrax is associated with **hemorrhagic mediastinitis**, enlarged and hemorrhagic lymph nodes, **pleural effusion**, and **pulmonary edema**.

The *gastrointestinal form* shows **ulcers** and **hemorrhagic inflammation** throughout the mucosa, particularly in the **ileum and cecum**, with associated mesenteric lymphadenitis.

Histologically, there is **extensive hemorrhage and necrosis with minimal inflammatory response**, reflecting the rapid cytotoxic action of anthrax toxins. Large gram-positive bacilli may be seen within blood vessels or tissues; spores are usually absent in tissue sections.

The M'Fadyean stain demonstrates the characteristic capsule as a pink or purple halo.

Anthrax: clinical manifestations

Cutaneous anthrax, the most prevalent form, begins as a painless, pruritic **papule**, progressing to a **vesicle** and then to a **necrotic ulcer** with a central black eschar. Regional lymphadenopathy, fever, and systemic symptoms may develop.

Inhalational anthrax has a biphasic course: an initial prodrome **resembling viral illness** (fever, malaise, nonproductive cough), followed by rapid deterioration with **dyspnea**, **chest pain**, **hypoxia**, and **shock**. Radiological findings include mediastinal widening and pleural effusions.

Gastrointestinal anthrax presents with **abdominal pain**, **vomiting**, **hematemesis** or **bloody diarrhea**, and can mimic acute abdomen.

The *oropharyngeal variant* may present with severe **sore throat**, cervical **lymphadenopathy**, and **respiratory obstruction**.

Meningeal anthrax, either primary or secondary to other forms, manifests as **hemorrhagic meningitis** with rapid neurologic decline, seizures, and coma.

Multisystem involvement is common in **disseminated disease**.

Anthrax: causes of death

Mortality in anthrax typically results from overwhelming **toxemia** and **septicemia**.

Lethal toxin induces **massive cytokine release**, **endothelial damage**, and **multiorgan failure**.

Edema toxin exacerbates **vascular leakage**, leading to **hypovolemia** and **shock**.

In inhalational and gastrointestinal anthrax, delayed diagnosis and rapid progression often result in **fulminant disease**. Hemorrhagic mediastinitis, severe pulmonary edema, or hemorrhagic meningoencephalitis may directly contribute to death.

Disseminated intravascular coagulation (**DIC**), acute respiratory distress syndrome (**ARDS**), and refractory hypotension are common terminal events.

Plague

Plague is a highly contagious, acute zoonotic infection caused by **Yersinia pestis**, a gram-negative, non-motile, facultative intracellular coccobacillus of the Enterobacteriaceae family.

It is primarily transmitted to humans **through the bite of infected fleas**, direct contact with contaminated animal tissues (usually **rodents**), or **inhalation** of infectious respiratory droplets.

Plague exists in three main clinical forms: **bubonic**, **pneumonic**, and **septicemic**, each with distinct features but the potential for rapid progression and high mortality if untreated.

Plague has caused multiple historical pandemics and remains endemic in certain regions, posing ongoing public health risks.

Plague: etiopathogenesis

The pathogenicity of Y. pestis is attributed to multiple virulence factors encoded on plasmids and chromosomal genes.

After inoculation, the **bacteria resist phagocytosis** through the F1 capsular antigen and protein Yop (Yersinia outer proteins), which inhibit phagocytic cell activation and cytokine production.

Inside lymphatic tissues, Y. pestis proliferates massively, leading to **necrotizing lymphadenitis** (**bubo formation**).

Septicemic dissemination results in **vascular injury**, **DIC**, and **endotoxemia**.

Pneumonic plague, the most contagious form, arises from either hematogenous spread or primary inhalation and leads to **necrotizing bronchopneumonia**. A key feature of plague pathogenesis is the ability of Y. pestis to evade immune detection in early stages, allowing for exponential growth and systemic spread.

Plague: morphology

Grossly, *bubonic plague* presents with markedly **enlarged**, **hemorrhagic**, and **necrotic lymph nodes** (*buboes*), commonly in the **inguinal** or **axillary** regions.

Cutaneous manifestations may include **petechiae** or **ecchymoses** due to septicemia-induced **DIC**.

In *pneumonic plague*, **lungs are heavy, congested, and filled with hemorrhagic**, **purulent exudate**.

The gastrointestinal tract may show **ulcerations** and **hemorrhages** in *septicemic cases*.

Microscopically, buboes reveal **central necrosis** surrounded by **neutrophilic infiltrates** and **extensive hemorrhage**.

Bacteria may be seen extracellularly and within phagocytes, especially in systemic organs like the spleen, liver, lungs, and bone marrow.

Warthin-Starry or Giemsa stains can help visualize the characteristic bipolar ("safety pin") appearance of Y. pestis.

Plague: clinical manifestations

Bubonic plague, the most common form, presents acutely with sudden **fever, chills, headache, myalgia, and painful lymphadenopathy**. The affected lymph nodes become tense, fluctuant, and may suppurate. Without treatment, bubonic plague can progress to septicemia or secondary pneumonia.

Primary *septicemic plague* manifests with **fulminant bacteremia**, high fever, hypotension, vomiting, purpura, and multiorgan failure.

Pneumonic plague, either primary or secondary, has an abrupt onset with high fever, chest pain, productive cough with bloody sputum, dyspnea, and cyanosis. It is the **most lethal form** and may be transmitted person-to-person via droplets. In advanced stages, symptoms escalate rapidly to **septic shock, coma**, and **death**.

Plague: causes of death

Death in plague results from overwhelming **bacterial proliferation, septic shock, and multiorgan failure**.

The release of lipopolysaccharide endotoxin leads to **systemic inflammatory response syndrome** (SIRS), **hypotension**, and **DIC**.

In bubonic plague, untreated suppurative lymphadenitis can evolve into septicemia. In pneumonic plague, extensive alveolar damage and hemorrhage cause respiratory failure. Central nervous system involvement, though rare, may manifest as meningoencephalitis.

Myocardial depression, acute **renal failure**, and **disseminated necrosis in organs** are common terminal events. The rapid progression of untreated pneumonic or septicemic forms often leads to death within 24–72 hours.

INFORMATIONAL AND METHODOLOGICAL PART

MAIN LITERATURE

1. Pathomorphology : textbook / ed. by I.V. Sorokina, V.D. Markovskyi, D.I. Halata. - 2nd ed. - Kyiv : AUS Medicine Publishing, 2020. - 327 p., [10] col. inserts : tab.

2. Klatt, E. C. Robbins and Cotran Atlas of Pathology : [with Student Consult Online Access] / Edward C. Klatt. - third edition. - Philadelphia : Elsevier, 2015. - 587 p. : il.

3. Robbins Basic pathology / [ed. by] Vinay Kumar, Abul K. Abbas, Jon C. Aster. - 9th ed. - [Philadelphia] : Elsevier ; Saunders. - 910 p. : ill., scheme, tab.

ADDITIONAL LITERATURE

1. Sobotta. Atlas of human anatomy. [V. 1]. General anatomy and musculoskeletal system / ed. by F. Paulsen, J. Waschke. - 15th ed. - München : Elsevier. Urban & Fischer, 2011. - 400 p. : ill., col. ill.

2. Sobotta. Atlas of human anatomy. [V. 2]. Internal organs / ed. by F. Paulsen, J. Waschke. - 15th ed. - München : Elsevier. Urban & Fischer, 2011. - 259 p. : ill., col. ill.

3. Sobotta. Atlas of human anatomy. [V. 3]. Head, neck, and neuroanatomy / ed. by F. Paulsen, J. Waschke. - 15th ed. - München : Elsevier. Urban & Fischer, 2011. - 370 p. : ill., col. ill.

4. Weir & Abrahams' imaging atlas of human anatomy / ed.: J. D. Spratt [and oth.] ; consultant eds.: J. Weir, P. H. Abrahams. – 5th ed. - [S.l.] : Elsevier, 2017. - xvi, 263 p. : ill.

NORMATIVE LEGAL ACTS AND DOCUMENTS

1. Order of the Ministry of Health of the Republic of Belarus No. 111 of 06/01/1993 "On further improvement of the pathological service of the Republic of Belarus"

Access mode: http://patan.by/menyu/administrativnyie-proczeduryi.html - The date fccess: 20.03.2022.

ELECTRONIC DATABASES

1. Physician's consultant. Electronic Medical Library = Consultant of the doctor. Electronic medical library [Electronic resource] / Publishing group "GEOTAR-Media", LLC "IPUZ". – Access mode: http://www.rosmedlib.ru/ . – Access date: 03/15/2022.

2. Springer Link [Electronic resource] / Springer International Publishing AG. – Access mode: https:link.springer.com. – Date of access: 03/15/2022.