LECTURE 8

ACUTE SPECIFIC SURGICAL INFECTION. ANAEROBIC INFECTION. GAS GANGRENE.TETANUS. ANTHRAX. WOUND DIPHTHERIA.

I.Actuality of theme. The knowledge about specific surgical infections is necessary for all physicians. Anaerobic necrotizing soft-tissue infections (NSTIs) are highly lethal. They are frequent enough that general and specialty physicians will likely have to be involved with the management of at least 1 patient with NSTI during their practice, but they are infrequent enough that familiarity with the disease will seldom be achieved. Establishing the diagnosis of NSTI can be the main challenge in treating patients with NSTI, and knowledge of all available tools is key for early and accurate diagnosis.

In recent times some countries have cultivated anaerobic microorganisms (for example anthrax bacteria) as a weapon for biological warfare.

Tetanus is still a major problem worldwide. Although low mortality from tetanus is possible with improved intensive care technology, the disease should be virtually preventable by the provision of proper tetanus prophylaxis to all patients at risk. However, tetanus immunization and prophylaxis in the acute injury setting is frequently misused and misunderstood

Clinicians and microbiologists should be aware of the possibility of cutaneous diphtheria in chronically infected skin lesions in patients returning from disease-endemic regions (it especially important in connection with widespread of tourism). Medical personnel should include this in civilian as well as military health services, since our cases indicate that toxigenic *C. diphtheriae* might affect not only travel-related skin injuries caused by leisure or tourist activities but also wounds in patients from war regions in diphtheria-endemic areas.

II. Aims of lecture :

Educational:

- To describe clinical appearence of antrax, anaerobic infection, tetanus, wound diphtheria (β=II);
- To elucidate the classification of anaerobic infection (β=II);
- To expound the methods of prevention and treatment of antrax, anaerobic infection, tetanus, wound diphtheria (β=II);
- 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 form for students skills of clinical thought in the process of intercourse with the patients. To teach students to adhere to principles of medical

deontology and bioethics in the process of socializing with a patient, his relatives, and also with colleagues.

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** Frequency and clinical appearence of antrax, anaerobic infection, wound diphtheria, tetanus; Classification of anaerobic infection; Diagnosis, prevention and treatment of antrax, anaerobic infection, tetanus, wound diphtheria.	II II II	Type of lecture – thematic (with controversial elements – critical analysis of results of meta-analyses, randomized controlled, trials, guidlines which are devoted for the problem of acute specific surgical infection). 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

Anthrax is described in the early literature of the Greeks, Romans, and Hindus. The fifth plague described in the book of Genesis may be among the earliest descriptions of anthrax. Most of the terms associated with anthrax relate to cutaneous or respiratory anthrax. Cutaneous anthrax results from exposure to the spores of Bacillus anthracis after handling sick animals or contaminated wool, hair, or animal hides. Pulmonary anthrax results from inhaling anthrax spores. Intestinal anthrax results from ingesting meat products that contain anthrax. Anthrax is present in animal grazing areas, particularly those of herbivores. Anthrax primarily is a disease of herbivores (eg, cattle, sheep, goats, horses). Pigs are not immune, but they are more resistant, as are dogs and cats. Birds usually are naturally resistant to anthrax. Buzzards and vultures are naturally resistant to anthrax but may transmit the spores on their talons and beaks. Humans are relatively resistant to cutaneous invasion by B anthracis, but the organisms may gain access through microscopic or gross breaks in the skin. In cutaneous anthrax, a "malignant pustule" develops at the site of the infection. This pustule is a central area of coagulation necrosis (ulcer) surrounded by a rim of vesicles filled with bloody or clear fluid. A black eschar forms at the ulcer site. Extensive edema surrounds the lesion. The organisms multiply locally and may spread to the bloodstream or other organs (eg, spleen) via the efferent lymphatics. Dissemination from the liver, spleen, and kidneys back into the bloodstream may result in bacteremia. In bacteremic anthrax, hemorrhagic lesions may develop anywhere on the body. Bacteremic anthrax with hematogenous spread most commonly follows inhalational anthrax. B anthracis remains in the capillaries of invaded organs, and the local and fatal effects of the infection result, in large part, to the toxins elaborated by B anthracis. Anthrax in the spore stage can exist indefinitely in the environment. Optimal growth conditions result in a vegetative phase and bacterial multiplication. Secondary hemorrhagic intestinal foci of anthrax result from B anthracis bacteremia. Primary intestinal anthrax predominantly affects the cecum and produces a local lesion not unlike the lesion that results from the cutaneous form. Oropharyngeal anthrax is a variant of intestinal anthrax and occurs in the oropharynx after ingesting meat products contaminated by anthrax. Oropharyngeal anthrax is characterized by throat pain and difficulty in swallowing. The lesion at the site of entry into the oropharynx resembles the cutaneous ulcer. Inhalational

anthrax occurs after inhaling spores into the lungs. Spores are ingested by alveolar macrophages and are carried to the mediastinal lymph nodes. Anthrax in the lungs does not cause pneumonia, but it does cause hemorrhagic mediastinitis and pulmonary edema. Hemorrhagic pleural effusions frequently accompany inhalational anthrax. Septicemic anthrax refers to overwhelming infection resulting from bloodstream invasion secondary to inhalational or intestinal anthrax. Death from anthrax occurs as a result of the effects of lethal toxins. Near death or just after death, animals bleed from all body orifices.

Cutaneous anthrax

Cutaneous anthrax begins as a pruritic papule that enlarges in 24-48 hours to form an ulcer surrounded by a satellite bulbus/lesion edematous halo. The cutaneous anthrax lesion usually measures approximately 2-3 cm in diameter and has a round, regular, and raised edge. Regional lymphadenopathy of the nodes draining the infected area may occur. The cutaneous anthrax ulcer characteristically is pruritic but not painful. The adenopathy associated with cutaneous anthrax may be painful.

The membrane/exudate of the ulcer contains numerous anthrax bacilli. The anthrax ulcer and surrounding edema evolve into a black eschar in 7-10 days and last for 7-14 days before separating and leaving a permanent scar. The edema surrounding the ulcer may persist through the eschar stage. Lymphadenopathy associated with cutaneous anthrax may persist long after disappearance of the ulcer/eschar. If the lesions of cutaneous anthrax affect the neck, neck swelling resulting from edema and enlarged cervical lymph nodes may impinge on the trachea and cause stridor and respiratory distress and, if severe, may be accompanied by asphyxiation.

Physicians must differentiate cutaneous anthrax and bubonic plague or lymphocutaneous tularemia. Patients with plague have painful adenopathy, usually in the groin or axilla. No ulcer is present, and ulcer edema and eschar characteristic of anthrax are absent. Patients with bubonic plague appear more toxemic than patients with uncomplicated cutaneous anthrax. Patients with anthrax have an appropriate history of contact with animal products. In contrast, patients with bubonic plague have a history of contact with infected cats that may be in contact with sylvatic rodents in plague-endemic areas. Ulceroglandular tularemia is characterized by purple ulcerative lesions that are painful, not pruritic, and not surrounded by a gelatinous edematous halo. Patients with anthrax, tularemia, or plague may complain of headache and have fever associated with shaking chills. The chancre of primary syphilis also may be confused with cutaneous anthrax. The chancre of primary syphilis is painless, as is the lesion of cutaneous anthrax, but the syphilitic chancre is not pruritic and is not surrounded by an edematous halo. Generalized rather than local adenopathy accompanies syphilis, which is the opposite of what is expected with cutaneous anthrax. Exudates from the ulcers of both ulceroglandular tularemia and cutaneous anthrax reveal organisms when properly stained. The ulcer of syphilis does not reveal organisms, but Treponema pallidum may be visualized using dark-field examination.

The preferred diagnostic procedure for cutaneous anthrax is staining the ulcer exudate with methylene blue or Giemsa stain. B anthracis readily grows on blood agar, and staining will microbiologically differentiate the organism and nonanthracis bacilli species. Warn laboratory personnel that contracting anthrax from specimens is a possibility and that they must take appropriate biohazard precautions. In patients with cutaneous anthrax who have fever and systemic symptoms that suggest extracutaneous spread, blood culture may be indicated. Treat blood cultures as biohazard II specimens. B anthracis is present in high numbers in the ulcer/eschar of cutaneous anthrax, bloody pleural fluid, the CSF in anthrax meningitis, or the blood in septicemic anthrax. Specimens may be stained/cultured to demonstrate the organism. Culture on sheep blood or peptone agar. The diagnosis of cutaneous anthrax usually is suggested by the characteristic appearance of skin lesions. Enzyme-linked immunosorbent assay (ELISA) serological diagnosis also is available. The ELISA measures titers to edema and lethal toxins, and the test is positive if a single acute-phase titer is highly elevated or if a 4-fold greater rise in the titer is observed between acute and convalescent specimens.

Treatment

The preferred agent used to treat anthrax is penicillin. Penicillin is the preferred agent to treat inhalational anthrax/anthrax meningitis. Ampicillin (meningeal doses), doxycycline, and chloramphenicol penetrate the CSF, which is important in meningeal anthrax. Doxycycline also is a preferred agent. Oral doxycycline and quinolones have excellent bioavailability; the same blood/tissue levels are obtained with PO and IV therapy. Treatment ordinarily continues for 1-2 weeks.

Postexposure prophylaxis to prevent inhalation anthrax should be continued for 60 days. Other antibiotics that may be useful include erythromycin, first-generation cephalosporins, chloramphenicol, clindamycin, vancomycin, carbapenems, cefoperazone, and extended-spectrum penicillins or trimethoprim-sulfamethoxazole (TMP-SMX). Avoid aztreonam and second-generation and third-generation cephalosporins (except cefoperazone).

Prevention:

Anthrax vaccine

A vaccine exists but is not readily available.

Administer human anthrax vaccine in a dose of 0.5 mL subcutaneously, and repeat at 2 weeks and at 1, 6, 12, and 18 months following the initial immunization.

Administer a booster of 0.5 mL of human anthrax vaccine annually. Administer to individuals who have exposure to anthrax-containing animals or animal products.

Assess the efficacy of the vaccine using the anthracin skin test.

Chemoprophylaxis

To prevent infection from aerosolized spores of B anthracis, use amoxicillin or doxycycline chemoprophylaxis 60 days postexposure.

Alternatively, any quinolone may be used for postexposure chemoprophylaxis.

An anaerobic infection is an infection caused by bacteria which cannot grow in the presence of oxygen. Anaerobic bacteria can infect deep wounds, deep tissues, and internal organs where there is little oxygen. These infections are characterized by abscess formation, foul-smelling pus, and tissue destruction.

Anaerobic bacteria grow in places which completely, or almost completely, lack oxygen. They are normally found in the mouth, gastrointestinal tract, and vagina, and on the skin. Commonly known diseases caused by anaerobic bacteria include gas gangrene, tetanus, and botulism. Nearly all dental infections are caused by anaerobic bacteria.Anaerobic bacteria can cause an infection when a normal barrier (such as skin, gums, or intestinal wall) is damaged due to surgery, injury, or disease. Usually, the immune system kills any invading bacteria, but sometimes the bacteria are able to grow and cause an infection. Body sites that have tissue destruction (necrosis) or a poor blood supply are low in oxygen and favor the growth of anaerobic bacteria. The low oxygen condition can result from blood vessel disease, shock, injury, and surgery.

- Lung. Anaerobic bacteria can cause pneumonia, lung abscesses, infecton of the lining of the lung (empyema), and dilated lung bronchi (bronchiectasis).
- Intraabdominal. Anaerobic infections within the abdomen include abscess formation, peritonitis, and appendicitis.

Indeed, most anaerobic infections are "mixed infections" which means that there is a mixture of different bacteria growing. The anaerobic bacteria that most frequently cause infections are *Bacteroides fragilis*, *Peptostreptococcus*, and *Clostridium* species.

The B fragilis group, a member of the Bacteroidaceae family, includes B fragilis (occurs with the greatest frequency in clinical infections), Bacteroides distasonis, Bacteroides ovatus, Bacteroides thetaiotaomicron, and Bacteroides vulgatus. These bacteria are resistant to penicillins, mostly through the production of beta-lactamase. They are part of the normal gastrointestinal florae and predominate in intra-abdominal infections and infections originating from those florae (eg, perirectal abscesses, decubitus ulcers). Pigmented Prevotella, such as Prevotella melaninogenica and Prevotella intermedia (which were previously called the Bacteroides melaninogenicus group), Porphyromonas (eg, Porphyromonas asaccharolytica), and nonpigmented Prevotella (eg, Prevotella oralis, Prevotella oris) are part of the normal oral and vaginal florae and are the predominant AGNB isolated from respiratory tract infections and their complications, including aspiration pneumonia, lung abscess, chronic otitis media, chronic sinusitis, abscesses around the oral cavity, human bites, paronychia, brain abscesses, and osteomyelitis. Prevotella bivia and Prevotella disiens (previously called Bacteroides) are important in obstetric and gynecologic infections.

Predisposing factors include neoplasms; hematologic disorders; organ transplantation; intestinal obstruction; decubitus ulcers; dental extraction; diabetes mellitus; postsplenectomy; use of cytotoxic agents or corticosteroids; total body irradiation; and recent gastrointestinal, obstetric, or gynecologic surgery.
Features typical of bacteremia due to anaerobes include metastatic lesions, hyperbilirubinemia, and suppurative thrombophlebitis.
The mortality rate is 15-30% and improves with early appropriate antimicrobial therapy and resolution of the primary infection.
Lab Studies:
Collection of specimens of anaerobic bacteria is important because documentation of an anaerobic infection is through culture of organisms from the infected site. Appropriate documentation of anaerobic infection requires proper collection of appropriate specimens, expeditious transportation, and careful laboratory processing.
Specimens must be obtained free of contamination. Inadequate techniques or media can lead to missing the presence of anaerobic bacteria or the assumption that only aerobic organisms are present in a mixed infection.

Tissue specimens can be transported in an anaerobic jar or in a sealed plastic bag rendered anaerobic.Gram stain of a smear of the specimen provides important preliminary information regarding the types of organisms present, suggests appropriate initial therapy, and serves as a quality control.
Cultures should be immediately placed under anaerobic conditions and should be incubated for 48 hours or longer. An additional 36-48 hours is generally required for species- or genus-level identification by using biochemical tests. Kits containing these tests are commercially available.
A rapid enzymatic test enables identification after only 4 hours of aerobic incubation.
Gas-liquid chromatography of metabolites is often used.
Nucleic acid probers and polymerase chain reaction methods are also being developed for rapid identification.
Routine susceptibility testing is time-consuming and often unnecessary. However, testing the susceptibility of isolates recovered from sterile body sites and/or those that are clinically important (ie, blood cultures, bone, CNS, serious infections) and have variable susceptibilities, especially those isolated in pure culture from properly collected specimens, is important.
Antibiotics that should be tested include penicillin, a broad-spectrum penicillin, a penicillin plus a beta-lactamase inhibitor, clindamycin, chloramphenicol, a second-generation cephalosporin (eg, cefoxitin), newer quinolones, metronidazole, and a carbapenem.
The recommended methods include agar microbroth and macrobroth dilution.

Treatment

The patient's recovery from anaerobic infection depends on prompt and proper management according to the following 3 principles:

- ✓ Toxins produced by anaerobes must be neutralized
- ✓ The environment must be changed to prevent local bacterial proliferation
- ✓ The spread of bacteria must be limited

The environment is controlled by debriding necrotic tissue, draining pus, improving circulation, alleviating obstruction, and increasing tissue oxygenation.

Certain types of adjunctive therapy, such as hyperbaric oxygen therapy, may be useful but remain unproven.

In many cases, antimicrobial therapy is the only form of therapy required, but it can also be an adjunct to a surgical approach.

Because anaerobic bacteria are generally recovered mixed with aerobic organisms, the appropriate choice for antimicrobial agents should provide adequate treatment of both groups of pathogens.

When choosing antimicrobials for the treatment of mixed infections, consider their aerobic and anaerobic antibacterial spectrum and their availability in oral or parenteral form.

Some antimicrobials have a limited range of activity. For example, metronidazole is active only against anaerobes and cannot be administered as a single agent in mixed infections. Others, such as imipenem, have wide spectra of activity against aerobes and anaerobes.

Because culture results are often not available, many patients are treated empirically.

Antimicrobial resistance patterns may vary. Some anaerobes have become, or may become, resistant to antimicrobials.

The B fragilis group is almost uniformly susceptible to metronidazole, carbapenems, chloramphenicol, and combinations of a penicillin and beta-lactamase inhibitors. Resistance to other agents varies.

Aside from susceptibility patterns, other factors influencing the choice of antimicrobials include their pharmacokinetics, their toxicity, their effect on the

normal florae, their bactericidal activity, and their ability to penetrate into sites of infection.

Although identification of organisms and their susceptibility is needed for optimal therapy, often the clinical setting and the Gram stain results from the specimen are helpful.

Antimicrobials useful in anaerobic infection are as follows:

Penicillins

Penicillin G is still the drug of choice against most non–beta-lactamase–producing AGNB. However, in addition to the B fragilis group, which is resistant to penicillin, other AGNB show increased resistance. These include pigmented Prevotella and Porphyromonas species, P bivia, P disiens, Bilophila wadsworthia, and Bacteroides splanchnicus.

The combination of beta-lactamase inhibitors (eg, clavulanic acid, sulbactam, tazobactam) with a beta-lactam antibiotic (eg, ampicillin, amoxicillin, ticarcillin, piperacillin) can overcome these beta-lactamase–producing AGNB.

In high concentrations, carbenicillin, ticarcillin, piperacillin, and mezlocillin have good activity against gram-negative enterics and most anaerobes; however, they are not completely resistant to beta-lactamase.

Cephalosporins

The B fragilis group, Prevotella species, and Porphyromonas species are resistant to first-generation cephalosporins by virtue of cephalosporinase production.

Cefoxitin is the most effective cephalosporin against the B fragilis group, although 5-15% may be resistant. Cefoxitin is inactive against most clostridial organisms, except Clostridium perfringens. Other second-generation cephalosporins, such as cefotetan and cefmetazole, have a longer half-life than cefoxitin and are as effective as cefoxitin against B fragilis; however, they are less efficacious against other members of the B fragilis group.

Carbapenems

These agents, including imipenem, meropenem, and ertapenem have excellent activity against a broad spectrum of aerobic and anaerobic bacteria.

Chloramphenicol

This agent shows excellent in vitro activity against most anaerobic bacteria, and resistance is rare; however, the development of less toxic newer agents has limited their use.

Clindamycin

This antimicrobial is effective against anaerobes and has good activity against aerobic gram-positive cocci. Resistance of the B fragilis group is 5-25%. Antibiotic-associated colitis due to Clostridium difficile, although associated with most antimicrobials, was first described following clindamycin therapy.

Metronidazole

It has excellent activity against anaerobes, including AGNB; however, this efficacy is limited to anaerobes. Microaerophilic streptococci, P acnes, and Actinomyces species are often resistant; therefore; adding an antimicrobial that is effective against these organisms (eg, penicillin) is often necessary.

Tigecycline

This glycylcycline has effective in vitro activity against both gram-positive and gram-negative anaerobes, as well as against gram-positive aerobic strains such as methicillin-resistant staphylococci, streptococci, and enterococci. Tigecycline was recently approved by the FDA for the treatment of complicated skin and skin-structure infections and complicated intra-abdominal infections.

Quinolones

Trovafloxacin, moxifloxacin, and gatifloxacin yield low minimum inhibitory concentrations (MICs) against most groups of anaerobes. Moxifloxacin was recently approved by the FDA for the treatment of complicated skin and skin-structure infections and complicated intra-abdominal infections. The use of the quinolones is restricted in growing children and pregnancy because of their possible adverse effects on the cartilage.

Surgical Care:

In most cases, surgical therapy is of critical importance. Surgical therapy includes draining abscesses, debriding necrotic tissues, decompressing closed-space infections, and relieving obstructions.

When surgical drainage is not used, the infection may persist and serious complications may develop.

Although the duration of therapy for anaerobic infections is generally longer than for aerobes and facultative infections, the duration of treatment must be individualized, depending on the response. In some cases, treatment may require 6-8 weeks, but therapy may be shortened with proper surgical drainage. An anti–gram-negative enteric agent is generally added to treat Enterobacteriaceae when treating intra-abdominal infections.

Clostridial soft-tissue infections

Clostridial soft-tissue infections include cellulitis, myositis, and clostridial myonecrosis. They usually occur after trauma. Symptoms may include edema, pain, gas with crepitation, foul-smelling exudates, intense coloration of the site, and progression to shock and renal failure.

Clostridial cellulitis occurs as a localized infection in a superficial wound, usually ≥ 3 days after injury. Infection may spread extensively along fascial planes, often with evident crepitation and abundant gas bubbling, but toxicity is much less severe than with extensive myonecrosis, and pain is minimal. Bullae frequently are evident, with foul-smelling, serous, brown exudate. Discoloration and gross edema of the extremity are rare. Clostridial skin infections associated with primary vascular occlusion of an extremity rarely progress to severe toxic myonecrosis or extend beyond the line of demarcation.

Clostridial myositis, suppurative infection of muscle without necrosis, is most common in parenteral drug users. It resembles staphylococcal pyomyositis and lacks the systemic symptoms of clostridial myonecrosis. Edema, pain, and frequently gas in the tissues occur. It spreads rapidly and may progress to myonecrosis.

Clostridial gas gangrene

Clostridial gas gangrene is a highly lethal necrotizing soft tissue infection of skeletal muscle caused by toxin- and gas-producing Clostridium species. The synonym clostridial myonecrosis better describes both the causative agent and the target tissue. Prior to the advent of antibiotics and mobile army surgical hospitals, as many as 5% of battlefield injuries were complicated by this condition. Presently, 90% of contaminated wounds demonstrate clostridial organisms, but fewer than 2% develop clostridial myonecrosis. This underscores the importance of host and local wound factors in the development of this process, rather than the mere presence of the organisms in the wound.

Clostridia are gram-positive, anaerobic, spore-forming bacilli commonly found throughout nature. Cultivated rich soil has the highest density of organisms. In addition, clostridia have been isolated from normal human colonic flora, skin, and the vagina. More than 150 Clostridium species have been identified, but only 6 have been demonstrated to be capable of producing the fulminant condition known as clostridial gas gangrene. Usually, more than 1 species is isolated from clinical specimens.

Clostridium perfringens, previously known as Clostridium welchii, is the most common cause of clostridial gas gangrene and is present in 80-90% of cases. Other clostridia species may include Clostridium novyi (40%), Clostridium septicum (20%), Clostridium histolyticum (10%), Clostridium bifermentans (10%), and Clostridium fallax (5%).

Infections are characterized by a very low level of host inflammation in response to organism-associated exotoxins. In fact, it is more of a response to the exotoxins than a classic immune response to invading organisms. Purulence often is absent. The process of myonecrosis can spread as fast as 2 cm/h. This results in systemic toxicity and shock that can be fatal within 12 hours. Overwhelming shock with accompanying renal failure usually leads to patient death.

Infection requires 2 conditions to coexist. First, organisms must be inoculated into the tissues. Second, oxygen tension must be low enough for the organisms to proliferate. These organisms are not strict anaerobes; 30% oxygen tension in the tissues allows for free growth of these bacteria, but 70% oxygen tension restricts their growth. Inoculation of organisms into low oxygen tension tissues is followed by an incubation period that usually ranges from 12-24 hours. However, this period can be as brief as 1 hour or as long as several weeks. The organisms then multiply and produce exotoxins that result in myonecrosis.

Although not very well understood, exotoxins appear to be tissue-destructive soluble antigens produced by clostridia. They include lecithinase, collagenase, hyaluronidase, fibrinolysin, hemagglutinin, and hemolysin toxins. C perfringens produces at least 17 identifiable exotoxins that are used for species typing (eg, type A, type B, type C).

Theta toxin causes direct vascular injury, cytolysis, hemolysis, leukocyte degeneration, and polymorphonuclear cell destruction. These effects on leukocytes may explain the relatively minor host inflammatory response that is observed in tissues of patients with clostridial myonecrosis.

Kappa toxin, also produced by C perfringens, is a collagenase that facilitates the rapid spread of necrosis through tissue planes by destroying connective tissue.

Alpha toxin is produced by most clostridia and has phospholipase C activity. This potent lecithinase causes lysis of red blood cells, myocytes, fibroblasts, platelets, and leukocytes. It also may decrease cardiac inotropy and trigger histamine release, platelet aggregation, and thrombus formation.

Approximately 80% of nontrauma patients have an overt or occult malignancy. Of these, approximately 40% are hematologic malignancies and an additional 34% are colorectal. Survival from this process should initiate a search for an occult malignancy if none has been documented previously in nontrauma patients.

Diagnosis

Early suspicion and intervention are essential. Clostridial cellulitis responds well to treatment, but myonecrosis has a mortality rate of ≥ 40% with treatment and 100% without.

Although localized cellulitis, myositis, and spreading myonecrosis may be clinically distinct, differentiation often requires surgical exploration. In myonecrosis, muscle tissue is visibly necrotic; the affected muscle is a lusterless pink, then deep red, and finally gray-green or mottled purple and does not contract on stimulation. X-rays may show local gas production, and CT and MRI delineate the extent of gas and necrosis.

Lab Studies:
White blood cell count may be normal or elevated. Immature forms usually are increased.
Elevated liver function test results may indicate progressive hepatic dysfunction.
Elevated blood urea nitrogen and creatinine may indicate azotemia, renal insufficiency, or renal failure.
Myonecrosis may elevate serum aldolase, potassium, lactate dehydrogenase, and creatine phosphokinase levels.
Profound anemia may result from severe intravascular hemolysis.
Arterial blood gas determinations and chemistry panel analysis may reveal metabolic acidosis.
Disseminated intravascular coagulation may result from exotoxin release.
A Gram stain of the wound discharge reveals gram-positive rods and an absence of polymorphonuclear cells. Other organisms also may be present in as many as 75% of cases. This test is essential for rapid diagnosis.
An assay for sialidases (neuraminidase) produced by clostridia also may be performed on serum and wound discharge. These tests provide rapid (<2 h) confirmation of Gram stain results.
Imaging Studies:
Radiographs reveal fine gas bubbles within the soft tissues, dissecting into the intramuscular fascial planes and muscles. Other necrotizing soft tissue infections produce abundant gas, in contrast to the paucity of gas of clostridial gas gangrene.
Intra-abdominal clostridial gas gangrene is evaluated most readily by a computed tomography scan that demonstrates extraluminal gas.
Other Tests:
Blood and bullous fluid cultures reveal clostridia but take at least 48 hours to perform. They are not useful because the delay almost certainly results in death.
Histologic Findings: Histologic analysis reveals necrotic muscle, clostridia, and a minimal inflammatory infiltrate.

Treatment

When clinical signs of clostridial infection are present, such as gas or myonecrosis, rapid, aggressive intervention is mandatory. Thorough drainage and debridement are as important as antibiotics; both should be instituted rapidly. Penicillin is the drug of choice; 1 to 2 million units IV q 2 to 3 h should be given immediately for severe cellulitis and myonecrosis. Addition of 600 mg IV q 6 h is beneficial. If gram-negative organisms are seen or suspected, a broad-spectrum antibiotic (eg, ticarcillin combined with clavulanate, ampicillin combined with sulbactam, or piperacillin combined with tazobactam) should be added.

Hyperbaric O_2 therapy may be helpful in extensive myonecrosis, particularly in extremities, as a supplement to antibiotics and surgery. Hyperbaric O_2 therapy may have potential to salvage tissue and lessen mortality and morbidity if started early *but should not delay surgical debridement*.

Tetanus

Tetanus is an acute poisoning from a neurotoxin produced by Clostridium tetani. Symptoms are intermittent tonic spasms of voluntary muscles. Spasm of the masseters accounts for the name lockjaw. Diagnosis is clinical. Treatment is immune globulin and intensive support. Tetanus bacilli form durable spores that can be found in soil and animal feces and remain viable for years. Worldwide, tetanus is estimated to cause over half a million deaths annually, mostly in newborns and young children, but the disease is so rarely reported that all figures are only rough estimates. Patients with burns, surgical wounds, or a history of injection drug abuse are especially prone to developing tetanus. However, tetanus may follow trivial or even inapparent wounds. Infection may also develop postpartum in the uterus (maternal tetanus) and in a newborn's umbilicus (tetanus neonatorum). Manifestations of tetanus are caused by an exotoxin (tetanospasmin). The toxin may enter the CNS along the peripheral motor nerves or may be bloodborne to nervous tissue. Tetanospasmin binds irreversibly to the ganglioside membranes of nerve synapses, blocking release of inhibitory transmitter from nerve terminals and thereby causing a generalized tonic spasticity, usually with superimposed intermittent tonic seizures. Once bound, the toxin cannot be neutralized.

Symptoms and Signs

The incubation period ranges from 2 to 50 days (average, 5 to 10 days). The most frequent symptom is jaw stiffness. Other symptoms include difficulty swallowing; restlessness; irritability; stiff neck, arms, or legs; headache; fever; sore throat;

chills; and tonic spasms. Later, the patient has difficulty opening his jaw (trismus). Facial muscle spasm produces a characteristic expression with a fixed smile and elevated eyebrows (risus sardonicus). Rigidity or spasm of abdominal, neck, and back muscles—even opisthotonos—may occur. Sphincter spasm causes urinary retention or constipation. Dysphagia may interfere with nutrition. Characteristic painful, generalized tonic spasms with profuse sweating are precipitated by minor disturbances such as a draft, noise, or movement. Mental status is usually clear, but coma may follow repeated spasms. During generalized spasms, the patient is unable to speak or cry out because of chest wall rigidity or glottal spasm. Spasms also interfere with respiration, causing cyanosis or fatal asphyxia. The immediate cause of death may not be apparent.
The patient's temperature is only moderately elevated unless a complicating infection, such as pneumonia, is present. Respiratory and pulse rates are increased. Reflexes are often exaggerated. Moderate leukocytosis is usual. Patients with protracted tetanus may manifest a very labile and overactive sympathetic nervous system, including periods of hypertension, tachycardia, and myocardial irritability.

In generalized tetanus, skeletal muscles throughout the body are affected. Localized tetanus can occur, with spasticity of a muscle group near the wound but without trismus. Spasticity may persist for weeks.

Cephalic tetanus, tetanus infection of the brain and cranial nerves, is a form of localized tetanus. It is more common in children, in whom it may occur with chronic otitis media. Its incidence is greatest in Africa and India. All cranial nerves can be involved, especially the 7th. Cephalic tetanus may become generalized.

Tetanus in a newborn is usually generalized and frequently fatal. It often begins in improperly cleansed umbilical stumps in children born of inadequately immunized mothers. Its onset during the first 2 wk of life is characterized by rigidity, spasms, and poor feeding. Bilateral deafness has occurred in surviving newborns.

Respiratory failure is the most common cause of death. Laryngeal spasm and abdominal wall, diaphragm, and chest wall muscle rigidity and spasms cause asphyxiation. Hypoxemia can also induce cardiac arrest, and pharyngeal spasm leads to aspiration of oral secretions with subsequent pneumonia, contributing to a hypoxemic death.

Diagnosis

A history of a recent wound in a patient with muscle stiffness or spasms is a clue. Tetanus can be confused with meningoencephalitis of bacterial or viral origin, but the combination of an intact sensorium, normal CSF, and muscle spasms suggests

tetanus. Trismus must be distinguished from peritonsillar or retropharyngeal abscess or another local cause. Phenothiazines can induce tetanus-like rigidity.

C. tetani can sometimes be cultured from the wound, but culture is not sensitive.

Treatment

Tetanus has a worldwide mortality rate of 50%, 15 to 60% in untreated adults, and 80 to 90% in newborns even if treated. Mortality is highest at the extremes of age and in drug abusers. The prognosis is poorer if the incubation period is short and symptoms progress rapidly or if treatment is delayed. The course tends to be milder when there is no demonstrable focus of infection.

Therapy requires maintaining adequate ventilation. Additional interventions include early and adequate use of human immune globulin to neutralize nonfixed toxin; prevention of further toxin production; sedation; control of muscle spasm, hypertonicity, fluid balance, and intercurrent infection; and continuous nursing care.

General principles: The patient should be kept in a quiet room. Three principles should guide all therapeutic interventions: prevent further toxin release by debriding the wound and giving metronidazole 500 mg IV q 6 to 8 h; neutralize toxin outside the CNS with human tetanus immune globulin and tetanus toxoid, taking care to inject into different body sites to avoid neutralizing the antitoxin; and minimize the effect of toxin already in the CNS.

Wound care: Because dirt and dead tissue promote C. tetani growth, prompt, thorough debridement, especially of deep puncture wounds, is essential. Antibiotics are not substitutes for adequate debridement and immunization.

Antitoxin: The benefit of human-derived antitoxin depends on how much tetanospasmin is already bound to the synaptic membranes—only free toxin is neutralized. For adults, human tetanus immune globulin 3000 units IM is given once (this large volume may be split and given at separate sites). Dose can range from 1,500 to 10,000 units, depending on wound severity. Antitoxin of animal origin is far less preferable because the patient's serum antitoxin level is not well maintained and a considerable risk of serum sickness exists. If horse serum must be used, however, the usual dose is 50,000 units IM or IV. If necessary, immune globulin or antitoxin can be injected directly into the wound, but this injection is not as important as proper wound care.

Management of muscle spasm: To control rigidity and spasms, benzodiazepines are the standard of care. They block reuptake of an endogenous inhibiting neurotransmitter, γ-aminobutyric acid (GABA), at the GABAA receptor. Diazepam can help control seizures, counter muscle rigidity, and induce sedation. Dosage varies and requires meticulous titration and close observation. The most severe cases may require 10 to 20 mg IV q 3 h (do not exceed 5 mg/kg). Less

severe cases can be controlled with 5 to 10 mg po q 2 to 4 h. Adults receive 5 to 10 mg po q 4 to 6 h or up to 40 mg/h IV drip. Although diazepam has been used most extensively, midazolam (adults, 0.1 to 0.3 mg/kg/h IV infusion) is water-soluble and preferred for prolonged therapy. Midazolam reduces the risk of lactic acidosis from propylene glycol solvent required for diazepam and lorazepam and reduces the risk of long-acting metabolites accumulating and causing coma.

Benzodiazepines may not prevent reflex spasms, and effective respiration may require neuromuscular blockade with vecuronium 0.1 mg/kg IV or other paralytic agents and mechanical ventilation. Pancuronium has been used but may worsen autonomic instability. Vecuronium is free from adverse cardiovascular effects but is short acting. Longer acting agents (eg, pipecuronium and rocuronium) also work, but no randomized clinical comparative trials have been performed.

Intrathecal baclofen (a GABAA agonist) is effective but has no clear advantage over benzodiazepines. It is given by continuous infusion; effective doses range between 20 and 2000 μg/day. A test dose of 50 μg is given first; if response is inadequate, 75 μg may be given 24 h later, and 100 μg 24 h after that. Those who do not respond to 100 μg are not candidates for chronic infusion. Coma and respiratory depression requiring ventilatory support are potential adverse effects.

Antibiotics: The role of antibiotic therapy is minor compared with wound debridement and general support. Typical antibiotics include penicillin G 6 million units IV q 6 h, doxycycline 100 mg po bid, and metronidazole 500 mg po q 8 h.

Supportive care: In moderate or severe cases, the patient should be intubated. Mechanical ventilation is essential when neuromuscular blockade is required to control muscle spasms that impair respirations. IV hyperalimentation avoids the hazard of aspiration secondary to gastric tube feeding. Because constipation is usual, stools should be kept soft. A rectal tube may control distention. Bladder catheterization is required if urinary retention occurs. Chest physiotherapy, frequent turning, and forced coughing are essential to prevent pneumonia. Analgesia with opioids is often needed.

Prevention

A series of 4 primary immunizations against tetanus, followed by boosters q 10 yr, with the adsorbed (for primary immunization) or fluid (for boosters) toxoid is superior to giving antitoxin at the time of injury. Tetanus toxoid comes by itself, mixed with diphtheria in both adult (Td) and child strengths (DT), and combined with both diphtheria and pertussis (DTP). Routine diphtheria, tetanus, and pertussis immunization and booster recommendations are discussed in Immunization. Adults

need to maintain immunity with regular boosters q 10 yr. Immunization in an unimmunized or inadequately immunized pregnant woman produces both active and passive immunity in the fetus and should be given at a gestational age of 5 to 6 mo with a booster at 8 mo. Passive immunity develops with maternal toxoid given before a gestational age of 6 mo.

Following injury, tetanus vaccination is given depending on wound type and vaccination history; tetanus immune globulin may also be indicated. Patients not previously vaccinated are given a 2nd and 3rd dose of toxoid at monthly intervals.

Cutaneous Diphtheria

Today, we often think of diphtheria of the skin in the context of wound diphtheria, umbilical diphtheria, or impetiginous diphtheria. Skin lesions can be extremely variable owing to the ability of *C. diphtheriae* to colonize any skin lesion of other origin (e.g., surgical wounds, pyoderma, eczema, impetigo, dermatitis, or insect bites). Often, an ulcerative lesion (ecthyma diphtheriticum) is the presenting lesion. It begins as a vesicle or pustule filled with straw-colored fluid, which breaks down quickly. The lesion progresses to form a punched-out ulcer, single or multiple, measuring several millimeters to a few centimeters, with slightly curved and elevated margins. In addition, the margins may be slightly undermined, or inverted. Common sites for diphtheric lesions are the lower legs, feet, and hands. The lesions are painful and may be covered with an adhering eschar (dark pseudomembrane) during the first 1–2 weeks. Then the lesion becomes anesthetic, and the pseudomembrane falls away, leaving a hemorrhagic base, sometimes with serous or serosanguinous exudate oozing from it. The surrounding tissue is edematous and pink, purple, or livid in color and may show blisters or bullae. Skin lesions yielding *C. diphtheriae* on cultures are indistinguishable from those associated with other bacteria and can include dry, nearly healed, scaly lesions.

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.

Literature

1.Черенько М. П., Ваврик Ж. М. Загальна хірургія з анестезіологією, основами реаніматології та догляду за хворими. –К.: Здоров'я, 2004. –616 с.
2. Гостищев В. К. Общая хирургия Учебник для медицинских вузов. 4-е изд.,перераб., доп. и испр.- М.: ГЭОТАР-Медиа,2006.- 832 с.

3.Петров С.В. Общая хирургия Учебное пособие. 3-е изд.,перераб. и доп. – М.: ГЭОТАР-Медиа, 2007 – 768 с.
4.Anaya D., Dellinger E. Necrotizing soft-tissue infection: diagnosis and management //Clin Infect Dis.- 2007.- Vol.44, N5.- P.705-710.
5.Cainzos M., Gonzalez-Rodriguez F. Necrotizing soft tissue infections.Curr Opin//Crit Care.-2007.- Vol.13, N4.- P.433-439.
6.Critical Care Infectious Diseases Textbook // by Jordi Rello (Editor), Jordi Vallés (Editor), Marin Kollef (Editor).- Springer; 1st edition (October 1, 2001).- 944 p.
7.De Benoist A., White J., Efstratiou A. et al. //Emerg Infect Dis.- 2004, N10.- P.511–513.
8.Dhalla S. Postsurgical tetanus //Can J Surg.- 2004.- Vol.47, N5.- P.375-379.
9. Hefny A., Eid H., Al-Hussona M. et al. Necrotizing fasciitis: a challenging diagnosis //Eur J Emerg Med.- 2007.- Vol.14, N1.- P.50-52.
10. Holty J., Bravata D., Liu H. et al. Systematic review: a century of inhalational anthrax cases from 1900 to 2005 // Ann Intern Med.-2006.- Vol.144, N4.- P.270-280.
11. Holty J., Kim R., Bravata D. Anthrax: a systematic review of atypical presentations //Ann Emerg Med.-2006.- Vol.48, N2.- P.200-211.
12. Howdieshell T., Heffernan D., Dipiro J.Surgical infection society guidelines for vaccination after traumatic injury// Surg Infect (Larchmt).- 2006.- Vol.7,N3.- P.275-303.
13.Lee P., Lemos B., O'Brien S., et al. Cutaneous diphtheroid infection and review of other cutaneous Gram-positive Bacillus infections //Cutis.- 2007.- Vol.79, N5.- P.371-377.
14.Rhee P, Nunley MK, Demetriades D, et al..Tetanus and trauma: a review and recommendations //J Trauma.-2005.- Vol.58, N5.- P.1082-1088.
15.Sabiston Textbook of Surgery //by Courtney M. Townsend, R. Daniel Beauchamp , B. Mark Evers, Kenneth Mattox.-Saunders; 17 edition (June 11, 2004).- 2416 p.
16.Salcido R. Necrotizing fasciitis: reviewing the causes and treatment strategies //Adv Skin Wound Care.- 2007.- Vol.20, N5.- P.288-293.
17. Schwartz's Principles of Surgery, 8/e (Schwartz's Principles of Surgery)// by F. Charles Brunicardi , Dana K. Andersen, Timothy R. Billiar, David L. Dunn, John G. Hunter , Raphael E. Pollock .- McGraw-Hill Professional; 8 edition (October 14, 2004).- 2000 p.
18.Taviloglu K., Yanar H. Necrotizing fasciitis: strategies for diagnosis and management //World J Emerg Surg.- 2007.- Vol.7, N2.- P.1-19.
19.Wenner K., Kenner J. Anthrax. //Dermatol Clin.-2004.- Vol.22, N3.- P.247-256.
20.Yilmazlar T., Ozturk E., Alsoy A., Ozguc H. Necrotizing Soft Tissue Infections: APACHE II Score, Dissemination, and Survival //World J Surg. – 2007.- N7.

A lecture is prepared on materials of meeting of cyclic methodical commission of Bogomolets National Medical University from 21 June 1998 in conformity with recommendations of Department of pedagogics and pedagogical psychology (associate professor Mileryan V.E.)