Lecture 1

Gram-positive cocci. Microbiological diagnostics. Filling the staphylococcal infection research algorithm. The rules for the collection and delivery of material for infectious and somatic diseases caused by gram-positive cocci. Principles of treatment and prevention. Gram-negative cocci. Microbiological diagnostics. Filling the research algorithm for meningococcal infection. The rules for the collection and delivery of material for infectious and somatic diseases caused by gram-negative cocci. Principles of treatment and prevention

Lecture plan:

1) Gram-positive cocci. Microbiological diagnostics.
2) the staphylococcal infection research algorithm.
3) The rules for the collection and delivery of material for infectious and somatic diseases caused by gram-positive cocci. Principles of treatment and prevention.
4) Gram-negative cocci. Microbiological diagnostics.
5) the research algorithm for meningococcal infection.
6) The rules for the collection and delivery of material for infectious and somatic diseases caused by gram-negative cocci. Principles of treatment and prevention

Learning Outcomes:

characterize main types of gram-positive and gram-negative cocci, their properties,
explain their role and pathogenesis of the development of pathological conditions,
justify the principles of laboratory diagnosis and prevention and treatment of the diseases caused by them
model isolation of a pure microbe culture and interpret the result

Microorganisms are a heterogeneous group of several distinct classes of living beings. Based on the difference in cellular organization and biochemistry, the kingdom protista has been divided into two groups namely prokaryotes and eukaryotes. Bacteria and blue-green algae are prokaryotes, while fungi, other algae, slime moulds and protozoa are eukaryotes. Bacteria are prokaryotic microorganisms that do not contain chlorophyll. They are unicellular and do not show true branching, except in higher bacteria like actinomycetales. Live bacteria do not show the structural detail under the light microscope due to lack of contrast. Hence staining techniques are used to produce colour contrast. Routine methods of staining of bacteria involve dying and fixing smears – procedures that kill them. Bacteria have an affinity to basic dyes due to acidic nature of their protoplasm. The commonly used staining techniques are Simple Stains Dyes such as methylene blue or basic fuchsin are used for simple staining. They provide colour contrast, but impart the same colour to all bacteria. Negative Staining Bacteria are mixed with dyes such as Indian ink or nigrosin that provide a uniformly coloured background against which the unstained bacteria stand out in contrast. Very slender bacteria like spirochetes that cannot be demonstrated by simple staining methods can be viewed by negative staining.

Gram-positive cocci:

Staphylococcus aureus is a gram-positive, catalase-positive, coagulase-positive cocci in clusters. S. aureus can cause inflammatory diseases, including skin infections, pneumonia, endocarditis, septic arthritis, osteomyelitis, and abscesses. S. aureus can also cause toxic shock syndrome (TSST-1), scalded skin syndrome (exfoliative toxin, and food poisoning (enterotoxin).

Staphylococcus epidermidis is a gram-positive, catalase-positive, coagulase-negative cocci in clusters and is novobiocin sensitive. S. epidermidis commonly infects prosthetic devices and IV catheters producing biofilms. Staphylococcus saprophyticus is novobiocin resistant and is a normal flora of the genital tract and perineum. S. saprophyticus accounts for the second most common cause of uncomplicated urinary tract infection (UTI).

Streptococcus pneumoniae is a gram-positive, encapsulated, lancet-shaped diplococci, most commonly causing otitis media, pneumonia, sinusitis, and meningitis. Streptococcus viridans consist of Strep. mutans and Strep mitis found in the normal flora of the oropharynx commonly cause dental carries and subacute bacterial endocarditis (Strep. sanguinis).

Streptococcus pyogenes is a gram-positive group A cocci that can cause pyogenic infections (pharyngitis, cellulitis, impetigo, erysipelas), toxigenic infections (scarlet fever, necrotizing fasciitis), and immunologic infections (glomerulonephritis and rheumatic fever). ASO titer detects S. pyogenes infections.
Streptococcus agalactiae is a gram-positive group B cocci that colonize the vagina and is found mainly in babies. Pregnant women need screening for Group-B Strep (GBS) at 35 to 37 weeks of gestation.
Enterococci is a gram-positive group D cocci found mainly in the colonic flora and can cause biliary tract infections and UTIs. Vancomycin-resistant enterococci (VRE) are an important cause of nosocomial infections.
All of the organisms are Gram-negative cocci or coccobacilli and all are oxidase positive with the exception of Acinetobacter. Moraxella and Neisseria are catalase positive and Kingella are catalase negative.
The natural habitat of the Neisseriaceae is mucous membranes of animals including man. Although Acinetobacter spp. may also colonize these sites, they are more often found in the environment, living as saprophytes. There are two main pathogenic species among the Neisseriaceae: Neisseria gonorrhoeae, the causative organism of gonorrhoea and N. meningitidis, the cause of endemic and epidemic pyogenic meningitis, and acute or chronic septicaemia.
Moraxellas are organisms of relatively low virulence but their role in human disease is being increasingly recognized. Moraxella catarrhalis colonizes the upper respiratory tract and its incidence rises in the winter months. It may cause pneumonia in patients with chronic obstructive airways disease and other chronic respiratory diseases such as bronchiectasis and pneumoconiosis. It is also associated with acute otitis media and sinusitis, and rarely with meningitis and osteomyelitis.
Moraxella lacunata is responsible for an acute angular blepharo-conjunctivitis. Of the other members of this genus M. nonliquefaciens has been isolated from patients with endophthalmitis and M. osloensis, M. phenylpyruvica and M. urethralis have been isolated in rare cases of septicaemia.
Kingella spp. are organisms of low pathogenicity. Three species are recognized: K. kingae, K. indologenes, and K. denitrificans. Infection usually occurs only in patients who are severely immunocompromised, and most reported infections have taken the form of septicaemia or septic arthritis.
Acinetobacter spp. are saprophytic or commensal organisms found in 7% of the normal population but more frequently in hospital patients. These organisms may be naturally resistant to many antibiotics which gives them a selective advantage in the hospital environment. When a patient is given courses of broad-spectrum antimicrobial chemotherapy and undergoes procedures which facilitate bacterial colonization such as endotracheal intubation and intravenous catheterization, colonization with acinetobacter may occur and pneumonia, septicaemia or suppuration in almost any site can develop. Acinetobacter colonize plastic prosthetic devices giving rise to soft tissue infections in i.v. cannulae sites and around intracranial shunts.
Meningitis is a serious infection of the meninges in the brain or spinal cord that is most commonly viral or bacterial in origin, although fungal, parasitic, and noninfectious causes are also possible. Enteroviruses and herpes simplex virus are the leading causes of viral meningitis, while Neisseria meningitidis and Streptococcus pneumoniae are the pathogens most commonly responsible for bacterial meningitis. Rarer forms of bacterial meningitis include tuberculous meningitis and Lyme-associated meningitis. The classic triad of meningitis is fever, headache, and neck stiffness. In infants and young children, the presentation is often nonspecific. Patients may also present with neurological deficits, altered mental status, and seizures, indicating increased intracranial pressure (ICP). The diagnosis is confirmed with lumbar puncture (LP) and CSF analysis. If increased ICP is suspected, a CT of the head should be performed first. Bacterial meningitis requires rapid initiation of empiric treatment. A life-threatening complication of bacterial meningitis (especially meningococcal meningitis) is Waterhouse-Friderichsen syndrome, which is characterized by disseminated intravascular coagulation and acute adrenal gland insufficiency. Viral meningitis typically resolves on its own and has a far less severe course than bacterial meningitis, which is generally fatal if left untreated. When N. meningitides or S. pneumoniae are identified as the pathogen, the CDC should be notified and preventative measures taken to prevent dissemination of the infection.

Reference:

1) Sizar O, Unakal CG. Gram Positive Bacteria. [Updated 2022 Feb 14]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470553/
2) https://www.amboss.com/us/knowledge/Meningitis

Lecture 2

Isolation of a pure culture of enterobacteria (1-4 days of the study). Escherichia. Shigella. Vibrios. Diseases caused. Features of microbiological diagnosis in connection with the pathogenesis of diseases. Principles of treatment, prevention

Lesson plan:
1) Enterobacteria spp. (1-4 days of the study).
2) Escherichia. Shigella. Vibrios. Diseases caused.
3) Features of microbiological diagnosis in connection with the pathogenesis of diseases. Principles of treatment, prevention

Learning Outcomes:
characterize microorganisms of the intestinal group of bacteria
differentiate the properties of Escherichia and Shigella and explain their role in the development of pathological conditions, pathogenesis, caused diseases,
justify features of microbiological diagnosis in connection with the pathogenesis of diseases,
justify principles of prevention and treatment
model isolation of a pure microbe culture and interpret the result

The Enterobacteriaceae are a large, heterogeneous group of gram-negative rods whose natural habitat is the intestinal tract of humans and animals. The family includes many genera (Escherichia, Shigella, Salmonella, Enterobacter, Klebsiella, Serratia, Proteus, and others). Some enteric organisms, such as Escherichia coli, are part of the normal microbiota and incidentally cause disease, but others, the salmonellae and shigellae, are regularly pathogenic for humans. The Enterobacteriaceae are facultative anaerobes or aerobes, ferment a wide range of carbohydrates, possess a complex antigenic structure, and produce a variety of toxins and other virulence factors. Enterobacteriaceae, enteric gram-negative rods, and enteric bacteria are the terms used in this chapter, but these bacteria may also be called coliforms. The Enterobacteriaceae are the most common group of gram-negative rods cultured in clinical laboratories and along with staphylococci and streptococci are among the most common bacteria that cause disease. The taxonomy of the Enterobacteriaceae is complex and rapidly changing since the introduction of techniques that measure evolutionary distance, such as nucleic acid hybridization and nucleic acid sequencing. According to the National Library of Medicine's Internet Taxonomy database (available at http://www.ncbi.nlm.nih.gov//Taxonomy//Browser/wwwtax.cgl?id=543), 63 genera have been defined; however, the clinically significant Enterobacteriaceae comprise 20–25 species, and other species are encountered infrequently. In this chapter, taxonomic refinements will be minimized, and the names commonly used in the medical literature are generally used. Members of the family Enterobacteriaceae have the following characteristics: They are gram-negative rods, either motile with peritrichous flagella or nonmotile; grow on peptone or meat extract media without the addition of sodium chloride or other supplements; grow well on MacConkey agar; grow aerobically and anaerobically (are facultative anaerobes); ferment rather than oxidize glucose, often with gas production; are catalase positive, oxidase negative (except for *Plesiomonas*) and reduce nitrate to nitrite; and have a 39–59% G + C DNA content. They can be differentiated to species level by a vast array of biochemical tests. In the United States, commercially prepared kits or automated systems are used to a large extent for this purpose. However, these are largely being replaced by other methods. The implementation of matrix-assisted laser desorption ionization time of flight mass spectroscopy (MALDI-TOF MS) for identification of culture isolates is replacing the more traditional panels of biochemicals currently in use in most clinical microbiology laboratories. This new technology seems to work quite well for identification of most of the common Enterobacteriaceae encountered in clinical material except for *Shigella* species. This technology is unable to differentiate *Shigella* from *E coli*. The major groups of Enterobacteriaceae are described and discussed

briefly in the following paragraphs. Specific characteristics of salmonellae, shigellae, and the other medically important enteric gram-negative rods and the diseases they cause are discussed separately later in this chapter.

Morphology and Identification

A. Typical Organisms The Enterobacteriaceae are short gram-negative rods (Figure 15-1A). Typical morphology is seen in growth on solid media in vitro, but morphology is highly variable in clinical specimens. Capsules are large and regular in *Klebsiella* species, less so in *Enterobacter* species, and uncommon in the other species.

B. Culture

E coli and most of the other enteric bacteria form circular, convex, smooth colonies with distinct edges. *Enterobacter* colonies are similar but somewhat more mucoid. *Klebsiella* colonies are large and very mucoid and tend to coalesce with prolonged incubation. The salmonellae and shigellae produce colonies similar to *E coli* but do not ferment lactose. Some strains of *E coli* produce hemolysis on blood agar.

C. Growth Characteristics

Carbohydrate fermentation patterns and the activity of amino acid decarboxylases and other enzymes are used in biochemical differentiation. Some tests, such as the production of indole from tryptophan, are commonly used in rapid identification systems, but others, such as the Voges-Proskauer reaction (production of acetylmethylcarbinol from dextrose), are used less often. Culture on "differential" media that contain special dyes and carbohydrates (eg, eosin-methylene blue [EMB], MacConkey, or deoxycholate medium) distinguishes lactose-fermenting (colored) from non–lactose-fermenting colonies (nonpigmented) and may allow rapid presumptive identification of enteric bacteria.

Many complex media have been devised to help in identification of the enteric bacteria. One such medium is triple sugar iron (TSI) agar, which is often used to help differentiate salmonellae and shigellae from other enteric gram-negative rods in stool cultures. The medium contains 0.1% glucose, 1% sucrose, 1% lactose, ferrous sulfate (for detection of H_2S production), tissue extracts (protein growth substrate), and a pH indicator (phenol red). It is poured into a test tube to produce a slant with a deep butt and is inoculated by stabbing bacterial growth into the butt. If only glucose is fermented, the slant and the butt initially turn yellow from the small amount of acid produced; as the fermentation products are subsequently oxidized to CO_2 and H_2O and released from the slant and as oxidative decarboxylation of proteins continues with formation of amines, the slant turns alkaline (red). If lactose or sucrose is fermented, so much acid is produced that the slant and butt remain yellow (acid). Salmonellae and shigellae typically yield an alkaline slant and an acid butt. Although *Proteus, Providencia*, and *Morganella* species produce an alkaline slant and acid butt, they can be identified by their rapid formation of red color in Christensen's urea medium. Organisms producing acid on the slant and acid and gas (bubbles) in the butt are other enteric bacteria.

1. *Escherichia—E coli* typically produces positive test results for indole, lysine decarboxylase, and mannitol fermentation and produces gas from glucose. An isolate from urine can be quickly identified as *E coli* by its hemolysis on blood agar, typical colonial morphology with an iridescent "sheen" on differential media such as EMB agar, and a positive spot indole test result. More than 90% of *E coli* isolates are positive for β-glucuronidase using the substrate 4-methylumbelliferyl-β-glucuronide (MUG). Isolates from anatomic sites other than urine, with characteristic properties (above plus negative oxidase test results) often can be confirmed as *E coli* with a positive MUG test result.

2. *Klebsiella–Enterobacter–Serratia* group—*Klebsiella* species exhibit mucoid growth, large polysaccharide capsules, and lack of motility, and they usually give positive test results for lysine decarboxylase and citrate. Most *Enterobacter* species give positive test results for motility, citrate, and ornithine decarboxylase and produce gas from glucose. *Enterobacter aerogenes* has small capsules. Some species of *Enterobacter* have been moved into the genus *Cronobacter*. *Serratia* species produces DNase, lipase, and gelatinase. *Klebsiella, Enterobacter*, and *Serratia* species usually give positive Voges-Proskauer reactions.\

3. *Proteus–Morganella–Providencia* group—The members of this group deaminate phenylalanine, are motile, grow on potassium cyanide medium (KCN), and ferment xylose. *Proteus* species move very

actively by means of peritrichous flagella, resulting in "swarming" on solid media unless the swarming is inhibited by chemicals, such as phenylethyl alcohol or CLED (cystine-lactose-electrolyte-deficient) medium. Whereas *Proteus* species and *Morganella morganii* are urease positive, *Providencia* species usually are urease negative. The *Proteus–Providencia* group ferments lactose very slowly or not at all.

4. *Citrobacter*—These bacteria typically are citrate positive and differ from the salmonellae in that they do not decarboxylate lysine. They ferment lactose very slowly if at all.

5. *Shigella*—Shigellae are nonmotile and usually do not ferment lactose but do ferment other carbohydrates, producing acid but not gas. They do not produce H_2S. The four *Shigella* species are closely related to *E coli*. Many share common antigens with one another and with other enteric bacteria (eg, *Hafnia alvei* and *Plesiomonas shigelloides*).

6. *Salmonella*—Salmonellae are motile rods that characteristically ferment glucose and mannose without producing gas but do not ferment lactose or sucrose. Most salmonellae produce H_2S. They are often pathogenic for humans or animals when ingested. Organisms originally described in the genus *Arizona* are included as subspecies in the *Salmonella* group.

7. Other Enterobacteriaceae—Yersinia species are discussed in Chapter 19. Other genera occasionally found in human infections include Cronobacter, Edwardsiella, Ewingella, Hafnia, Cedecea, Plesiomonas, and Kluyvera.

Antigenic Structure

Enterobacteriaceae have a complex antigenic structure. They are classified by more than 150 different heat-stable somatic O (lipopolysaccharide) antigens, more than 100 heat-labile K (capsular) antigens, and more than 50 H (flagellar) antigens (Figure 15-1B). In Salmonella serotype Typhi, the capsular antigens are called Vi antigens. The antigenic classification of Enterobacteriaceae often indicates the presence of each specific antigen; for example, the antigenic formula of an E coli may be O55:K5:H21.

O antigens are the most external part of the cell wall lipopolysaccharide and consist of repeating units of polysaccharide. Some O-specific polysaccharides contain unique sugars. O antigens are resistant to heat and alcohol and usually are detected by bacterial agglutination. Antibodies to O antigens are predominantly IgM.

Although each genus of Enterobacteriaceae is associated with specific O groups, a single organism may carry several O antigens. Thus, most shigellae share one or more O antigens with E coli. E coli may cross-react with some Providencia, Klebsiella, and Salmonella species. Occasionally, O antigens may be associated with specific human diseases (eg, specific O types of E coli are found in diarrhea and in urinary tract infections).

K antigens are external to O antigens on some but not all Enterobacteriaceae. Some are polysaccharides, including the K antigens of E coli; others are proteins. K antigens may interfere with agglutination by O antisera, and they may be associated with virulence (eg, E coli strains producing K1 antigen are prominent in neonatal meningitis, and K antigens of E coli cause attachment of the bacteria to epithelial cells before gastrointestinal or urinary tract invasion).

Klebsiellae form large capsules consisting of polysaccharides (K antigens) covering the somatic (O or H) antigens and can be identified by capsular swelling tests with specific antisera. Human infections of the respiratory tract are caused particularly by capsular types 1 and 2 and those of the urinary tract by types 8, 9, 10, and 24.

H antigens are located on flagella and are denatured or removed by heat or alcohol. They are preserved by treating motile bacterial variants with formalin. Such H antigens agglutinate with anti-H antibodies, mainly IgG. The determinants in H antigens are a function of the amino acid sequence in flagellar protein (flagellin). Within a single serotype, flagellar antigens may be present in either or both of two forms, called phase 1 (conventionally designated by lowercase letters) and phase 2 (conventionally designated by Arabic numerals), as shown in 15-3. The organism tends to change from one phase to the other; this is called phase variation. H antigens on the bacterial surface may interfere with agglutination by anti-O antibody.

There are many examples of overlapping antigenic structures between Enterobacteriaceae and other bacteria. Most Enterobacteriaceae share the O14 antigen of E coli. The type 2 capsular polysaccharide of Klebsiella is very similar to the polysaccharide of type 2 pneumococci. Some K antigens cross-react

with capsular polysaccharides of Haemophilus influenzae or Neisseria meningitidis. Thus, E coli O75:K100:H5 can induce antibodies that react with H influenzae type b.

Toxins and Enzymes E coli are members of the normal intestinal microbiota (see Chapter 10). Other enteric bacteria (Proteus, Enterobacter, Klebsiella, Morganella, Providencia, Citrobacter, and Serratia species) are also found as members of the normal intestinal microbiota but are considerably less common than E coli. The enteric bacteria are sometimes found in small numbers as part of the normal microbiota of the upper respiratory and genital tracts. The enteric bacteria generally do not cause disease, and in the intestine, they may even contribute to normal function and nutrition. When clinically important infections occur, they are usually caused by E coli, but the other enteric bacteria are causes of hospital-acquired infections and occasionally cause community-acquired infections. The bacteria become pathogenic only when they reach tissues outside of their normal intestinal or other less common normal microbiota sites. The most frequent sites of clinically important infection are the urinary tract, biliary tract, and other sites in the abdominal cavity, but any anatomic site (eg, bloodstream, prostate gland, lung, bone, meninges) can be the site of disease. Some of the enteric bacteria (eg, Serratia marcescens, E aerogenes) are opportunistic pathogens. When normal host defenses are inadequate—particularly in infancy or old age, in the terminal stages of other diseases, after immunosuppression, or with indwelling venous or urethral catheters—localized clinically important infections can result, and the bacteria may reach the bloodstream and cause sepsis.

Pathogenesis and Clinical Findings

The clinical manifestations of infections with E coli and the other enteric bacteria depend on the site of the infection and cannot be differentiated by symptoms or signs from processes caused by other bacteria.

A. E coli

1. Urinary tract infection—E coli is the most common cause of urinary tract infection and accounts for approximately 90% of first urinary tract infections in young women (see Chapter 48). The symptoms and signs include urinary frequency, dysuria, hematuria, and pyuria. Flank pain is associated with upper tract infection. None of these symptoms or signs is specific for E coli infection. Urinary tract infection can result in bacteremia with clinical signs of sepsis.

Most of the urinary tract infections that involve the bladder or kidney in an otherwise healthy host are caused by a small number of O antigen types that have specifically elaborated virulence factors that facilitate colonization and subsequent clinical infections. These organisms are designated as uropathogenic E coli. Typically, these organisms produce hemolysin, which is cytotoxic and facilitates tissue invasion. Strains that cause pyelonephritis express K antigen and elaborate a specific type of pilus, P fimbriae, which binds to the P blood group antigen.

Over the last decade, a pandemic clone, E coli O25b/ST131, has emerged as a significant pathogen. This organism has been successful largely as a result of its acquisition of plasmid-mediated resistance factors that encode resistance to β-lactam antibiotics (elaboration of extended spectrum β-lactamases), fluoroquinolones, and aminoglycosides (see the review by Johnson et al, 2010).

2. E coli–associated diarrheal diseases—E coli that cause diarrhea are extremely common worldwide. These E coli are classified by the characteristics of their virulence properties (see later discussion), and each group causes disease by a different mechanism—at least six of which have been characterized. The small or large bowel epithelial cell adherence properties are encoded by genes on plasmids. Similarly, the toxins often are plasmid or phage mediated. Some clinical aspects of diarrheal diseases are discussed in Chapter 48.

Enteropathogenic E coli (EPEC) are an important cause of diarrhea in infants, especially in developing countries. EPEC adhere to the mucosal cells of the small bowel. Pathogenicity requires two important factors, the bundle forming pilus encoded by a plasmid EPEC adherence factor (EAF) and the chromosomal locus of enterocyte effacement (LEE) pathogenicity island that promote the tight adherence characteristic of EPEC (attachment and effacement). After attachment, there is loss of microvilli (effacement); formation of filamentous actin pedestals or cuplike structures; and, occasionally, entry of the EPEC into the mucosal cells. Characteristic lesions can be seen on electron micrographs of small bowel biopsy lesions. The result of EPEC infection in infants is characterized by severe, watery diarrhea,

vomiting, and fever, which are usually self-limited but can be prolonged or chronic. EPEC diarrhea has been associated with multiple specific serotypes of E coli; strains are identified by O antigen and occasionally by H antigen typing. A two-stage infection model using HEp-2 or HeLa cells also can be performed. Tests to identify EPEC are performed in reference laboratories. The duration of the EPEC diarrhea can be shortened and the chronic diarrhea cured by antibiotic treatment.

Enterotoxigenic E coli (ETEC) are a common cause of "traveler's diarrhea" and a very important cause of diarrhea in children less than 5 years of age in developing countries. ETEC colonization factors (pili known as colonization factor antigens [CFAs]) specific for humans promote adherence of ETEC to epithelial cells of the small bowel. Some strains of ETEC produce a heat-labile enterotoxin (LT) (molecular weight [MW], 80,000) that is under the genetic control of a plasmid and is closely related to cholera toxin. Its subunit B attaches to the GM1 ganglioside in the apical membrane of enterocytes and facilitates the entry of subunit A (MW, 26,000) into the cell, where the latter activates adenylyl cyclase. This markedly increases the local concentration of cyclic adenosine monophosphate (cAMP) after which ensues a complex cascade that involves the cystic fibrosis transmembrane conductance regulator. The end result is an intense and prolonged hypersecretion of water and chlorides and inhibition of the reabsorption of sodium. The gut lumen is distended with fluid, and hypermotility and diarrhea ensue, lasting for several days. LT is antigenic and cross-reacts with the enterotoxin of Vibrio cholerae, which has an identical mechanism of action. LT stimulates the production of neutralizing antibodies in the serum (and perhaps on the gut surface) of persons previously infected with enterotoxigenic E coli. Persons residing in areas where such organisms are highly prevalent (eg, in some developing countries) are likely to possess antibodies and are less prone to develop diarrhea on reexposure to the LT-producing E coli. Assays for LT include (1) fluid accumulation in the intestines of laboratory animals, (2) typical cytologic changes in cultured Chinese hamster ovary cells or other cell lines, (3) stimulation of steroid production in cultured adrenal tumor cells, (4) binding and immunologic assays with standardized antisera to LT, and (5) detection of the genes that encode the toxins. These assays are done only in reference laboratories.

Some strains of ETEC produce the heat-stable enterotoxin STa (MW, 1500–4000), which is under the genetic control of a heterogeneous group of plasmids. STa activates guanylyl cyclase in enteric epithelial cells and stimulates fluid secretion. Many STa-positive strains also produce LT. The strains with both toxins produce a more severe diarrhea.

The plasmids carrying the genes for enterotoxins (LT, ST) also may carry genes for the CFAs that facilitate the attachment of E coli strains to intestinal epithelium. Recognized colonization factors occur with particular frequency in some serotypes. Certain serotypes of ETEC occur worldwide; others have a limited recognized distribution. It is possible that virtually any E coli may acquire a plasmid encoding for enterotoxins. There is no definite association of ETEC with the EPEC strains causing diarrhea in children. Likewise, there is no association between enterotoxigenic strains and those able to invade intestinal epithelial cells.

Care in the selection and consumption of foods potentially contaminated with ETEC is highly recommended to help prevent traveler's diarrhea. Antimicrobial prophylaxis can be effective but may result in increased antibiotic resistance in the bacteria and probably should not be uniformly recommended. When diarrhea develops, antibiotic treatment effectively shortens the duration of disease.

Shiga toxin-producing E coli (STEC) are named for the cytotoxic toxins they produce. There are at least two antigenic forms of the toxin referred to as Shiga-like toxin 1 and Shiga-like toxin 2. STEC has been associated with mild non-bloody diarrhea, hemorrhagic colitis, a severe form of diarrhea, and with hemolytic uremic syndrome, a disease resulting in acute renal failure, microangiopathic hemolytic anemia, and thrombocytopenia. Shiga-like toxin 1 is identical to the Shiga toxin of Shigella dysenteriae type 1, and Shiga-like toxin 2 also has many properties that are similar to the Shiga toxin; however, the two toxins are antigenically and genetically distinct. A low infectious dose (< 200 CFU) is associated with infection. Of the more than 150 E coli serotypes that produce Shiga toxin, O157:H7 is the most common and is the one that can be identified most readily in clinical specimens. STEC O157:H7 does not use sorbitol, unlike most other E coli, and is negative (clear colonies) on sorbitol MacConkey agar (sorbitol is used instead of lactose); O157:H7 strains also are negative on MUG tests (see earlier discussion). Many of the non-O157 serotypes may be sorbitol positive when grown in culture. Specific

antisera are used to identify the O157:H7 strains. Tests for the detection of both Shiga toxins using commercially available enzyme immunoassays (EIAs) are done in many laboratories. Other sensitive test methods include cell culture cytotoxin testing using Vero cells and polymerase chain reaction for the direct detection of toxin genes directly from stool samples. Many cases of hemorrhagic colitis and its associated complications can be prevented by thoroughly cooking ground beef and by avoiding unpasteurized products such as apple cider. In 2011, the largest outbreak of hemorrhagic colitis attributed to a non-O157 serotype—namely, E coli O104:H4—was related to consumption of contaminated sprouts in Germany. This organism had increased virulence characterized by enhanced adherence as well as the production of shiga-like toxins (see reference by Buchholz et al, 2011).

Enteroinvasive E coli (EIEC) produce a disease very similar to shigellosis. The disease occurs most commonly in children in developing countries and in travelers to these countries. Similar to Shigella, EIEC strains are nonlactose or late lactose fermenters and are nonmotile. EIEC produce disease by invading intestinal mucosal epithelial cells.

Enteroaggregative E coli (EAEC) causes acute and chronic diarrhea (>14 days in duration) in persons in developing countries. These organisms also are the cause of foodborne illnesses in industrialized countries and have been associated with traveler's diarrhea and persistent diarrhea in patients with HIV. They are characterized by their specific patterns of adherence to human cells. This group of diarrheagenic E coli is quite heterogeneous, and the exact pathogenic mechanisms are still not completely elucidated. Some strains of EAEC produce ST-like toxin (see earlier discussion on E coli O104:H11); others a plasmid-encoded enterotoxin that produces cellular damage; and still others, a hemolysin. Diagnosis can be suspected clinically but requires confirmation by tissue culture adhesion assays not readily available in most clinical laboratories.

3. Sepsis—When normal host defenses are inadequate, E coli may reach the bloodstream and cause sepsis. Newborns may be highly susceptible to E coli sepsis because they lack IgM antibodies. Sepsis may occur secondary to urinary tract infection and often the major clone associated with invasion is E coli O25b/ST131.

4. Meningitis—E coli and group B streptococci are the leading causes of meningitis in infants. Approximately 80% of E coli from meningitis cases have the K1 antigen. This antigen cross-reacts with the group B capsular polysaccharide of N meningitidis. The mechanisms of virulence associated with the K1 antigen are reviewed in the reference by Kim et al (2005).

B. Klebsiella–Enterobacter–Serratia; Proteus–Morganella–Providencia; and Citrobacter

The pathogenesis of disease caused by these groups of enteric gram-negative rods is similar to that of the nonspecific factors in disease caused by E coli.

1. Klebsiella—Klebsiella pneumoniae is present in the respiratory tract and feces of about 5% of normal individuals. It causes a small proportion (~1%) of bacterial pneumonias. K pneumoniae can produce extensive hemorrhagic necrotizing consolidation of the lung. It produces urinary tract infection and bacteremia with focal lesions in debilitated patients. Other enterics also may produce pneumonia. Recently a particular clone of K pneumoniae has emerged as a cause of community acquired pyogenic liver abscess that is seen mostly among Asian males worldwide. This particular K1 encapsulated strain phenotypically appears hypermucoviscous when grown in culture. Klebsiella species rank among the top 10 bacterial pathogens responsible for hospital-acquired infections. Multilocus sequencing typing has identified global emergence of two particularly important clones. Sequence type 16 has elaborated extended spectrum β-lactamases resulting in resistance to a broad range of penicillins and cephalosporins (but not carbapenem antibiotics). ST 258 is a multidrug resistant strain called a "carbapenamase producer" because it is resistant to all β-lactam antibiotics including the broad spectrum carbapenem agents. Typically it is resistant to other antimicrobial agents as a result of acquisition of plasmids that carry multiple resistance genes. Two other Klebsielleae are associated with inflammatory conditions of the upper respiratory tract: K pneumoniae subspecies ozaenae has been isolated from the nasal mucosa in ozena, a fetid, progressive atrophy of mucous membranes; and K pneumoniae subspecies rhinoscleromatis form rhinoscleroma, a destructive granuloma of the nose and pharynx. Klebsiella granulomatis (formerly Calymmatobacterium granulomatis) causes a chronic genital

ulcerative disease, granuloma inguinale, an uncommon sexually transmitted disease. The organism grows with difficulty on media containing egg yolk. Ampicillin or tetracycline is effective treatment.

2. Enterobacter—Three species/complexes of Enterobacter—Enterobacter cloacae complex, E aerogenes complex, and Enterobacter sakazakii (now in the genus Cronobacter)—cause the majority of Enterobacter infections. These bacteria ferment lactose, may contain capsules that produce mucoid colonies, and are motile. These organisms cause a broad range of hospital-acquired infections such as pneumonia, urinary tract infections, and wound and device infections. Most strains possess a chromosomal β-lactamase called ampC, which renders them intrinsically resistant to ampicillin and first- and second-generation cephalosporins. Mutants may hyperproduce β-lactamase, conferring resistance to third-generation cephalosporins. Like K pneumoniae, some hospital-acquired strains have plasmids that make them multidrug resistant including the carbapenem class of antimicrobial agents.

3. Serratia—Serratia marcescens is a common opportunistic pathogen in hospitalized patients. Serratia (usually nonpigmented) causes pneumonia, bacteremia, and endocarditis (especially in narcotics addicts) and in hospitalized patients. Only about 10% of isolates form the red pigment (prodigiosin) that has long characterized S marcescens. S marcescens is often multiply resistant to aminoglycosides and penicillins; infections can be treated with third-generation cephalosporins.

4. Proteus—Proteus species produce infections in humans only when the bacteria leave the intestinal tract. They are found in urinary tract infections and produce bacteremia, pneumonia, and focal lesions in debilitated patients or those receiving contaminated intravenous infusions. P mirabilis causes urinary tract infections and occasionally other infections. Proteus vulgaris and M morganii are also important nosocomial pathogens.

Proteus species produce urease, resulting in rapid hydrolysis of urea with liberation of ammonia. Thus, in urinary tract infections with Proteus species, the urine becomes alkaline, promoting stone formation and making acidification virtually impossible. The rapid motility of Proteus may contribute to its invasion of the urinary tract.

Strains of Proteus vary greatly in antibiotic susceptibility. P mirabilis is often inhibited by penicillins; the most active antibiotics for other members of the group are aminoglycosides and cephalosporins.

5. Providencia—Providencia species (Providencia rettgeri, Providencia alcalifaciens, and Providencia stuartii) are members of the normal intestinal microbiota. All cause urinary tract infections and occasionally other infections and are often resistant to antimicrobial therapy.

6. Citrobacter—Citrobacter species can cause urinary tract infections and sepsis principally among debilitated hospitalized patients. In addition, Citrobacter koseri has been associated with meningitis in infants less than 2 months of age.

Diagnostic Laboratory Tests

A. Specimens

Specimens include urine, blood, pus, spinal fluid, sputum, or other material, as indicated by the localization of the disease process.

B. Smears

The Enterobacteriaceae resemble each other morphologically. The presence of large capsules is suggestive of Klebsiella species.

C. Culture

Specimens are plated on both blood agar and differential media. With differential media, rapid preliminary identification of gram-negative enteric bacteria is often possible (see Chapter 47).

D. Nucleic Acid Amplification Tests (NAATs)

A variety of multiplex NAATs designed to detect the most common pathogens responsible for particular syndromes, are currently available and many more are entering clinical trials. These panel tests detect members of the Enterobacteriaceae in specimens such as positive blood cultures, cerebrospinal fluid, respiratory specimens, and stool. In some of these assays resistance markers are also detected. The reader should consult the literature for the most up to date information on these assays.

Immunity

Specific antibodies develop in systemic infections, but it is uncertain whether significant immunity to the organisms follows.

Treatment

No single specific therapy is available. The sulfonamides, ampicillin, cephalosporins, fluoroquinolones, and aminoglycosides have marked antibacterial effects against the enterics, but variation in susceptibility is great, and laboratory tests for antibiotic susceptibility are essential. Multiple drug resistance is common and is under the control of transmissible plasmids.

Certain conditions predisposing to infection by these organisms require surgical correction, such as relief of urinary tract obstruction, closure of a perforation in an abdominal organ, or resection of a bronchiectatic portion of lung.

Treatment of gram-negative bacteremia and impending septic shock requires rapid institution of antimicrobial therapy, restoration of fluid and electrolyte balance, and treatment of disseminated intravascular coagulation.

Various means have been proposed for the prevention of traveler's diarrhea, including daily ingestion of bismuth subsalicylate suspension (bismuth subsalicylate can inactivate E coli enterotoxin in vitro) and regular doses of tetracyclines or other antimicrobial drugs for limited periods. Because none of these methods are entirely successful or lacking in adverse effects, it is widely recommended that caution be observed in regard to food and drink in areas where environmental sanitation is poor and that early and brief treatment (eg, with ciprofloxacin or trimethoprim–sulfamethoxazole) be substituted for prophylaxis.

Epidemiology, Prevention, and Control

The enteric bacteria establish themselves in the normal intestinal tract within a few days after birth and from then on constitute a main portion of the normal aerobic (facultative anaerobic) microbial flora. E coli is the prototype. Enterics found in water or milk are accepted as proof of fecal contamination from sewage or other sources.

Control measures are not feasible as far as the normal endogenous microbiota is concerned. Enteropathogenic E coli serotypes should be controlled like salmonellae (see below). Some of the enterics constitute a major problem in hospital infection. It is particularly important to recognize that many enteric bacteria are "opportunists" that cause illness when they are introduced into debilitated patients. Within hospitals or other institutions, these bacteria commonly are transmitted by personnel, instruments, or parenteral medications. Their control depends on handwashing, rigorous asepsis, sterilization of equipment, disinfection, restraint in intravenous therapy, and strict precautions in keeping the urinary tract sterile (ie, closed drainage). For control of the multidrug-resistant pathogens, especially carbapenamase producers, surveillance of hospitalized patients with prompt implementation of contact precautions for colonized patients is often employed. Most gram-negative bacteria possess complex lipopolysaccharides in their cell walls.

Reference:

Maheshwari, Nanda. Clinical Microbiology and Pathology [Text] : for DMLT Students / N. Maheshwari ; Damyanti DMLT Institute. - 3rd ed. - New Delhi ; London ; Philadelphia : Jaypee, 2016. - 498 p. : il. - ISBN 978-93-5250-018-5 :

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Lecture 3

Salmonella. Features of microbiological diagnosis in connection with the pathogenesis of caused diseases. Principles of treatment, prevention. Differential diagnosis of bacteria of the intestinal group. Campylobacter. Helicobacter. Features of microbiological diagnosis in connection with the pathogenesis of diseases. Principles of treatment, prevention.

Plan of lecture:

Bacterial Infections of the Gastrointestinal Tract;

General characteristics of Salmonella – medical diagnostics, principles, treatment and prevention;

General characteristics of Campylobacter - medical diagnostics, principles, treatment and prevention;

General characteristics of Helicobacter - medical diagnostics, principles, treatment and prevention.

Learning Outcomes:

Describe properties of Salmonella, and explain their role in the development of pathological conditions, pathogenesis, caused diseases;
Justify features of microbiological diagnosis in connection with the pathogenesis of diseases;
Justify principles of prevention and treatment;
Argue the role of campylo - and helicobacter in the development of pathological conditions.

A wide range of gastrointestinal diseases are caused by bacterial contamination of food. Recall that food-borne disease can arise from either infection or intoxication. In both cases, bacterial toxins are typically responsible for producing disease signs and symptoms. The distinction lies in where the toxins are produced. In an infection, the microbial agent is ingested, colonizes the gut, and then produces toxins that damage host cells. In an intoxication, bacteria produce toxins in the food before it is ingested. In either case, the toxins cause damage to the cells lining the gastrointestinal tract, typically the colon. This leads to the common signs and symptoms of diarrhoea or watery stool and abdominal cramps, or the more severe dysentery. Symptoms of food-borne diseases also often include nausea and vomiting, which are mechanisms the body uses to expel the toxic materials.

Most bacterial gastrointestinal illness is short-lived and self-limiting; however, loss of fluids due to severe diarrhoeal illness can lead to dehydration that can, in some cases, be fatal without proper treatment. Oral rehydration therapy with electrolyte solutions is an essential aspect of treatment for most patients with GI disease, especially in children and infants.

Salmonella gastroenteritis, also called salmonellosis, is caused by the rod-shaped, gram-negative bacterium Salmonella. Two species, S. enterica and S. bongori, cause disease in humans, but S. enterica is the most common. The most common serotypes of S. enterica are Enteritidis and Typhi. We will discuss typhoid fever caused by serotypes Typhi and Paratyphi A separately. Here, we will focus on salmonellosis caused by other serotypes.

Salmonella is a part of the normal intestinal microbiota of many individuals. However, salmonellosis is caused by exogenous agents, and infection can occur depending on the serotype, size of the inoculum, and overall health of the host. Infection is caused by ingestion of contaminated food, handling of eggshells, or exposure to certain animals. Salmonella is part of poultry's microbiota, so exposure to raw eggs and raw poultry can increase the risk of infection. Hand-washing and cooking foods thoroughly greatly reduce the risk of transmission. Salmonella bacteria can survive freezing for extended periods but cannot survive high temperatures.

Once the bacteria are ingested, they multiply within the intestines and penetrate the epithelial mucosal cells via M cells where they continue to grow. They trigger inflammatory processes and the hypersecretion of fluids. Once inside the body, they can persist inside the phagosomes of macrophages. Salmonella can cross the epithelial cell membrane and enter the bloodstream and lymphatic system. Some strains of Salmonella also produce an enterotoxin that can cause an intoxication.

Infected individuals develop fever, nausea, abdominal cramps, vomiting, headache, and diarrhoea. These signs and symptoms generally last a few days to a week. According to the Centers for Disease Control and Prevention (CDC), there are 1,000,000 cases annually, with 380 deaths each year. However, because the disease is usually self-limiting, many cases are not reported to doctors and the overall incidence may be underreported. Diagnosis involves culture followed by serotyping and DNA fingerprinting if needed. Positive results are reported to the CDC. When an unusual serotype is detected, samples are sent to the CDC for further analysis. Serotyping is important for determining treatment. Oral rehydration therapy is commonly used. Antibiotics are only recommended for serious cases. When antibiotics are needed, as in immunocompromised patients, fluoroquinolones, third-generation cephalosporins, and ampicillin are recommended. Antibiotic resistance is a serious concern.

Typhoid Fever

Certain serotypes of S. enterica, primarily serotype Typhi (S. typhi) but also Paratyphi, cause a more severe type of salmonellosis called typhoid fever. This serious illness, which has an untreated mortality rate of 10%, causes high fever, body aches, headache, nausea, lethargy, and a possible rash. Some individuals carry S. typhi without presenting signs or symptoms (known as asymptomatic carriers) and continually shed them through their faeces. These carriers often have the bacteria in the gallbladder or intestinal epithelium. Individuals consuming food or water contaminated with these faeces can become

infected. S. typhi penetrate the intestinal mucosa, grow within the macrophages, and are transported through the body, most notably to the liver and gallbladder. Eventually, the macrophages lyse, releasing S. typhi into the bloodstream and lymphatic system. Mortality can result from ulceration and perforation of the intestine. A wide range of complications, such as pneumonia and jaundice, can occur with disseminated disease. S. typhi have Salmonella pathogenicity islands (SPIs) that contain the genes for many of their virulence factors. Two examples of important typhoid toxins are the Vi antigen, which encodes for capsule production, and chimeric A2B5 toxin, which causes many of the signs and symptoms of the acute phase of typhoid fever.

Clinical examination and culture are used to make the diagnosis. The bacteria can be cultured from faeces, urine, blood, or bone marrow. Serology, including ELISA, is used to identify the most pathogenic strains, but confirmation with DNA testing or culture is needed. A PCR test can also be used, but is not widely available.

The recommended antibiotic treatment involves fluoroquinolones, ceftriaxone, and azithromycin. Individuals must be extremely careful to avoid infecting others during treatment. Typhoid fever can be prevented through vaccination for individuals traveling to parts of the world where it is common.

Campylobacter is a genus of gram-negative, spiral or curved bacteria. They may have one or two flagella. Campylobacter jejuni gastroenteritis, a form of campylobacteriosis, is a widespread illness that is caused by Campylobacter jejuni. The primary route of transmission is through poultry that becomes contaminated during slaughter. Handling of the raw chicken in turn contaminates cooking surfaces, utensils, and other foods. Unpasteurized milk or contaminated water are also potential vehicles of transmission. In most cases, the illness is self-limiting and includes fever, diarrhoea, cramps, vomiting, and sometimes dysentery. More serious signs and symptoms, such as bacteraemia, meningitis, pancreatitis, cholecystitis, and hepatitis, sometimes occur. It has also been associated with autoimmune conditions such as Guillain-Barré syndrome, a neurological disease that occurs after some infections and results in temporary paralysis. HUS following infection can also occur. The virulence in many strains is the result of haemolysin production and the presence of Campylobacter cytolethal distending toxin (CDT), a powerful deoxyribonuclease (DNase) that irreversibly damages host cell DNA.

Diagnosis involves culture under special conditions, such as elevated temperature, low oxygen tension, and often medium supplemented with antimicrobial agents. These bacteria should be cultured on selective medium (such as Campy CV, charcoal selective medium, or cefaperazone charcoal deoxycholate agar) and incubated under microaerophilic conditions for at least 72 hours at 42 °C. Antibiotic treatment is not usually needed, but erythromycin or ciprofloxacin may be used.

Peptic Ulcers

The gram-negative bacterium Helicobacter pylori is able to tolerate the acidic environment of the human stomach and has been shown to be a major cause of peptic ulcers, which are ulcers of the stomach or duodenum. The bacterium is also associated with increased risk of stomach cancer (Figure 25.19). According to the CDC, approximately two-thirds of the population is infected with H. pylori, but less than 20% have a risk of developing ulcers or stomach cancer. H. pylori is found in approximately 80% of stomach ulcers and in over 90% of duodenal ulcers.

H. pylori colonizes epithelial cells in the stomach using pili for adhesion. These bacteria produce urease, which stimulates an immune response and creates ammonia that neutralizes stomach acids to provide a more hospitable microenvironment. The infection damages the cells of the stomach lining, including those that normally produce the protective mucus that serves as a barrier between the tissue and stomach acid. As a result, inflammation (gastritis) occurs and ulcers may slowly develop. Ulcer formation can also be caused by toxin activity. It has been reported that 50% of clinical isolates of H. pylori have detectable levels of exotoxin activity in vitro. This toxin, VacA, induces vacuole formation in host cells. VacA has no primary sequence homology with other bacterial toxins, and in a mouse model, there is a correlation between the presence of the toxin gene, the activity of the toxin, and gastric epithelial tissue damage.

Signs and symptoms include nausea, lack of appetite, bloating, burping, and weight loss. Bleeding ulcers may produce dark stools. If no treatment is provided, the ulcers can become deeper, more tissues can be

involved, and stomach perforation can occur. Because perforation allows digestive enzymes and acid to leak into the body, it is a very serious condition.
Diagnosis is made by considering the patient history (such as exposure to antibiotics), clinical presentation, imaging, endoscopy, lab tests, and other available data. Detecting the toxin in stool samples is used to confirm diagnosis. Although culture is preferred, it is rarely practical in clinical practice because the bacterium is an obligate anaerobe. Nucleic acid amplification tests, including PCR, are considered preferable to ELISA testing for molecular analysis.
The first step of conventional treatment is to stop antibiotic use, and then to provide supportive therapy with electrolyte replacement and fluids. Metronidazole is the preferred treatment if the C. difficile diagnosis has been confirmed. Vancomycin can also be used, but it should be reserved for patients for whom metronidazole was ineffective or who meet other criteria (e.g., under 10 years of age, pregnant, or allergic to metronidazole).
A newer approach to treatment, known as a faecal transplant, focuses on restoring the microbiota of the gut in order to combat the infection. In this procedure, a healthy individual donates a stool sample, which is mixed with saline and transplanted to the recipient via colonoscopy, endoscopy, sigmoidoscopy, or enema. It has been reported that this procedure has greater than 90% success in resolving C. difficile infections.
Questions for self-control:
Properties of Salmonella, and explain their role in the development of pathological conditions, pathogenesis, caused diseases;
Microbiological diagnosis in connection with the pathogenesis of diseases;
Principles of prevention and treatment;
The role of campylo - and helicobacter in the development of pathological conditions.
Recommended readings:
Levinson, Warren. Review of Medical Microbiology and Immunology [Electronic resource] : monograph / W. Levinson. - 13th ed. - New York ; Chicago ; San Francisco : McGraw Hill, 2014. - 1950 p. - ISBN 978-0-07-181812-4 : W. p.
Maheshwari, Nanda. Clinical Microbiology and Pathology [Text] : for DMLT Students / N. Maheshwari ; Damyanti DMLT Institute. - 3rd ed. - New Delhi ; London ; Philadelphia : Jaypee, 2016. - 498 p. : il. - ISBN 978-93-5250-018-5 : 14400.01 KZT
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Lecture 4

The causative agents of zoonotic infections. Brucellosis, plague, anthrax, tularemia. Features of microbiological diagnosis in connection with the pathogenesis of diseases. Statement of the reaction of Ascoli, Hedelson, Wright. Interpretation of the results. Principles of treatment, prevention.

Plan of the lesson:
1. Introduction in basis of zoonotic infections;
2. Brucellosis, plague, anthrax, tularemia – general characteristics, principles of treatment, prevention.

Learning outcomes:
Pathogenesis of the development of diseases;
Justify features of microbiological diagnosis in connection with the pathogenesis of diseases;
Justify principles of prevention and treatment;
Explain the concept of quarantine infections and the rules of the anti-epidemic regime in the occurrence and development of anthrax and plague;
Model serological diagnosis of anthrax and brucellosis with interpretation of the results.

Zoonotic disease, also called zoonosis, any of a group of diseases that can be transmitted to humans by nonhuman vertebrate animals, such as mammals, birds, reptiles, amphibians, and fish. A large number of domestic and wild animals are sources of zoonotic disease, and there are numerous means of transmission. Public health veterinarians have a critical role in zoonotic disease surveillance, prevention,

and control, but risk reduction increasingly requires multidisciplinary teams and a unified concept of medicine in humans and other animal species.

Brucellosis. Species in the genus Brucella are gram-negative facultative intracellular pathogens that appear as coccobacilli. Several species cause zoonotic infections in animals and humans, four of which have significant human pathogenicity: B. abortus from cattle and buffalo, B. canis from dogs, B. suis from swine, and B. melitensis from goats, sheep, and camels. Infections by these pathogens are called brucellosis, also known as undulant fever, "Mediterranean fever," or "Malta fever." Vaccination of animals has made brucellosis a rare disease in the US, but it is still common in the Mediterranean, south and central Asia, Central and South America, and the Caribbean. Human infections are primarily associated with the ingestion of meat or unpasteurized dairy products from infected animals. Infection can also occur through inhalation of bacteria in aerosols when handling animal products, or through direct contact with skin wounds. In the US, most cases of brucellosis are found in individuals with extensive exposure to potentially infected animals (e.g., slaughterhouse workers, veterinarians).

Two important virulence factors produced by Brucella spp. are urease, which allows ingested bacteria to avoid destruction by stomach acid, and lipopolysaccharide (LPS), which allows the bacteria to survive within phagocytes. After gaining entry to tissues, the bacteria are phagocytized by host neutrophils and macrophages. The bacteria then escape from the phagosome and grow within the cytoplasm of the cell. Bacteria phagocytized by macrophages are disseminated throughout the body. This results in the formation of granulomas within many body sites, including bone, liver, spleen, lung, genitourinary tract, brain, heart, eye, and skin. Acute infections can result in undulant (relapsing) fever, but untreated infections develop into chronic disease that usually manifests as acute febrile illness (fever of 40–41 °C [104–105.8 °F]) with recurring flu-like signs and symptoms.

Brucella is only reliably found in the blood during the acute fever stage; it is difficult to diagnose by cultivation. In addition, Brucella is considered a BSL-3 pathogen and is hazardous to handle in the clinical laboratory without protective clothing and at least a class II biological safety cabinet. Agglutination tests are most often used for serodiagnosis. In addition, enzyme-linked immunosorbent assays (ELISAs) are available to determine exposure to the organism. The antibiotics doxycycline or ciprofloxacin are typically prescribed in combination with rifampin; gentamicin, streptomycin, and trimethoprim-sulfamethoxazole (TMP-SMZ) are also effective against Brucella infections and can be used if needed.

Plaque. The gram-negative bacillus Yersinia pestis causes the zoonotic infection plague. This bacterium causes acute febrile disease in animals, usually rodents or other small mammals, and humans. The disease is associated with a high mortality rate if left untreated. Historically, Y. pestis has been responsible for several devastating pandemics, resulting in millions of. There are three forms of plague: bubonic plague (the most common form, accounting for about 80% of cases), pneumonic plague, and septicemic plague. These forms are differentiated by the mode of transmission and the initial site of infection. In bubonic plague, Y. pestis is transferred by the bite of infected fleas. Since most flea bites occur on the legs and ankles, Y. pestis is often introduced into the tissues and blood circulation in the lower extremities. After a 2- to 6-day incubation period, patients experience an abrupt onset fever (39.5–41 °C [103.1–105.8 °F]), headache, hypotension, and chills. The pathogen localizes in lymph nodes, where it causes inflammation, swelling, and hemorrhaging that results in purple buboes . Buboes often form in lymph nodes of the groin first because these are the nodes associated with the lower limbs; eventually, through circulation in the blood and lymph, lymph nodes throughout the body become infected and form buboes. The average mortality rate for bubonic plague is about 55% if untreated and about 10% with antibiotic treatment.

Septicaemic plague occurs when Y. pestis is directly introduced into the bloodstream through a cut or wound and circulates through the body. The incubation period for septicaemic plague is 1 to 3 days, after which patients develop fever, chills, extreme weakness, abdominal pain, and shock. Disseminated intravascular coagulation (DIC) can also occur, resulting in the formation of thrombi that obstruct blood vessels and promote ischaemia and necrosis in surrounding tissues. Necrosis occurs most commonly in extremities such as fingers and toes, which become blackened. Septicaemic plague can quickly lead to death, with a mortality rate near 100% when it is untreated. Even with antibiotic treatment, the mortality rate is about 50%.

Pneumonic plague occurs when Y. pestis causes an infection of the lungs. This can occur through inhalation of aerosolized droplets from an infected individual or when the infection spreads to the lungs from elsewhere in the body in patients with bubonic or septicaemic plague. After an incubation period of 1 to 3 days, signs and symptoms include fever, headache, weakness, and a rapidly developing pneumonia with shortness of breath, chest pain, and cough producing bloody or watery mucus. The pneumonia may result in rapid respiratory failure and shock. Pneumonic plague is the only form of plague that can be spread from person to person by infectious aerosol droplet. If untreated, the mortality rate is near 100%; with antibiotic treatment, the mortality rate is about 50%.

The high mortality rate for the plague is, in part, a consequence of it being unusually well equipped with virulence factors. To date, there are at least 15 different major virulence factors that have been identified from Y. pestis and, of these, eight are involved with adherence to host cells. In addition, the F1 component of the Y. pestis capsule is a virulence factor that allows the bacterium to avoid phagocytosis. F1 is produced in large quantities during mammalian infection and is the most immunogenic component.Successful use of virulence factors allows the bacilli to disseminate from the area of the bite to regional lymph nodes and eventually the entire blood and lymphatic systems.

Culturing and direct microscopic examination of a sample of fluid from a bubo, blood, or sputum is the best way to identify Y. pestis and confirm a presumptive diagnosis of plague. Specimens may be stained using either a Gram, Giemsa, Wright, or Wayson's staining technique. The bacteria show a characteristic bipolar staining pattern, resembling safety pins, that facilitates presumptive identification. Direct fluorescent antibody tests (rapid test of outer-membrane antigens) and serological tests like ELISA can be used to confirm the diagnosis. The confirmatory method for identifying Y. pestis isolates in the US is bacteriophage lysis.

Prompt antibiotic therapy can resolve most cases of bubonic plague, but septicaemic and pneumonic plague are more difficult to treat because of their shorter incubation stages. Survival often depends on an early and accurate diagnosis and an appropriate choice of antibiotic therapy. In the US, the most common antibiotics used to treat patients with plague are gentamicin, fluoroquinolones, streptomycin, levofloxacin, ciprofloxacin, and doxycycline.

Tularemia

Infection with the gram-negative bacterium Francisella tularensis causes tularemia (or rabbit fever), a zoonotic infection in humans. F. tularensis is a facultative intracellular parasite that primarily causes illness in rabbits, although a wide variety of domesticated animals are also susceptible to infection. Humans can be infected through ingestion of contaminated meat or, more typically, handling of infected animal tissues (e.g., skinning an infected rabbit). Tularemia can also be transmitted by the bites of infected arthropods, including the dog tick (Dermacentor variabilis), the lone star tick (Amblyomma americanum), the wood tick (Dermacentor andersoni), and deer flies (Chrysops spp.). Although the disease is not directly communicable between humans, exposure to aerosols of F. tularensis can result in life-threatening infections. F. tularensis is highly contagious, with an infectious dose of as few as 10 bacterial cells. In addition, pulmonary infections have a 30%–60% fatality rate if untreated.For these reasons, F. tularensis is currently classified and must be handled as a biosafety level-3 (BSL-3) organism and as a potential biological warfare agent.

Following introduction through a break in the skin, the bacteria initially move to the lymph nodes, where they are ingested by phagocytes. After escaping from the phagosome, the bacteria grow and multiply intracellularly in the cytoplasm of phagocytes. They can later become disseminated through the blood to other organs such as the liver, lungs, and spleen, where they produce masses of tissue called granulomas. After an incubation period of about 3 days, skin lesions develop at the site of infection. Other signs and symptoms include fever, chills, headache, and swolle A direct diagnosis of tularemia is challenging because it is so contagious. Once a presumptive diagnosis of tularemia is made, special handling is required to collect and process patients' specimens to prevent the infection of health-care workers. Specimens suspected of containing F. tularensis can only be handled by BSL-2 or BSL-3 laboratories registered with the Federal Select Agent Program, and individuals handling the specimen must wear protective equipment and use a class II biological safety cabinet.

Tularemia is relatively rare in the US, and its signs and symptoms are similar to a variety of other infections that may need to be ruled out before a diagnosis can be made. Direct fluorescent-antibody (DFA) microscopic examination using antibodies specific for F. tularensis can rapidly confirm the presence of this pathogen. Culturing this microbe is difficult because of its requirement for the amino acid cysteine, which must be supplied as an extra nutrient in culturing media. Serological tests are available to detect an immune response against the bacterial pathogen. In patients with suspected infection, acute- and convalescent-phase serum samples are required to confirm an active infection. PCR-based tests can also be used for clinical identification of direct specimens from body fluids or tissues as well as cultured specimens. In most cases, diagnosis is based on clinical findings and likely incidents of exposure to the bacterium. The antibiotics streptomycin, gentamycin, doxycycline, and ciprofloxacin are effective in treating tularemia.n and painful lymph nodes.
Antrax.
Anthrax is a serious infectious disease caused by gram-positive, rod-shaped bacteria known as Bacillus anthracis. Anthrax can be found naturally in soil and commonly affects domestic and wild animals around the world. Although it is rare in the United States, people can get sick with anthrax if they come in contact with infected animals or contaminated animal products. Anthrax can cause severe illness in both humans and animals.
The only ways to confirm an anthrax diagnosis are:
To measure antibodies or toxin in blood
To test directly for Bacillus anthracis in a sample
blood
skin lesion swab
spinal fluid
respiratory secretions
Samples must be taken before the patient begins taking antibiotics for treatment.

The questions for self-control:

1. Pathogenesis of the zoonotic diseases;
2. Features of microbiological diagnosis in connection with the pathogenesis of diseases;
3. Principles of prevention and treatment;
4. Explain the concept of quarantine infections and the rules of the anti-epidemic regime in the occurrence and development of anthrax and plague;
5. Model serological diagnosis of anthrax and brucellosis with interpretation of the results.

Recommended reading:

Maheshwari, Nanda. Clinical Microbiology and Pathology [Text] : for DMLT Students / N. Maheshwari ; Damyanti DMLT Institute. - 3rd ed. - New Delhi ; London ; Philadelphia : Jaypee, 2016. - 498 p. : il. - ISBN 978-93-5250-018-5

Lecture 5
Pathogenic and conditionally pathogenic corynebacterium. Bordetella. Algorithm for laboratory diagnosis of diphtheria, pertussis and pertussis. Features of microbiological diagnosis in connection with the pathogenesis of diseases. Formulation of the Ouchterlony reaction. Interpretation of the results. Principles of treatment, prevention.
Plan of the lecture:
Corynebacterium spp. – diagnosis, interpretations, treatment and prevention;
Bortadella - diagnosis, interpretations, treatment and prevention;
Learning Outcomes:
differentiate causative agents of diphtheria and pertussis, their properties, explain pathogenesis of the development of diseases,

justify features of microbiological diagnosis in connection with the pathogenesis of diseases,
justify principles of prevention and treatment
explain a concept of toxinemic infections

The causative agent of diphtheria, Corynebacterium diphtheriae, is a club-shaped, gram-positive rod that belongs to the phylum Actinobacteria. Diphtheroids are common members of the normal nasopharyngeal microbiota. However, some strains of C. diphtheriae become pathogenic because of the presence of a temperate bacteriophage-encoded protein—the diphtheria toxin. Diphtheria is typically a respiratory infection of the oropharynx but can also cause impetigo-like lesions on the skin. Although the disease can affect people of all ages, it tends to be most severe in those younger than 5 years or older than 40 years. Like strep throat, diphtheria is commonly transmitted in the droplets and aerosols produced by coughing. After colonizing the throat, the bacterium remains in the oral cavity and begins producing the diphtheria toxin. This protein is an A-B toxin that blocks host-cell protein synthesis by inactivating elongation factor (EF)-2. The toxin's action leads to the death of the host cells and an inflammatory response. An accumulation of greyish exudate consisting of dead host cells, pus, red blood cells, fibrin, and infectious bacteria results in the formation of a pseudomembrane. The pseudomembrane can cover mucous membranes of the nasal cavity, tonsils, pharynx, and larynx. This is a classic sign of diphtheria. As the disease progresses, the pseudomembrane can enlarge to obstruct the fauces of the pharynx or trachea and can lead to suffocation and death. Sometimes, intubation, the placement of a breathing tube in the trachea, is required in advanced infections. If the diphtheria toxin spreads throughout the body, it can damage other tissues as well. This can include myocarditis (heart damage) and nerve damage that may impair breathing.

The presumptive diagnosis of diphtheria is primarily based on the clinical symptoms (i.e., the pseudomembrane) and vaccination history, and is typically confirmed by identifying bacterial cultures obtained from throat swabs. The diphtheria toxin itself can be directly detected in vitro using polymerase chain reaction (PCR)-based, direct detection systems for the diphtheria tox gene, and immunological techniques like radial immunodiffusion or Elek's immunodiffusion test.

Broad-spectrum antibiotics like penicillin and erythromycin tend to effectively control C. diphtheriae infections. Regrettably, they have no effect against preformed toxins. If toxin production has already occurred in the patient, antitoxins (preformed antibodies against the toxin) are administered. Although this is effective in neutralizing the toxin, the antitoxins may lead to serum sickness because they are produced in horses. Widespread vaccination efforts have reduced the occurrence of diphtheria worldwide. There are currently four combination toxoid vaccines available that provide protection against diphtheria and other diseases: DTaP, Tdap, DT, and Td. In all cases, the letters "d," "t," and "p" stand for diphtheria, tetanus, and pertussis, respectively; the "a" stands for acellular. If capitalized, the letters indicate a full-strength dose; lowercase letters indicate reduced dosages. According to current recommendations, children should receive five doses of the DTaP vaccine in their youth and a Td booster every 10 years. Children with adverse reactions to the pertussis vaccine may be given the DT vaccine in place of the DTaP.

The causative agent of pertussis, commonly called whooping cough, is Bordetella pertussis, a gram-negative coccobacillus. The disease is characterized by mucus accumulation in the lungs that leads to a long period of severe coughing. Sometimes, following a bout of coughing, a sound resembling a "whoop" is produced as air is inhaled through the inflamed and restricted airway—hence the name whooping cough. Although adults can be infected, the symptoms of this disease are most pronounced in infants and children. Pertussis is highly communicable through droplet transmission, so the uncontrollable coughing produced is an efficient means of transmitting the disease in a susceptible population.

Following inhalation, B. pertussis specifically attaches to epithelial cells using an adhesin, filamentous hemagglutinin. The bacteria then grow at the site of infection and cause disease symptoms through the production of exotoxins. One of the main virulence factors of this organism is an A-B exotoxin called the pertussis toxin (PT). When PT enters the host cells, it increases the cyclic adenosine monophosphate (cAMP) levels and disrupts cellular signalling. PT is known to enhance inflammatory responses involving histamine and serotonin. In addition to PT, B. pertussis produces a tracheal cytotoxin that damages

ciliated epithelial cells and results in accumulation of mucus in the lungs. The mucus can support the colonization and growth of other microbes and, as a consequence, secondary infections are common. Together, the effects of these factors produce the cough that characterizes this infection.
A pertussis infection can be divided into three distinct stages. The initial infection, termed the catarrhal stage, is relatively mild and unremarkable. The signs and symptoms may include nasal congestion, a runny nose, sneezing, and a low-grade fever. This, however, is the stage in which B. pertussis is most infectious. In the paroxysmal stage, mucus accumulation leads to uncontrollable coughing spasms that can last for several minutes and frequently induce vomiting. The paroxysmal stage can last for several weeks. A long convalescence stage follows the paroxysmal stage, during which time patients experience a chronic cough that can last for up to several months. In fact, the disease is sometimes called the 100-day cough.
In infants, coughing can be forceful enough to cause fractures to the ribs, and prolonged infections can lead to death. The CDC reported 20 pertussis-related deaths in 2012,[9] but that number had declined to five by 2015.[10]
During the first 2 weeks of infection, laboratory diagnosis is best performed by culturing the organism directly from a nasopharyngeal (NP) specimen collected from the posterior nasopharynx. The NP specimen is streaked onto Bordet-Gengou medium. The specimens must be transported to the laboratory as quickly as possible, even if transport media are used. Transport times of longer than 24 hours reduce the viability of B. pertussis significantly.
Within the first month of infection, B. pertussis can be diagnosed using PCR techniques. During the later stages of infection, pertussis-specific antibodies can be immunologically detected using an enzyme-linked immunosorbent assay (ELISA).
Pertussis is generally a self-limiting disease. Antibiotic therapy with erythromycin or tetracycline is only effective at the very earliest stages of disease. Antibiotics given later in the infection, and prophylactically to uninfected individuals, reduce the rate of transmission. Active vaccination is a better approach to control this disease. The DPT vaccine was once in common use in the United States. In that vaccine, the P component consisted of killed whole-cell B. pertussis preparations. Because of some adverse effects, that preparation has now been superseded by the DTaP and Tdap vaccines. In both of these new vaccines, the "aP" component is a pertussis toxoid.
Widespread vaccination has greatly reduced the number of reported cases and prevented large epidemics of pertussis. Recently, however, pertussis has begun to reemerge as a childhood disease in some states because of declining vaccination rates and an increasing population of susceptible children.

Questions for self-control:

1. Causative agents of diphtheria and pertussis, their properties, explain pathogenesis of the development of diseases,
2. Features of microbiological diagnosis in connection with the pathogenesis of diseases,
3. Principles of prevention and treatment
4. A concept of toxinemic infections

Recommended reading:

Centers for Disease Control and Prevention. "2015 Provisional Pertussis Surveillance Report." 2016. http://www.cdc.gov/pertussis/downloads/pertuss-surv-report-2015-provisional.pdf. Accessed May 14, 2019

Lecture 6.
Pathogenic and opportunistic mycobacteria. Tuberculosis. Features of microbiological diagnosis in connection with the pathogenesis of diseases. Algorithm for laboratory diagnosis of tuberculosis. Principles of treatment, prevention

Leprosy. Features of microbiological diagnosis in connection with the pathogenesis of diseases. Principles of treatment, prevention.

Plan of the lecture:

Mycobacterium spp.- description;

Tuberculosis –pathogenesis, diagnosis, treatment and prevention;

Leprosy - pathogenesis, diagnosis, treatment and prevention.

Learning Outcomes:

differentiate causative agent of tuberculosis and leprosy, its properties, explain pathogenesis of the development of the disease,

justify features of microbiological diagnosis in connection with the pathogenesis of the diseases,

justify principles of prevention and treatment

explain vaccination rules for the prevention of tuberculosis

discuss general principles of DOTS treatment of tuberculosis

Tuberculosis (TB) is one of the deadliest infectious diseases in human history. Although tuberculosis infection rates in the United States are extremely low, the CDC estimates that about one-third of the world's population is infected with Mycobacterium tuberculosis, the causal organism of TB, with 9.6 million new TB cases and 1.5 million deaths worldwide in 2014.

M. tuberculosis is an acid-fast, high G + C, gram-positive, nonspore-forming rod. Its cell wall is rich in waxy mycolic acids, which make the cells impervious to polar molecules. It also causes these organisms to grow slowly. M. tuberculosis causes a chronic granulomatous disease that can infect any area of the body, although it is typically associated with the lungs. M. tuberculosis is spread by inhalation of respiratory droplets or aerosols from an infected person. The infectious dose of M. tuberculosis is only 10 cells.

After inhalation, the bacteria enter the alveoli. The cells are phagocytized by macrophages but can survive and multiply within these phagocytes because of the protection by the waxy mycolic acid in their cell walls. If not eliminated by macrophages, the infection can progress, causing an inflammatory response and an accumulation of neutrophils and macrophages in the area. Several weeks or months may pass before an immunological response is mounted by T cells and B cells. Eventually, the lesions in the alveoli become walled off, forming small round lesions called tubercles. Bacteria continue to be released into the centre of the tubercles and the chronic immune response results in tissue damage and induction of apoptosis (programmed host-cell death) in a process called liquefaction. This creates a caseous centre, or air pocket, where the aerobic M. tuberculosis can grow and multiply. Tubercles may eventually rupture and bacterial cells can invade pulmonary capillaries; from there, bacteria can spread through the bloodstream to other organs, a condition known as miliary tuberculosis. The rupture of tubercles also facilitates transmission of the bacteria to other individuals via droplet aerosols that exit the body in coughs. Because these droplets can be very small and stay aloft for a long time, special precautions are necessary when caring for patients with TB, such as the use of face masks and negative-pressure ventilation and filtering systems.

Eventually, most lesions heal to form calcified Ghon complexes. These structures are visible on chest radiographs and are a useful diagnostic feature. But even after the disease has apparently ended, viable bacteria remain sequestered in these locations. Release of these organisms at a later time can produce reactivation tuberculosis (or secondary TB). This is mainly observed in people with alcoholism, the elderly, or in otherwise immunocompromised individuals

Because TB is a chronic disease, chemotherapeutic treatments often continue for months or years. Multidrug resistant (MDR-TB) and extensively drug-resistant (XDR-TB) strains of M. tuberculosis are a growing clinical concern. These strains can arise due to misuse or mismanagement of antibiotic therapies. Therefore, it is imperative that proper multidrug protocols are used to treat these infections. Common antibiotics included in these mixtures are isoniazid, rifampin, ethambutol, and pyrazinamide.

A TB vaccine is available that is based on the so-called bacillus Calmette-Guérin (BCG) strain of M. bovis commonly found in cattle. In the United States, the BCG vaccine is only given to health-care workers and members of the military who are at risk of exposure to active cases of TB. It is used more

broadly worldwide. Many individuals born in other countries have been vaccinated with BCG strain. BCG is used in many countries with a high prevalence of TB, to prevent childhood tuberculous meningitis and miliary disease.

The Mantoux tuberculin skin test is regularly used in the United States to screen for potential TB exposure. However, prior vaccinations with the BCG vaccine can cause false-positive results. Chest radiographs to detect Ghon complex formation are required, therefore, to confirm exposure.

Hansen's disease (also known as leprosy) is caused by a long, thin, filamentous rod-shaped bacterium Mycobacterium leprae, an obligate intracellular pathogen. M. leprae is classified as gram-positive bacteria, but it is best visualized microscopically with an acid-fast stain and is generally referred to as an acid-fast bacterium. Hansen's disease affects the PNS, leading to permanent damage and loss of appendages or other body parts.

Hansen's disease is communicable but not highly contagious; approximately 95% of the human population cannot be easily infected because they have a natural immunity to M. leprae. Person-to-person transmission occurs by inhalation into nasal mucosa or prolonged and repeated contact with infected skin. Armadillos, one of only five mammals susceptible to Hansen's disease, have also been implicated in transmission of some cases.

In the human body, M. leprae grows best at the cooler temperatures found in peripheral tissues like the nose, toes, fingers, and ears. Some of the virulence factors that contribute to M. leprae's pathogenicity are located on the capsule and cell wall of the bacterium. These virulence factors enable it to bind to and invade Schwann cells, resulting in progressive demyelination that gradually destroys neurons of the PNS. The loss of neuronal function leads to hypoesthesia (numbness) in infected lesions. M. leprae is readily phagocytized by macrophages but is able to survive within macrophages in part by neutralizing reactive oxygen species produced in the oxidative burst of the phagolysosome. Like L. monocytogenes, M. leprae also can move directly between macrophages to avoid clearance by immune factors.

The extent of the disease is related to the immune response of the patient. Initial symptoms may not appear for as long as 2 to 5 years after infection. These often begin with small, blanched, numb areas of the skin. In most individuals, these will resolve spontaneously, but some cases may progress to a more serious form of the disease. Tuberculoid (paucibacillary) Hansen's disease is marked by the presence of relatively few (three or less) flat, blanched skin lesions with small nodules at the edges and few bacteria present in the lesion. Although these lesions can persist for years or decades, the bacteria are held in check by an effective immune response including cell-mediated cytotoxicity. Individuals who are unable to contain the infection may later develop lepromatous (multibacillary) Hansen's disease. This is a progressive form of the disease characterized by nodules filled with acid-fast bacilli and macrophages. Impaired function of infected Schwann cells leads to peripheral nerve damage, resulting in sensory loss that leads to ulcers, deformities, and fractures. Damage to the ulnar nerve (in the wrist) by M. leprae is one of the most common causes of crippling of the hand. In some cases, chronic tissue damage can ultimately lead to loss of fingers or toes. When mucosal tissues are also involved, disfiguring lesions of the nose and face can also occur.

Hansen's disease is diagnosed on the basis of clinical signs and symptoms of the disease, and confirmed by the presence of acid-fast bacilli on skin smears or in skin biopsy specimens. M. leprae does not grow in vitro on any known laboratory media, but it can be identified by culturing in vivo in the footpads of laboratory mice or armadillos. Where needed, PCR and genotyping of M. leprae DNA in infected human tissue may be performed for diagnosis and epidemiology.

Hansen's disease responds well to treatment and, if diagnosed and treated early, does not cause disability. In the United States, most patients with Hansen's disease are treated in ambulatory care clinics in major cities by the National Hansen's Disease program, the only institution in the United States exclusively devoted to Hansen's disease. Since 1995, WHO has made multidrug therapy for Hansen's disease available free of charge to all patients worldwide. As a result, global prevalence of Hansen's disease has declined from about 5.2 million cases in 1985 to roughly 176,000 in 2014. Multidrug therapy consists of dapsone and rifampicin for all patients and a third drug, clofazimin, for patients with multibacillary disease.

Currently, there is no universally accepted vaccine for Hansen's disease. India and Brazil use a tuberculosis vaccine against Hansen's disease because both diseases are caused by species of Mycobacterium. The effectiveness of this method is questionable, however, since it appears that the vaccine works in some populations but not in others.

Questions for self-control:
Causative agent of tuberculosis and leprosy, its properties, explain pathogenesis of the development of the disease,
Features of microbiological diagnosis in connection with the pathogenesis of the diseases,
Principles of prevention and treatment
Vaccination rules for the prevention of tuberculosis
General principles of DOTS treatment of tuberculosis

Recommended reading:
Levinson, Warren. Review of Medical Microbiology and Immunology [Electronic resource] : monograph / W. Levinson. - 13th ed. - New York ; Chicago ; San Francisco : McGraw Hill, 2014. - 1950 p. - ISBN 978-0-07-181812-4 : W. p.
Maheshwari, Nanda. Clinical Microbiology and Pathology [Text] : for DMLT Students / N. Maheshwari ; Damyanti DMLT Institute. - 3rd ed. - New Delhi ; London ; Philadelphia : Jaypee, 2016. - 498 p. : il. - ISBN 978-93-5250-018-5 :
Ind.: p. 489-498.

Lecture 7
Pathogens of sexually transmitted diseases. Spirochetes. Mycoplasmas. Chlamydia Algorithm for laboratory diagnosis of sexually transmitted diseases. Features of microbiological diagnosis in connection with the pathogenesis of diseases. Principles of treatment, prevention

Plan of the lecture:
1) Pathogens of sexually transmitted diseases.
2) Spirochetes. Mycoplasmas. Chlamydia
3) Algorithm for laboratory diagnosis of sexually transmitted diseases.
4) Principles of treatment, prevention
Learning Outcomes:
1. differentiate causative agent of sexually transmitted diseases, its properties, explain pathogenesis of the development of the disease,
2. justify features of microbiological diagnosis in connection with the pathogenesis of the disease,
3. justify principles of prevention and treatment

Sexually transmitted infections are disease processes from close physical contact between males and females by transmission through sexual contact. Sexually transmitted infections affected all types of people and can be prevented with proper education and barrier control. This activity outlines the evaluation and management of sexually transmitted infections and reviews the role of the interprofessional team in managing patients with this condition.
Objectives:
Describe the evaluation of sexually transmitted infections.
Outline the complications of a sexually transmitted infection.
Identify the management of patients with sexually transmitted infections.
Access free multiple choice questions on this topic.
Go to:
Introduction

What are sexually transmitted infections (STIs), and why are they important? This article will detail important points and reference important articles for providers to use to assist in the evaluation and treatment of patients that present with signs and symptoms related to sexually transmitted infections. Providers should use this article as a guide to further enhance their knowledge and provide a better encounter with their patients.

Sexually transmitted infections, also known as sexually transmitted diseases, involve the transmission of an organism between sexual partners through different routes of sexual contact, either oral, anal, or vaginal. STIs become a concern and burden on the healthcare systems, as many infections go untreated and lead to complications that will be discussed within this review article. We will discuss the natural history and patterns of the spread of the most common sexually transmitted infections. We will conclude with proper evaluation, treatment, and prevention

Etiology

Sexually transmitted infections (STIs) are a worldwide health problem and should be recognized by all health agencies in public sectors. We will explore the etiology of the most common STIs, including complications, physical, and the mental burden they place on infected persons. STIs go underrecognized and have a higher incidence in medically underserved populations. The presenting condition or disease depends on the specific organism, route, signs, and symptoms of the disease. Risk factors that increase transmission of STIs include having unprotected sexual contact with multiple partners, history of STIs, sexual assault, use of alcohol, use of recreational drugs, and intravenous drug use.

Epidemiology

In an ideal world, healthcare providers would have a centralized data collection system to be able to analyze and fully assess the incidence and distribution of such sexually transmitted infections. As health providers, we use various published studies, an official government, or health organizations to assess STI's statistical importance, such as the incidence, distribution, and statistical data. Sexually transmitted diseases (STD) have a high incidence in most countries, especially between the ages of 15 to 50 years of age, including infants. The use of this data and information help clinicians better trend and treat STIs. Providers must recognize that most of all, STIs correlate with patient behavior and should also be addressed during clinical evaluation.

Pathophysiology

This article is to serve as a general presentation of sexually transmitted infections to include most common infections such as human immunodeficiency virus, gonorrhea, chlamydia, genital herpes, human papillomavirus, trichomoniasis, and syphilis. Pathophysiology is the analysis of the physiologic burden of a disease process within an infected person. Within this section, we will discuss the above most common and provide a link to further evaluate other STIs that may be of concern. Sexually transmitted infections can either be bacterial, viral, or parasites, which are transmitted through sexual activity with the exchange of bodily fluids from the infected partner. STIs invade the human body through microscopic abrasions within the mucosal membranes of the penis, vagina, anus, or any other mucosal surfaces. Transmission of STIs can include the use of intravenous drugs, exposure through the vagina during childbirth, or breastfeeding. Organisms invade normal cells and overburden the immune system creating typical signs and symptoms of the disease.

We will discuss basic symptomatology, including genital, extragenital, or disseminated with the use of a history and physical exam to assist with differential diagnosis and recommended treatments. We will review updated treatment regimens by the Center for Disease Control and Prevention and various data collections to have a general overview of sexually transmitted infections. As a provider in the frontlines of STI diagnosis, it is key to understand curable versus incurable sexually transmitted infections. We will cover the most common to be aware of as a provider and note other STI depending on region prevalence.

Human Immunodeficiency Virus(HIV) Acquired Immunodeficiency Syndrome (AIDS)

Enveloped retrovirus encapsulated with two single-stranded RNA.

Primary HIV signs and symptoms are described as flu-like, often diagnosed as an acute viral syndrome.

The duration of onset of symptoms ranges from 4 to 10 weeks.

AIDS is described as the late stage of HIV disease.

Gonorrhea

Gram-negative diplococci bacteria are known as Neisseria gonorrhoeae.
The second most common sexually transmitted infection compared to Chlamydia trachomatis.
Gonorrhea uses glucose to invade mucus epithelial cells. Gonorrhea modifies cellular proteins that allow further penetration of other organisms.
The proliferation of gonorrhea leads to a localized inflammatory reaction leading to signs and symptoms of a sexually transmitted infection.
Chlamydia
Gram-negative obligate, nonmotile intracellular bacteria known as Chlamydia trachomatis.
The most common sexually transmitted infection in the United States, according to the CDC and WHO.
Two infectious forms exist, the elementary body (EB) and the reticulate body (RB). The EB form invades the cell, and the RB form will produce other infectious EB that will infect other non-infectious forms.
Human Papillomavirus (HPV)
HPV is a double-stranded DNA virus that replicates in the basal cell layer of the stratified squamous epithelial cells. This replication cycle induces hyperplasia to carcinoma.
HPV types 16 and 18 are oncogenic strains that induce neoplasm formation HPV types 6 and 11 are common strains that induce anogenital warts, commonly known as condyloma acuminata.
Syphilis
Spirochete bacterium known as Treponema pallidum.
Syphilis infections are increasing compared to previous reports, according to the CDC.
Syphilis presents with a chancre, which is a painless well-demarcated lesion at the site of inoculation.
Syphilis presents in various forms of infection, depending on the duration of infection known as Primary, Secondary, or Tertiary.
Genital Herpes
Genital herpes is caused by the herpes simplex virus 1(HSV-1) or herpes simplex virus 2 (HSV-2).
HSV-1/HSV-2 is a double-stranded DNA virus coated by a lipoglycoprotein with an affinity to infect target cells.
HSV-1 usually associated with orolabial infections, but according to CDC, HSV-1 is now leading in the cause of genital herpes in young and homosexual patients.
Trichomoniasis
Single-celled flagellated anaerobic protozoa are known as Trichomonas vaginallis.
Trichomoniasis is direct damage to the epithelium. The injuries lead to micro ulcerations, specifically in the vagina, cervix, urethra, and paraurethral glands.

History and Physical
Medical professionals are trained to communicate with patients, partners, and families to be able to understand their chief complaint and formulate a differential diagnosis effectively. At the same time, taking a detailed history is mandatory, whether it occurs in a primary clinic or the Emergency Department. Our role as a provider is to be able to communicate with the patient who presents with signs and symptoms of an undiagnosed sexually transmitted infection or infections. As a provider, you should be aware that all adolescents below the age of 18 have the right to an STI screening and treatment without parental consent.[6] Further details should be investigated with individual state health care systems or reference the "Sexually transmitted disease treatment guidelines 2015" that was distributed by the CDC. While performing the sexual history collection, an easy pneumonic that can help guide your questions can be remembered as the "other 5 P's".
Partners
Practices
Prevention against pregnancy
Protection against sexually transmitted infections
Past history of sexually transmitted infections
The physical exam should be guided by the presenting chief complaint and symptoms collected in the review of systems. Physical exam should be done in a private setting with a chaperone at the bedside who you can then document their name in your EHR. The physical exam, along with the history, will provide a

concise differential diagnosis and guide the evaluation, treatment, and management plan of the suspected disease process. At the end of your exam, present the patient with an open-ended question to ensure that there is an open dialogue, and if the patient has any other details about their sexual practice, you as the provider should know.
The physical exam will be broken down by the most common signs and symptoms, the most common physical exam finding, and diagnosis.
HIV
Females and Males:

Signs and symptoms: Patients may present asymptomatic or with an acute viral syndrome to include systemic like symptoms: malaise, fatigue, anorexia, fever, chills, arthralgias, myalgias, or cutaneous presentations.
Physical Exam: Depending on the chief complaint will guide the physical exam. In general, pt should have a thorough history and physical exam to rule out a broad differential diagnosis.
Gonorrhea
Females:

Signs and symptoms: Patients may present with dysuria, urgency, urinary frequency, lower pelvic pain, and abnormal vaginal bleeding.
Physical Exam: If suspecting systemic infection, a thorough physical exam should be performed.

Genitourinary exam: May include inflammation of the external vagina causing excoriations from pruritus, mucopurulent discharge, and friable inflamed mucosal tissue of the cervix.
Males:

Signs and symptoms: Patients may present with testicular pain, dysuria, purulent discharge from meatus, pain with defecation secondary to inflammation of the rectal area, and or prostate. Although the provider should observe systemic signs and symptoms consistent with disseminated gonococcal infection i.e., sore throat, or redness of eyes, joint pain, cutaneous lesions.
Physical Exam: Genitourinary exam: There may be palpable tenderness over the epididymis, purulent discharge from the meatus, Palpable tenderness to the prostate or rectum. As the provider and you are concerned about disseminated gonococcal infection, the provider should perform a thorough physical exam.
Chlamydia
Females:

Signs and symptoms: Most infections can be asymptomatic but may present with vaginal discharge, abnormal vaginal bleeding, lower pelvic pain, urinary frequency, or dysuria. If systemic infection is present, the patient may be febrile, with abdominal pain, nausea, vomiting, fatigue, and malaise.
Physical Exam: Genitourinary exam: inflammation of the cervix with mucopurulent discharge, ectropion, vaginal discharge, tenderness of the cervix, tenderness of the adnexal regions, and abdominal tenderness. If systemic and Fitz-Hugh-Curtis syndrome is on your differential, there may be right upper quadrant tenderness secondary to perihepatitis.
Males:

Signs and symptoms: The most common presenting symptoms are dysuria, testicular pain, pain with defecation secondary to inflammation of the rectal area, and or prostate.
Physical Exam: Genitourinary exam: tenderness to the testicles specifically over the epididymis, tenderness with palpation to the prostate, or rectum region.
HPV:
Females and Males:

Signs and symptoms: Most complaints are cosmetic in nature or an incidental finding due to the asymptomatic nature of HPV types 6 and 11. Patients may also present with ulcerative lesions secondary to oncogenic HPV types 16 and 18
Physical Exam: On exam, there may be an exophytic lesion described as a cauliflower-like growth known as condylomata acuminata. Lesions can be observed over the external genital region, perineum, and or perianal area. Exam for females entails a speculum exam with screening to rule out cervical cancer.
Syphilis:
Females and males:

Signs and symptoms: Presenting symptoms of a syphilis infection depends on the phase of the infection at the current state of evaluation. Symptoms can be broken down by primary, secondary, latent, and tertiary phases, which are best detailed and discussed in the referenced article "Syphilis."
Physical Exam: The physical exam is dependent on the presenting phase of the syphilis infection.

Primary: Presents with a painless well-demarcated lesion/ulcer known as a chancre at the site of inoculation.
Secondary: Presents with systemic symptoms involving a cutaneous lesion and rash. Lesions known as condylomata lata are wart-like lesions that present and resolve during the secondary phase. The rash is specific for palmar regions of the hands and feet.
Latent: Seroconversion of the patient to have positive syphilis serum screenings.
Tertiary: presentation can be within months or years from inoculation. Systemic symptoms can range to cardiovascular, neurologic, and cutaneous symptoms described as gummatous lesions. Neurosyphilis can present with stroke-like symptoms, cranial nerve deficits, a change in mental status, general paresis, or tabes dorsalis.
Herpes
Females and males:
Signs and symptoms: Primary infections tend to induce systemic symptoms, including vesicular lesions over affected areas, pruritus, dysuria, fever, headaches, malaise, and lymphadenopathy. Reactivation usually presents with a prodromal phase to include tingling, itching, and rash consistent with vesicular lesions. Recurrent infections tend to be less intense with a shorter duration.
Physical Exam: The provider should focus on the affected area, whether it is localized or systemic. A primary herpes infection tends to be worse and diffuse symptomatically involving various symptoms. Females may have diffuse vesicular lesions to the internal and external vaginal area.[21] Males may have diffuse vesicular lesions to the glans of the penis, penile shaft, scrotum, perineal/perianal area, and the external/internal rectum. A recurrent herpes infection isolated vesicular lesions over a neuronal tract where the virus is dormant.
Trichomoniasis
Females:
Signs and symptoms: Female can remain asymptomatic with trichomonas vaginalis infection but at times may present with a complaint of foul-smelling discharge, pruritus, dyspareunia, dysuria, and vaginal spotting.
Physical Exam: The exam will show irritation of the external and internal vagina, including classic physical findings "strawberry cervix" as known as colpitis macularis. A foul frothy vaginal discharge may be present on the exam.
Males:
Signs and symptoms: Males can remain asymptomatic with a trichomonas vaginalis infection but can also present with testicular pain, dysuria, or rectal pain.
Physical Exam: Tenderness with palpation to the epididymis and prostate on rectal exam. No overlying skin lesions or inflammatory processes will be seen.
Granuloma Inguinale
Females and males:

Signs and symptoms: Patients will present with highly vascularized lesions over the genitals, perineum that tend to be painless.
Physical Exam: Exam will show ulcer-like lesions that are beefy red consistent with high vascularization that bleeds easily with manipulation. 4 main lesions can be seen on the exam: (1) Ulcerovegetative: large painless ulcer present on the patients physical exam. (2) Nodular: soft and erythematous that tend to ulcerate throughout the infectious process. (3) Cicatricial: dry ulcerations that tend to transition into plaques. (4) Hypertrophic: lesions are thick and painless.
Lymphogranuloma venereum (LGV)
Females and males:
Signs and symptoms: Patients will present with painful lymphadenopathy localized to the inguinal area. Patients may note the initial presentation of a pustule that gradually progressed to large painful ulceration.
Physical Exam: LGV presents with two stages: Primary phase is a small painless papule/pustule that will ulcerate and can be visualized throughout the affected genital area. During the secondary phase, patients present with unilateral lymphadenopathy that is fluctuant with palpation or maybe suppurative in a presentation known as Buboes.[24] Buboes tend to rupture in the acute phase and progress to a thickened mass.
Mycoplasma Genitalium
Females

Signs and symptoms: Patients may present with pelvic pain, dysuria, similar type symptoms as gonorrhea or chlamydia infection. Vaginal irritation, discharge, or foul smell.
Physical Exam: Exam will show irritation of the external and internal vagina, vaginal discharge, cervical tenderness, adnexal tenderness, or abnormal vaginal spotting.
Males:

Signs and symptoms: Patients may present with suprapubic pain, dysuria, urinary frequency, urgency, or testicular pain.
Physical exam: Exam can be benign or tenderness to the epididymis with palpation or tenderness to the prostate on rectal exam.
This is a brief overview of the most common signs and symptoms, physical exam findings, and diagnosis of sexually transmitted infections that can be evaluated in an acute setting such as the emergency department or a routine visit with the patient's primary care provider. The information and references cited should be used for a more in-depth approach to the signs and symptoms of a sexually transmitted infection.

Evaluation
Screening recommendations can be found in a detailed presentation through “Sexually transmitted disease treatment guidelines 2015,” that was distributed by the CDC. The information provided will be extrapolated from the guidelines and should be used at the discretion of the provider in conjunction with the patient.
Depending on the clinical presentation of the patient and acuity, a patient with a primary complaint concerning a sexually transmitted infection should involve ruling out localized versus a systemic infection. Initial diagnostic testing will be guided by the presenting sexually transmitted infection concerning the CDC Sexually transmitted disease treatment guidelines that were updated in 2015.
Most common laboratory testing performed include:
Nucleic Acid Amplification Test (NAAT)
Cerebrospinal Fluid (CSF)
Fluorescent Treponemal Antibody Absorption Test (FTA-ABS)
Rapid Plasma Reagin (RPR)
Treponema pallidum Particle Agglutination (TP-PA)
Venereal Disease Research Laboratory (VDRL)
Chlamydia:

Female: Diagnosis with the use of NAAT vaginal swab or first catch urine sample or self endocervical swab.
Male: Diagnosis with the use of NAAT of a first catch urine sample or urethral sample.
Gonorrhea
Female: Diagnosis with the use of NAAT vulvovaginal or endocervical swab.
Male: Diagnosis with the use of NAAT of a first catch urine sample or urethral sample.
Trichomoniasis
Female: Diagnosis with the use of NAAT of the vagina, endocervical swab, urine analysis, or urethral sample. A wet mount will show motile flagellated protozoa to assist with the diagnosis.
Genital Herpes
Female/Male: Diagnosis by clinical examination, NAAT from genital ulceration, or viral culture.
Genital Warts
Female/Male: Diagnosis by clinical examination or biopsy if warranted.
Syphilis
Female/Male: Diagnosis will be guided by dark field microscopy and serologic tests to include RPR, VDRL, FTA-ABS, or TP-PA. Each test is performed in an algorithmic process. Patients who are presenting with neurosyphilis will need a cerebral spinal fluid sample to assist with the diagnostic workup.
HIV
Female/Male: Diagnosis with the use of blood sample or saliva for antibodies as a preliminary test then followed up with more specific tests, including PCR or specific assays. PCR for diagnostic and confirmation of HIV infection. Specific assays to isolate antibodies or specific viral antigen for confirmation.

Treatment / Management
When approaching treatment and management of a sexually transmitted infection (STI) previously termed as a sexually transmitted disease (STD). During the year 2013, the Center for Disease Control (CDC) and Prevention initiated a goal to update the Sexually Transmitted Treatment Guidelines 2015 with persons who are experts in the field. There are specific sections in this treatment guideline that direct specific care for select populations such as pregnant women, adolescents, persons in correctional facilities, men who have sex with men, women who have sex with women, and transgender men/women. These topics should be explored and reviewed on a case by case issue.
The treatment and management of the patient should be supported by the history and physical exam, whether the patient is evaluated in the Emergency Department or a primary care office. Primary treatments will be discussed, and further reference articles will be cited for further management options for providers. If the primary treatment is not tolerated or the patient is allergic, providers should consult their pharmacy department for further recommendations.
HIV: Primary treatment and management consist of establishing viral load, CD4 count, and starting a patient on highly active antiretroviral therapy (HAART).
HAART included the following classes. Through the guidance of an Infectious disease physician should medications be started? If a patient is seen for an acute concern such as sexual assault or exposure to an STI through high-risk sexual activity with a concern for HIV, a single combination medication should be started with close primary care followup.
Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)
NRTI fixed-dose combinations
Integrase inhibitors
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
CC chemokine receptor five inhibitors (CCR5 Inhibitor)
Protease Inhibitors
Chlamydia: Primary treatment and management should be supported by history, the physical exam, and clinical presentation. Consideration of coinfections with the most common sexually transmitted infections should be considered and treated simultaneously

One dose of azithromycin 1 gram needs to be taken by mouth or doxycycline 100 milligrams to be taken by mouth for seven days. Other formulations can be taken but should be evaluated on a case by case presentation along with the concerns of the patient.
After initial treatment, follow up tests should be discussed with the patient.
Gonorrhea: Primary treatment and management should be supported by history, the physical exam, and the clinical presentation. Consideration of coinfections with the most common sexually transmitted infections should be considered and treated simultaneously.
One dose of 3rd generation cephalosporin, specifically ceftriaxone 250 milligrams to be given by intramuscular injection. One dose of azithromycin 1 gram to be taken by mouth to treat possible coinfection of chlamydia.
After initial treatment, follow up tests should be discussed with the patient.
Syphilis: Treatment and management of secondary, latent, and tertiary syphilis should be independent on the treatment of primary syphilis infection.
Primary, secondary, and early syphilis infection can be treated with Penicillin G Benzathine 2.4 million units to be given by intramuscular injection.
Tertiary syphilis should be treated as an inpatient due to the three doses of penicillin G benzathine 2.4 million units once a week for a total of 3 weeks.
Neurosyphilis should be treated as an inpatient with intravenous penicillin G aqueous 18-24 million units daily divided into 3 to 4 million units every 4 hours or a continuous infusion for a total of 14 days.
Genital Herpes: Treatment and management of a primary infection should include systemic infection followed by symptomatic treatment and starting antiviral medications. The provider and patient should discuss medication options, including the financial strain that may hinder appropriate treatment. Treatment of reactivation herpes infection should be treated with what medication works best for the patient.
Acyclovir, valacyclovir, and famciclovir are three types of primary treatment that can be started on patients. There are various formulations and treatment courses that should be started after the best management plan is discussed with the patient.
Trichomoniasis: Treatment and management should be established with that patient after diagnosis.
One dose of metronidazole 2 grams to be taken by mouth
Metronidazole 500 mg by mouth twice daily with food for seven days
One dose of tinidazole 2 grams to be taken by mouth
Granuloma inguinale: Treatment and management should be guided by history, the physical exam, and clinical presentation as granuloma inguinale is not very common in the United States.
Azithromycin 1 gram to be taken by mouth once per week until lesions resolve completely. Other formulations and dosages can be taken depending on clinical presentation and the guidance of an infectious disease specialist.
LGV: Treatment and management should be guided by history, the physical exam, and clinical presentation as LGV is not very common in the United States.
Doxycycline 100 milligrams taken by mouth twice daily for 21 days.
Mycoplasma genitalium: Concern for an M. genitalium infection should be considered if the patient is suspected of a chlamydia or gonorrhea infection.
One time dose of azithromycin 500 milligrams taken by mouth plus continued azithromycin regimen at 250 milligrams once daily for four days
Differential Diagnosis
A broad differential should be approached when evaluating a patient, whether in an Emergency Department or a primary care setting. Sexually transmitted infections can be localized to the oropharynx, integumentary system, external and internal genitals depending is a male or female, perianal/perineal, and rectum. As the provider, you should establish primary concern and differentiate other diagnoses that may be present. A thorough history, the physical exam, and the clinical presentation should support the definitive diagnosis and also rule out your differential diagnosis.
When approaching a differential diagnosis specifically for sexually transmitted infections, the provider should evaluate each system i.e., cardiovascular, respiratory, gastrointestinal, genitourinary, central

nervous system, musculoskeletal, and the integumentary system. By breaking it down into systems specifically for each sexually transmitted infection will help you as a provider to determine if it is the primary infectious process associated with the STI or a secondary associated symptom of a systemic infectious process. You should also recognize if there is a superimposed infection along with the primary sexually transmitted infection.

Differential STIs should be assessed by system and symptomatology: Each of the following systems can be affected by STIs, leading to direct or indirect involvement.

Cardiovascular: HIV, Syphilis, HSV-1/HSV-2

Respiratory: HIV, chlamydia

Gastrointestinal: HIV, HSV-1/HSV-2, chlamydia, gonorrhea, HPV

Genitourinary: HIV, HSV-1/HSV-2, chlamydia, gonorrhea, HPV

Central nervous system: HIV, syphilis, HSV-1/HSV-2, gonorrhea, HPV

Musculoskeletal: HIV, HSV-1/HSV-2, chlamydia, gonorrhea, HPV

Integumentary system:HIV, HSV-1/HSV-2, chlamydia, gonorrhea, HPV

The use of different resources should be entertained to understand why a differential diagnosis is important and how to use the differential to better serve your patient population.

Prognosis

Throughout this article and literature reviewed, the prognosis depends on the diagnosis of the disease and the progression of the disease at the time of diagnosis. If the disease process is found in the acute phase and can be treated effectively with antivirals, antibiotics, or antifungals, the outcome is dependent on the treatment course. Medication adherence plays a primary role in the prognosis of an infection that is treatable or a chronic condition such as HIV, HSV-1/HSV-2, partially treated STIs, or asymptomatic STIs that continue untreated.

Complications

Sexually transmitted infections (STIs) that remain untreated lead to systemic infections leading to prolonged medical recovery also to include psychological, financial, and general health complications. STIs complications arise from partially treated or untreated infections. Medically underserved populations show an increase in undiagnosed untreated STIs due to the fact they have no attainable healthcare system. An increase of complications can be seen if resources are not allocated to the public sector, such as planned parenthood to provide needed resources to educate people of safe sex practices to included prevention, treatment, and health promotion.

There is a wide array of complications from STIs if left untreated. Females tend to be at higher risk for complications from STIs to include systemic infection from untreated PID, sterility, and infertility from complicated gonorrhea/chlamydial infections. Females, while pregnant, have a higher percentage of preterm labor if they are positive for certain STIs. Females and males have a risk of neoplasm secondary to certain HPV strain types. HIV infections, if not properly managed, will progress to AIDS, a fatal late complication of the infection secondary to a severely immunocompromised state.

Deterrence and Patient Education

Healthcare providers should understand the most common sexually transmitted diseases and should be comfortable with counseling patients on modifiable human behavior while providing a gold standard of care in line with the presenting disease process. Patients should be provided information on prevention, counseling, and proper treatment for their sexually transmitted infections.

Pearls and Other Issues

Key pearls for sexually transmitted infections is to be able to have an open dialogue with your patients regarding their sexual history and current practices. Establishing a good relationship creates a neutral environment and optimizes the treatment course. Do not shame or judge a person's sexual history or sexual practices because this can lead to reservations by the patient to discuss their general and sexual health.

Whether a patient is seen in the emergency department or a primary care office the disposition of the patient should be determined on the clinical presentation. If the patient has a complicated systemic infection admission is most likely warranted but if they have a self-limiting complaint that can be easily treated with proper follow up the patient should be discharged home. Pitfalls a provider may encounter

would most likely be limited education with the prevention, treatment, and limited resources for their patient population.

Enhancing Healthcare Team Outcomes

Sexually transmitted infections are a worldwide concern and issue as they go untreated patients succumb to their disastrous effects, including health, financial burden, psychological, and physical. Data collection for STIs is limited by area. Having access to a national data collection service can help with the prevalence and incidence of certain STIs to allocate resources directed towards prevention and treatment. Continued resources such as planned parenthood would include an interprofessional team and care coordinators to provide these services. Whether patients are seen in the emergency department or their primary care office, patient-centered care should remain the priority.

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Lecture 8

The causative agents of anaerobic infections. Algorithm for laboratory diagnosis of anaerobic infections. Features of microbiological diagnosis in communication with the pathogenesis of diseases. Principles of treatment, prevention. Rickettsia, Borrelia. Features of microbiological diagnosis in connection with the pathogenesis of diseases. Principles of treatment, prevention

Plan of the lecture:

1) The causative agents of anaerobic infections. Algorithm for laboratory diagnosis of anaerobic infections. Features of microbiological diagnosis in communication with the pathogenesis of diseases. Principles of treatment, prevention.
2) Rickettsia, Borrelia. Features of microbiological diagnosis in connection with the pathogenesis of diseases. Principles of treatment, prevention

Learning Outcomes:

1. differentiate causative agent of anaerobic infections, its properties, explain pathogenesis of the development of the disease,
2. justify features of microbiological diagnosis in connection with the pathogenesis of the disease,
3. justify principles of prevention and treatment

Anaerobic bacteria are part of the normal flora of human skin and mucosal membranes. The site of anaerobic infection is commonly the site of normal colonization. The spectrum of infections ranges from local abscesses to life-threatening infections. Anaerobic bacteria differ from aerobic bacteria in their oxygen requirement. Oxygen is toxic to anaerobes which can be explained by the absence of enzymes in the anaerobes of catalase, superoxide dismutase, and peroxidase enzymes. Anaerobes are fastidious organisms and are difficult to grow if proper collection and culture methods are not used. The diagnosis requires clinical suspicion and proper microbiological identification.

Based on oxygen requirement, bacteria can be divided into the following groups:

Obligate aerobes require oxygen as a terminal electron acceptor and do not have any other source of energy, such as fermentation.

Obligate anaerobes obtain energy through fermentation and use organic compounds as a terminal electron acceptor

Facultative anaerobes can grow in the presence or absence of oxygen.

The obligate anaerobes can further be subdivided into 2 types based on a percentage of oxygen that can prove toxic. *Strict obligate anaerobes* will not survive if there is more than half a percent oxygen in the environment, while moderate obligate anaerobes can still grow in a 2 to 8% oxygen environment.

Common sites of anaerobic infections include oral, abdominal, and pelvic cavities; however, anaerobes can cause infections of other regions such as the head, neck, and skin. Clinically significant anaerobes associated with human infections are as follows:

Gram-Positive

Gram-Positive, Spore-forming Bacilli

Clostridium: These are spore-forming anaerobes responsible for some of the more serious human infections. They account for close to 10% of all anaerobic infections. Significant members of this family are *Clostridium difficile,* which causes *C. difficile* infection. *Clostridium perfringens,* which causes gas gangrene or soft tissue infections. *Clostridium septicum* also causes gas gangrene.

Gram-positive, Non-spore-forming Bacilli

Actinomyces: These colonize the human gastrointestinal (GI) tract, and infections result from a break in the mucocutaneous barrier. The 3 most common anatomic sites affected by *Actinomyces* are cervicofacial, thoracic, and abdominal

Propionibacterium: This species is part of the normal flora of skin and mucosa. The most significant member of this family is *Propionibacterium acne* which plays a role in the pathogenesis of acne vulgaris.

Bifidobacterium: This is normal flora of intestinal tracts. It is usually non-pathogenic; however, pediatric infections have been documented in the form of chronic otitis media, abdominal abscesses, and peritonitis.

Lactobacillus: These organisms are also normally found in the GI tract and can be recovered from numerous food products. They have low pathogenic potential; however, cases of abdominal abscesses, aspiration pneumonia, and bacteremia, particularly in neonates, have been described.

Peptococcus and *Peptostreptococcus*: These anaerobes are part of the mouth, GI tract, upper respiratory tract, and urogenital tract, as well as the skin. They can be pathogenic and cause numerous infections such as chronic otitis media, chronic sinusitis, aspiration pneumonia, pelvic inflammatory disease, including tube-ovarian abscesses.

Other members include *Eubacterium, Bifidobacterium, Arcanobacterium,* and microaerophilic *Streptococcus (Streptococcus anginosus, Streptococcus constellatus, Streptococcus inter medius).*

Gram-negative

Bacteroides: These are the most frequently recovered anaerobic pathogens from clinical specimens. They are part of human colonic and normal female genital flora. These organisms are most commonly the cause of intra-abdominal infections, particularly abscesses. The majority of these abscesses are mixed infections. They can also cause extra-abdominal infections such as aspiration pneumonia, brain abscesses, among others.

Fusobacterium: One of the species from this group of anaerobes, *Fusobacterium necrophorum,* is a common cause of peritonsillar abscesses associated with a complication of internal jugular vein thrombosis, known as Lemierre syndrome.

Campylobacter: This is one of the most common causes of acute bacterial gastroenteritis.

Prevotella: These are normal flora of the human oral cavity and intestinal tract. In children, they are frequently associated with head and neck infections such as peritonsillar abscesses, retropharyngeal abscesses as well as perineal or perianal infections such as pilonidal abscesses.

Veillonella: Occasionally associated with abdominal abscesses and aspiration pneumonia in children.

Anaerobes are part of the indigenous or native flora, particularly the oral cavity, human bowel, and female genital tract. The colonization with anaerobes varies with age, organ site, and environmental factors. For example, infants exclusively breastfed have gut flora with predominantly *Bifidobacterium*, with few *Bacteroides* and *Enterococcus* species. On the other hand, infants who are fed cow's milk have gut flora similar to that of an adult's, which contain gram-negative anaerobes and facultative bacillili Anaerobes are part of indigenous flora, which resists colonization and invasion from non-indigenous flora. However, infections from anaerobes do occur and usually result from a breakdown of the mucocutaneous barrier or immunosuppression. Anaerobic organ infections include, but are not restricted

to, brain abscesses, dental infections, aspiration pneumonia, lung abscesses, bite infections (animal/human), abdominal abscesses, and necrotizing infections of soft tissue.

The pathogenesis of anaerobic infections includes disruption of the mucosal surface and entry of the anaerobic bacteria with the invasion of the deep tissue. The mechanisms of entry include local trauma, surgery, viscus perforation (for example, appendicitis), tissue necrosis, and impaired clearance of a sterile site (chronic sinusitis, pneumonia). The site and the extent of infection are based on the virulence factors of the organism and host immunity.

The virulence factors which assist anaerobic infections are adhesions factors (fimbriae and lectin), invasion factors (phospholipase C, lipopolysaccharides, and proteases), factors involved in tissue destruction (fibrinolysis, acetylglucosaminidase, and collagenase production), capsular resistance to phagocytosis, and others. Serious infections are seen in the immunocompromised host.

When implicated in an abscess, anaerobes are usually part of a polymicrobial infection. Experimental rat models with mixed infections have shown that the growth of anaerobes, as well as aerobes, is enhanced in polymicrobial infections.

The majority of anaerobic infections in children are local, and bloodstream infections compromise less than 2% of the cases. The approach to anaerobic infections includes the identification of predisposing factors. They are as follows:

An organ site infection contagious to a site with indigenous colonization (oral cavity, bowel)

Obstruction: For example, nasal foreign body, appendiceal obstruction, bowel obstruction

Perforation: Of hollow viscus such as bowel perforation.

Host's inability to clear secretions, for example, children with cerebral palsy, are predisposed to aspiration pneumonia.

Animal and human bites resulting in penetrating trauma from oral anaerobe

Other important clues of anaerobic infection include the presence of a condition predisposing an individual to an anaerobic infection, for example, tissue necrosis, a foul-smelling discharge, infection leading to thrombophlebitis, no improvement with antibiotics in suspected anaerobic activity.

The clinicians should obtain an anaerobic culture when suspicion of anaerobic infection is present

Common Organ Site Infections in Anaerobic and Aerobic Infections

Head and neck infection: Anaerobes are commonly implicated in dental infections such as dental abscesses, gingivitis, and periodontitis. Exam findings of dental caries or poor dentition are usually present. Anaerobes are also implicated along with other aerobes in suppurative infections of retropharyngeal abscess, peritonsillar abscess, cervical lymphadenitis, deep neck abscesses, and parotitis. The anaerobe associated with Fusobacterium is linked with a complication of peritonsillar abscess known as Lemierre syndrome. Lemierre syndrome is caused by jugular vein septic thrombophlebitis and metastatic emboli to the lungs and liver

Anaerobes are also caused by chronic otitis media and chronic sinusitis, along with other aerobes such as *Staphylococcus aureus* and *Pseudomonas.*

Central nervous system (CNS) infections: Anaerobes are commonly isolated in cultures from brain abscesses which result from a complication of sinusitis, otitis media, dental infections. The 3 anaerobes commonly isolated are *Fusobacterium*, *Prevotella*, and *Bacteroides*. The same organisms are also seen in epidural infections.

Intra-abdominal infections: Damage to the intestinal wall as seen in the perforated appendix gives enteric anaerobes access to the peritoneal cavity. Over days to weeks, it results in the formation of abdominal abscesses. Abdominal abscesses are almost always mixed infections containing both aerobes and anaerobes. The most common anaerobe implicated in abdominal infections is Bacteroides fragilis, followed by *Lactobacillus* and *Clostridium* species.

Anaerobes are also a common cause of liver abscesses. The common anaerobes associated are *Bacteroides* and *Fusobacterium* species.

Pelvic inflammatory disease: Anaerobes are all are involved in pelvic inflammatory diseases (PID). In a sexually active female with signs and symptoms compatible with pelvic inflammatory disease, empiric antimicrobial therapy against anaerobes and anaerobes is indicated. The common anaerobes involved in PID are *Prevotella*, *Porphyromonas*, *Clostridium*.

Pulmonary infections are seen in children who are unable to control upper airway secretions or lack a normal cough reflex, such as in children with cerebral palsy and tracheoesophageal malformations. Aspiration results in pneumonia which can develop into an abscess if untreated. The predominant pathogens involved in aspiration pneumonia are part of the oropharyngeal flora and include *Peptostreptococcus, Prevotella, Bacteroides fragilis, and Fusobacterium.*

Skin and soft tissue infections: Anaerobes can cause a perirectal abscess or facial abscess in children. *Bacteroides fragilis* and *Clostridium* species are usually involved in perirectal infections, and *Prevotella*, *Porphyromonas*, and *Fusobacterium* are involved in oral infections.

Identification of Serious Anaerobic Infections

Timely identification is important to start empiric therapy. Life-threatening infections such as tetanus, gas gangrene, or infantile botulism are caused by the spore-forming anaerobes, *Clostridium tetanus, Clostridium perfringens,* or *Clostridium botulism.* A history of injury, for example, penetrating nail injury or the presence of a devitalized tissue, should prompt evaluation for tetanus in an immunized child. Gas gangrene is caused by *Clostridium perfringens* or *Clostridium septicum*. It is a medical emergency that requires surgical debridement in addition to antibiotic therapy with penicillin-containing antibiotics in combination with clindamycin. Botulism manifests as descending paralysis, particularly in infants. History of consumption of damaged canned food, use of honey, or living or traveling to endemic regions (high clostridial spore counts) is frequent. Physical examination findings are of an afebrile infant with acute onset of feeding difficulty and bulbar involvement (absence of a gag reflex). For suspected cases, expert review is provided by the California Department of Health. Stool should be sent to check for *Clostridium botulism* spores. The mainstay of management is supportive care with or without botulism immunoglobulin (BabyBIG) In an adolescent with a sore throat, neck pain, and tachycardia out of proportion to fever, Lemierre syndrome should be considered. A neck Doppler ultrasound should be done to look for thrombophlebitis of internal jugular veins and chest x-ray to look for septic emboli. **Local Infections Including Abscesses** Abscesses can be limited to CNS, head, and neck region. The abdominal region can be diagnosed with appropriate anaerobic culture. The specimen should be collected from a sterile site, preferably bypassing the normal flora and with needle aspiration or surgical exploration. Tissue or fluid aspirate is preferred over a swab. After collection, the sample should be sent in an anaerobic transport medium, and it should be inoculated in an oxygen-free environment.

Treatment Step 1 Management of anaerobic infection depends on the site of infection, the host, and presence or absence of abscess. As a general rule, an *abscess should always be drained*, and the culture sent for aerobic and anaerobic culture. Also, surgical debridement of necrotic tissue in clostridium necrotizing fasciitis is crucial in treatment.

Step 2 After obtaining appropriate cultures, the child should be placed on empiric antibiotics with activity against anaerobes. The following are the choices: *Metronidazole*: Has excellent activity against Gram-negatives such as *Bacteroides fragilis*. Its activity against Gram positives is good, although less reliable. Metronidazole has excellent bioavailability (100%), and it penetrates well into the tissue, including the central nervous system and abdominal cavity. Metronidazole gives a metallic taste in the mouth, which is frequently cited as the reason for discontinuation. *Clindamycin* is active against many anaerobes. The resistance of clindamycin to *Bacteroides fragilis* is increasing, and it is less reliable as compared to metronidazole, penicillin/beta-lactamase inhibitor, or a carbapenem. Clindamycin, whether administered IV or orally, penetrates well into the tissue, including abscesses, bones, joints. Clindamycin, however, does not enter the central nervous system. *Penicillin/beta-lactamase inhibitor combination*: Penicillin alone is active against anaerobes that do not produce beta-lactamase, such as *Clostridium perfringens*. However, most gram-negative anaerobes produce beta-lactamase and combination penicillins such as oral amoxicillin/clavulanate or intravenous (IV)/intramuscular (IM) ampicillin/sulbactam, ticarcillin/clavulanate, and piperacillin/tazobactam. *Second-generation cephalosporin:* Regarding cephalosporins, the second-generation cephalosporins of cefoxitin, cefotetan, and cefmetazole are more active against *Bacteroides fragilis.* However, given increasing resistance, they are not recommended as empiric treatment. It is commonly used in surgical prophylaxis.*Carbapenems*: Have excellent activity against anaerobes as well as aerobes involved in intra-abdominal and other sites such as CNS. Meropenem is slightly more active than imipenem against gram-negative

bacteria.*Quinolones*: Have good oral absorption and tissue penetration. However, resistance is increasing, and they should be reserved for children with beta-lactam allergy. Quinolones with activity against anaerobes include levofloxacin and moxifloxacin.
Botulism can be confused with other neurological conditions such as Guillain Barre syndrome and infectious causes of paralysis such as enterovirus infection or West Nile Virus paralysis or paresis.Aerobic abscesses from *Escherichia coli*, Pseudomonas such as brain abscess, head and neck abscesses, lung infections, and intra-abdominal infections.

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Lectures 9-10.
Adenoviruses. Poxviruses. Rhabdoviruses. Role in human pathology. The principles of treatment. Prevention. Orthomyxoviruses (influenza virus). Paramyxoviruses (viruses of parainfluenza, mumps, measles, respiratory syncytial virus). Statement of RGA, RTGA, RTGA in paired sera. Interpretation of the results
Plan of the lecture:
Adenoviruses spp. – diagnosis, interpretations, treatment and prevention;
Poxviruses spp - diagnosis, interpretations, treatment and prevention;
Rhabdoviruses spp - diagnosis, interpretation, treatment and prevention;

Learning Outcomes:
differentiate causative agents of respiratory infections, their properties,
explain their role in the development of pathological conditions,
justify principles of laboratory diagnosis and prevention and treatment of diseases caused by them
interpret the results of laboratory diagnosis .

Adenoviruses were first isolated in 1953 in a human adenoid cell culture. Since then, approximately 100 serotypes have been recognized, at least 52 of which infect humans. All human serotypes are included in a single genus within the family Adenoviridae. There are 7 subgroups for human adenoviruses (A through G). The viruses in each subgroup share many properties. The first human adenoviruses to be identified, numbered 1 to 7, are the most common. Common disorders caused by the adenoviruses include respiratory tract infection, pharyngoconjunctivitis (pinkeye), hemorrhagic cystitis, and gastroenteritis. Several adenoviruses have oncogenic potential in animals but not humans, and for this reason have been extensively studied by molecular biologists. These studies have elucidated many viral and eukaryotic cellular processes. For example, analysis of the gene for the adenovirus hexon protein led to the discovery of introns and the splicing of eukaryotic messenger ribonucleic acid (mRNA). Adenovirus is also being used in genetic therapies to deliver deoxyribonucleic acid (DNA) for gene replacement and modification therapy (e.g., cystic fibrosis), to express genes for other viruses (e.g., human immunodeficiency virus [HIV]) as a vaccine, and as oncolytic therapy.
Structure and Replication. Adenoviruses are double-stranded DNA viruses with a genome of approximately 36,000 base pairs, large enough to encode 30 to 40 genes. The adenovirus genome is a linear double-stranded DNA with a terminal protein (molecular mass, 55 kDa) covalently attached at each 5′ end. The virions have a unique structure. The nonenveloped icosadeltahedral capsid comprises 240 capsomeres that consist of hexons and pentons and has a diameter of 70 to 90 nm. The 12 pentons, which are located at each of the vertices, have a penton base and a fiber. The fiber contains the viral attachment proteins. The penton base and fiber are toxic to cells. The pentons and fibers also carry typespecific antigens. The core complex within the capsid includes viral DNA and at least two major proteins. There are at least 11 proteins A, Electron micrograph of adenovirus virion with fibers. B, Model of adenovirus virion with fibers. Adenovirus A B in the adenovirus virion, 9 of which have an identified structural

function. The virus replication cycle takes approximately 32 to 36 hours and produces approximately 10,000 virions. Attachment of the viral fiber proteins to a glycoprotein member of the immunoglobulin superfamily of proteins (≈100,000 fiber receptors are present on each cell) initiates infection for most adenoviruses. This same receptor is used by many coxsackievirus B viruses; thus it is given the name coxsackie adenovirus receptor. Some adenoviruses use the class I major histocompatibility complex (MHC I) molecule as a receptor. Internalization is initiated by interaction of the penton base with an αv integrin followed by receptor-mediated endocytosis in a clathrin-coated vesicle. The virus lyses the endosomal vesicle, and the capsid delivers the DNA genome to the nucleus. The penton and fiber proteins of the capsid are toxic to the cell and can inhibit cellular macromolecular synthesis. A map of the adenovirus genome shows the locations of the viral genes. The genes are transcribed from both DNA strands and in both directions at different times during the replication cycle. Genes for related functions are clustered together. Most of the RNA transcribed from the adenovirus genome is processed into several individual mRNAs in the nucleus. Adenovirus encodes its own DNA polymerase and proteins that promote cell growth and suppress apoptosis and host immune and inflammatory responses. Transcription of mRNA occurs in two phases. Early proteins promote cell growth and include a DNA polymerase that is involved in the replication of the genome. As for the papovaviruses, several adenovirus mRNAs are transcribed from the same promoter and share initial sequences but are produced through the splicing out of different introns. Transcription of the early E1 gene, processing of the primary transcript (splicing out of introns to yield three mRNAs), and translation of the immediate early E1A transactivator protein are required for transcription of the early proteins. The early proteins include more DNA-binding proteins, the DNA polymerase, and proteins to help the virus escape the immune response. The E1A protein is also an oncogene, and together with the E1B protein, it can stimulate cell growth by binding to the cellular growth-suppressor proteins p105RB (p105RB retinoblastoma gene product) (E1A) and p53 (E1B). In permissive cells, stimulation of cell division facilitates transcription and replication of the genome, with cell death resulting from virus replication.

Viral DNA replication occurs in the nucleus and is mediated by the viral-encoded DNA polymerase. The polymerase uses the 55-kDa viral protein (terminal protein) with an attached cytosine monophosphate as a primer to replicate both strands of the DNA. The terminal protein remains attached to the DNA. Late gene transcription starts after DNA replication. Most of the individual late mRNAs are generated from a large (83% of the genome) primary RNA transcript that is processed into individual mRNAs. Capsid proteins are produced in the cytoplasm and then transported to the nucleus for viral assembly. Empty procapsids first assemble, and then the viral DNA and core proteins enter the capsid through an opening at one of the vertices. The replication and assembly processes are inefficient and prone to error, producing as few as one infectious unit per 2300 particles. DNA, protein, and numerous defective particles accumulate in nuclear inclusion bodies. The virus remains in the cell and is released when the cell degenerates and lyses.

Pathogenesis and Immunity. Adenoviruses are capable of causing lytic (e.g., mucoepithelial cells), latent (e.g., lymphoid and adenoid cells), and transforming (hamster, not human) infections. These viruses initially infect epithelial cells lining the oropharynx, as well as the respiratory and enteric organs. The viral fiber proteins determine the target cell specificity. The toxic activity of the penton base protein can result in inhibition of cellular mRNA transport and protein synthesis, cell rounding, and tissue damage. The histologic hallmark of adenovirus infection is a dense, central intranuclear inclusion (that consists of viral DNA and protein) within an infected epithelial celI. These inclusions may resemble those seen in cells infected with cytomegalovirus, but adenovirus does not cause cellular enlargement (cytomegaly). Mononuclear cell infiltrates and epithelial cell necrosis are seen at the site of infection. Viremia may occur after local replication of the virus, with subsequent spread to visceral organs. This dissemination is more likely to occur in immunocompromised patients than in immunocompetent ones. The virus has a propensity to become latent and persist in lymphoid and other tissue such as adenoids, tonsils, and Peyer patches and can be reactivated in immunosuppressed patients. Although certain adenoviruses (groups A and B) are oncogenic in certain rodents, adenovirus transformation of human cells has not been observed. Antibody is important for resolving lytic adenovirus infections and protects the person from reinfection with the same serotype but not other serotypes. Neutralizing antibody is directed at the fiber proteins.

Cell-mediated immunity is important in limiting virus outgrowth, and immunosuppressed people suffer more serious and recurrent disease. Adenoviruses have several mechanisms to evade host defenses and help them persist in the host. They encode small virus-associated RNAs (VA RNAs) that prevent activation of the interferon-induced protein kinase R– mediated inhibition of viral protein synthesis. The viral E3 and E1A proteins block apoptosis induced by cellular responses to the virus or by T-cell or cytokine (e.g., tumor necrosis factor [TNF]-α) actions. Some strains of adenoviruses can inhibit CD8+ cytotoxic T-cell action by preventing.

Epidemiology. Adenovirus virions resist drying, detergents, gastrointestinal tract secretions (acid, protease, and bile), and even mild chlorine treatment. These virions are spread in aerosols and by the fecal-oral route, by fingers, by fomites (including towels and medical instruments), and in ponds or poorly chlorinated swimming pools. Crowds and close proximity, as occurs in classrooms and military barracks, promotes spread of the virus. Adenoviruses may be shed intermittently and over long periods from the pharynx and especially in feces. Most infections are asymptomatic, a feature that greatly facilitates their spread in the community. Adenoviruses 1 through 7 are the most prevalent serotypes. From 5% to 10% of cases of pediatric respiratory tract disease are caused by adenovirus types 1, 2, 5, and 6, and the infected children shed virus for months after infection. Adenovirus causes 15% of the cases of gastroenteritis requiring hospitalization. Serotypes 4 and 7 seem especially able to spread among military recruits because of their close proximity and rigorous lifestyle.

Clinical Syndromes. Adenoviruses primarily infect children and less commonly adults. Disease from reactivated virus occurs in immunocompromised children and adults. Specific clinical syndromes are associated with specific adenovirus types.

Acute Febrile Pharyngitis and Pharyngoconjunctival. Fever Adenovirus causes pharyngitis, which is often accompanied by conjunctivitis (pharyngoconjunctival fever). Pharyngitis alone occurs in young children, particularly those younger than 3 years, and may mimic streptococcal infection. Affected patients have mild, flulike symptoms (including nasal congestion, cough, coryza, malaise, fever, chills, myalgia, and headache) that may last 3 to 5 days. Pharyngoconjunctival fever occurs more often in outbreaks involving older children.

Acute Respiratory Disease. Acute respiratory disease is a syndrome consisting of fever, runny nose, cough, pharyngitis, and possible conjunctivitis. The high incidence of infection of military recruits stimulated the development and use of a vaccine for these serotypes.

Other Respiratory Tract Diseases. Adenoviruses cause coldlike symptoms, laryngitis, croup, and bronchiolitis. They can also cause a pertussis-like illness in children and adults that consists of a prolonged clinical course and true viral pneumonia.

Conjunctivitis and Epidemic Keratoconjunctivitis. Adenoviruses cause a follicular conjunctivitis (pinkeye) in which the mucosa of the palpebral conjunctiva becomes pebbled or nodular, and both conjunctivae (palpebral and bulbar) become inflamed. Such conjunctivitis may occur sporadically or in outbreaks that can be traced to a common source. Swimming pool conjunctivitis is a familiar example of a common-source adenovirus infection. Epidemic keratoconjunctivitis may be an occupational hazard for industrial workers. The most striking such epidemic occurred in people working in the naval shipyards of Pearl Harbor in Hawaii, where it caused more than 10,000 cases during 1941 and 1942. Irritation of the eye by a foreign body, dust, debris, and so forth is a risk factor for acquisition of this infection.

Laboratory Diagnosis. For the results of virus isolation to be significant, the isolate should be obtained from a site or secretion relevant to the disease symptoms. The presence of adenovirus in the throat of a patient with pharyngitis is usually diagnostic if laboratory findings eliminate other common causes of pharyngitis, such as Streptococcus pyogenes. Direct analysis of the clinical sample without virus isolation can be used for rapid detection and identification of adenoviruses. Immunoassays (e.g., fluorescent antibody and enzyme-linked immunosorbent assay) and genome assays (e.g., different variations of polymerase chain reaction [PCR] and DNA probe analysis) can be used to detect, type, and group the virus in clinical samples and tissue cultures. These approaches must be used for enteric adenovirus serotypes 40 to 42, which do not grow readily in available cell cultures. Serologic testing is rarely used except for epidemiologic purposes. The isolation of most adenovirus types is best accomplished in cell cultures derived from epithelial cells (e.g., primary human embryonic kidney cells, continuous

[transformed] lines, such as HeLa and human epidermal carcinoma cells). Within 2 to 20 days, the virus causes a lytic infection with characteristic inclusion bodies and cell death. Recovery of virus from cell culture requires an average of 6 days. The characteristic intranuclear inclusions can be seen in infected tissue during histologic examination. However, such inclusions are rare and must be distinguished from those produced by cytomegalovirus.

• Treatment, Prevention, and Control. Careful handwashing and chlorination of swimming pools can reduce transmission of adenovirus. There is no approved treatment for adenovirus infection, but cidofovir and ribavirin have been used to treat adenovirus-infected immunosuppressed individuals. Live oral vaccines have been used to prevent infections with adenovirus types 4 and 7 in military recruits but are not used in civilian populations

Therapeutic Adenoviruses. Adenoviruses have been used and are being considered for gene delivery for correction of human diseases, including immune deficiencies (e.g., adenosine deaminase deficiency), cystic fibrosis, and lysosomal storage diseases. The virus is inactivated by deletion or mutation of the E1 and other viral genes (e.g., E2, E4). The appropriate gene is inserted into the viral genome, replacing this DNA, and is controlled by an appropriate promoter. The resultant virus vector must be grown in a cell that expresses the missing viral functions (E1, E4) to complement the deficiency and allow production of virus. Types 4 and 7 and replication defective mutants of types 5, 26, and 35 are being developed to carry genes of HIV, Ebola, and other viruses as attenuated vaccines for these deadly viruses. For one of the latest innovations, T lymphocytes are infected with an adenovirus-encoding membranebound antibody to a surface cancer protein (chimeric antigen receptor [CAR]) to allow the T cells to recognize and attack the cancer. Adenoviruses lacking a functional E1B gene create a virus that selectively grows and kills tumor cells that lack p53 providing oncolytic therapy. Despite the genetically engineered attenuation, these viruses still may cause serious disease in immunocompromised individuals.

The Poxviruses include the human viruses variola (smallpox) (genus Orthopoxvirus) and molluscum contagiosum (genus Molluscipoxvirus) as well as some viruses that naturally infect animals but can cause incidental infection in humans (zoonoses). Many of these viruses share antigenic determinants with smallpox, allowing the use of an animal poxvirus for a human vaccine.

Structure and Replication. Poxviruses are the largest viruses, almost visible on light microscopy. They measure 230 × 300 nm and are ovoid to brick shaped with a complex morphology. The poxvirus virion particle must carry many enzymes, including a deoxyribonucleic acid (DNA)-dependent ribonucleic acid (RNA) polymerase, to allow viral messenger RNA (mRNA) synthesis to occur in the cytoplasm. The viral genome consists of a large, double-stranded, linear DNA that is fused at both ends. The structure and replication of vaccinia virus isrepresentative of the other poxviruses . The genome of vaccinia virus consists of approximately 189,000 base pairs. The replication of poxviruses is unique among the DNAcontaining viruses in that the entire multiplication cycle takes place within the host cell cytoplasm. Thus poxviruses must encode the enzymes required for mRNA and DNA synthesis as well as activities other DNA viruses normally obtain from the host cell.

Pathogenesis and Immunity. After being inhaled, smallpox virus replicates in the upper
respiratory tract . Dissemination occurs via lymphatic and cell-associated viremic spread. Internal and dermal tissues are inoculated after a second, more intense viremia, causing simultaneous eruption of the characteristic “pocks.” Molluscum contagiosum and the other poxviruses, however, are acquired through direct contact with lesions and do not spread extensively. Molluscum contagiosum stimulates cell growth and causes a wartlike lesion rather than a lytic infection.

Epidemiology. Smallpox and molluscum contagiosum are strictly human viruses. Smallpox is transmitted by aerosols and by contactwith lesion material or by a fomite. Molluscum contagiosum is spread by direct contact (e.g., sexual contact, wrestling, self-inoculation) or by fomites (e.g., towels). In contrast, thenatural hosts for the other poxviruses are vertebrates other than humans (e.g., cow, sheep, goats), and they infect humans only through accidental or occupational exposure (zoonosis).

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Lecture 11

Picornaviruses - causative agents of poliomyelitis, Coxsackie viruses, ECHO. Principles of treatment, prevention. Statement of reaction of color test. Interpretation of the results. Color sample mechanism Arboviruses. Role in human pathology. The principles of treatment. Prevention Rubella virus. Role in the pathology of pregnant women. Principles of treatment, prevention.

Plan of the lecture:
1) Picornaviruses - causative agents of poliomyelitis, Coxsackie viruses, ECHO.
2) Arboviruses. Role in human pathology. The principles of treatment. Prevention Rubella virus. Role in the pathology of pregnant women. Principles of treatment, prevention.

Learning Outcomes:
differentiate causative agents of poliomyelitis, rubella, their properties,
explain their role in the development of pathological conditions,
justify principles of laboratory diagnosis and prevention and treatment of the diseases caused by them
interpret color test results

Structure

The picornavirus virion is an icosahedral, nonenveloped, small (22 to 30 nm) particle. The capsid proteins encase a sense RNA strand consisting of approximately 7,500 nucleotides. The RNA carries a covalently bound noncapsid viral protein (VPg) at its 5′ end and a polyadenylated tail at its 3′ end.

Classification and Antigenic Types

Classification is based on morphology, physicochemical and biologic properties, antigenic structures, genomic sequence and mode of replication. The family PICORNAVIRIDAE comprises five genera, namely, enteroviruses, rhinoviruses, hepatoviruses, cardioviruses, and aphthoviruses.

The enteroviruses are subdivided into human polioviruses (1–3); human coxsackieviruses A1–22, 24 (CA1–22 and CA24, CA23 = echovirus 9); human coxsackieviruses (B1–6 (CB1–6); human echoviruses 1–7, 9, 11–27, 29–33 (E1–7, 9, 11–27, 29–33; E8=E1; E10 = Reovirus; E28 = Rhinovirus 1A and E34 = CA24 prime strain); human enterovirus 68–71 (EV68–71); vilyuish virus; simian enteroviruses 1–18 (SEV1–18); porcine enteroviruses 1–11 (PEV1–11); bovine enteroviruses 1–2 (BEV1–2).

Multiplication

Picornaviruses multiply in the cytoplasm, and their RNA acts as a messenger to synthesize viral macromolecules. Viral RNA replicates in complexes associated with cytoplasmic membranes via two distinct, partially double-stranded RNAs - the “replicative intermediates.” One complex uses the sense RNA strand, and the other uses the antisense RNA strand as template.

Pathogenesis

Enterovirus can replicate in epithelium of the nasopharynx and regional lymphoid tissue, conjunctiva, intestines, mesenteric nodes, and the reticuloendothelial system. Viremia may cause virus transfer to the spinal cord, brain, meninges, heart, liver, and skin. Some chronic enterovirus infections result in postviral fatigue syndrome. Rhinoviruses infect and replicate mainly in nasopharyngeal epithelium and regional lymph nodes. Hepatitis A virus replicates in the intestinal epithelium, viremia transports the virus to the liver where secondary virus multiplication in the hepatocytes and Kupffer cells results in infectious hepatitis A.

Host Defenses

Interferon and virus-specific IgA, IgM, and IgG antibodies are important in host defense. Neutralizing antibody confers serotype-specific immunity.

Epidemiology

Picornaviruses are widely prevalent. Enteroviruses are transmitted by the fecal-oral route, via salivary and respiratory droplets, and in some cases via conjunctival secretions and skin lesion exudates. Cockroaches and flies may be vectors. Rhinoviruses are transmitted by saliva, respiratory discharge, and contaminated inanimate objects. Immunity is serotype specific.

Diagnosis

Viruses must be isolated and identified in the clinical laboratory. Serology is used to confirm the virus as the cause of infection and for the assessment of immune status.

Control

Poliomyelitis can be prevented by Salk-type (inactivated) and Sabin-type (live) attenuated poliovirus vaccines. Hepatitis A can be prevented by inactivated hepatitis A vaccine (Havrix). Control can be achieved via public education on transmission modes and personal hygiene. Adequate sewage disposal and uncontaminated water supplies are critical for prevention of enteroviral infections. There is no specific therapy.

Enteroviruses

Poliovirus

Poliovirus has tropism for epithelial cells of the alimentary tract and cells of the central nervous system. Infection is asymptomatic or causes a mild, undifferentiated febrile illness. Spinal and bulbar poliomyelitis occasionally occurs. Paralytic poliomyelitis is not always preceded by minor illness. Paralysis is usually irreversible, and there is residual paralysis for life. All three poliovirus serotypes (1 to 3) can give rise to paralytic poliomyelitis.

Coxsackieviruses

Most infections are inapparent or mild. Rashes and vesicular lesions are most commonly caused by group A coxsackieviruses and pleurodynia and viral pericarditis/myocarditis by group B coxsackieviruses. The coxsackievirus A24 variant causes epidemic and pandemic outbreaks of acute hemorrhagic conjunctivitis. Occasionally, coxsackieviruses are associated with paralytic and encephalitic diseases. Coxsackieviruses are characterized by their pathogenicity for suckling mice. They are classified by antibody neutralization tests as coxsackievirus group A (A1 to A24) and coxsackievirus group B (B1 to B6).

Echoviruses

Echoviruses have been associated with febrile and respiratory illnesses, aseptic meningitis, rash, occasional conjunctivitis, and paralytic diseases.

New Enteroviruses

Enterovirus types 68 and 69 cause respiratory illnesses; type 70 causes acute hemorrhagic conjunctivitis and occasionally polio-like radiculomyelitis; type 71 can cause meningitis, encephalitis and outbreaks of hand-foot-mouth disease with or without encephalitis.

Rhinoviruses

Rhinoviruses cause mainly respiratory infections including the common cold. There are to date 115 serotypes. Immunity is type specific.

Hepatovirus

There is only one serotype of Hepatitis A virus. This virus causes gastroenteritis infections and hepatitis A. The family *Picornaviridae* comprises five genera: *Enterovirus, Hepatovirus* and *Rhinovirus*, which infect humans: *Apthovirus* (foot-and-mouth disease virus), which infects cloven-hoofed animals and occasionally humans; and *Cardiovirus*, which infects rodents. At the time of writing, 67 human enterovirus serotypes and 115 rhinovirus serotypes are known. Picornaviruses do not have a common group-specific antigen. However, antigenic sharing is observed between a few serotypes. Each serotype has a type-specific antigen, which is identifiable by neutralization tests. Picornaviruses are found worldwide, the enteroviruses primarily in alimentary tracts of humans and animals but can be in nerve and muscle cells. Rhinoviruses are found in the respiratory tract. Although enteroviruses are transmitted mostly by the fecal-oral route, they can also be transmitted by salivary and respiratory droplets. Some serotypes are spread by conjunctival secretions and exudates from skin lesions.

In temperate countries, outbreaks of enterovirus illnesses occur most frequently in summer and autumn, whereas rhinovirus infections appear more often in autumn and spring. In the tropics, there is no apparent seasonal occurrence. Enteroviruses in excreta that contaminate the soil are carried by surface waters to lakes, beaches, vegetation, and community water supplies. These sources may serve as foci of infection. Shellfish that feed in freshwater or seawater beds contaminated by excreta harbor enteroviruses. Cockroaches in sewage pipelines and flies that settle on excreta may act as transient vectors. Humans are the only natural host for these agents. Disorders caused by coxsackieviruses are shown in Table 53-1. Most infection is inapparent or mild. Illnesses include acute nonspecific febrile disease and common cold-like or influenza like-respiratory diseases, pharyngitis, croup, and pneumonia.

Rashes and vesicular lesions are most commonly caused by group A viruses. Herpangina presents as small, scattered oral vesicles with red areolae in the posterior oropharynx, tonsils, tongue, and palate, which progress to shallow ulcers and heal within a week. Coxsackievirus A10 causes acute lymphonodular pharyngitis with solid white to yellow papules. Coxsackievirus A16, A10 and A5 give rise to sporadic cases and outbreaks of hand-foot-mouth diseases characterized by fever, an oral vesicular exanthema, and sparse symmetric maculopapular eruptions that involve the hands, feet, mouth, buttocks, and occasionally other sites.

Coxsackieviruses also cause exanthematous diseases that may be mistaken for rubella and an aseptic meningitis that is clinically indistinguishable from meningitis caused by polioviruses and a list of other viruses. Occasionally, they cause paralytic and encephalitic diseases or other cerebral dysfunction.

Pleurodynia, also known as epidemic myalgia, devil's grip and Bornholm disease, is caused primarily by group B coxsackieviruses. Onset is usually abrupt, with fever, headache, and stabbing pain in muscles of the chest and/or upper abdomen. The pain is intensified by respiration and movement and may persist for a few weeks. The disease is self-limiting, but relapses, with recurrences of fever and other symptoms, are common. Occasional complications include pleuritis and orchitis.

The most important cause of viral pericarditis and myocarditis in children and adults is coxsackievirus B. Patients develop fever, tachycardia, dyspnea, precordial pain, and occasionally pericardial friction rub. Electrocardiography and radiography are helpful in confirming the diagnosis. The prognosis for uncomplicated pericarditis is good, but when myocarditis is also present the situation is serious.

Neonatal myocarditis in the first month of life may result in severe and frequently fatal disease. The myocarditis is accompanied by involvement of various organs, especially the central nervous system and liver. Onset may be abrupt, with lethargy, feeding difficulties, fever and often signs of cardiac or respiratory distress. The infant may die within days or may recover over the next few weeks. These infections are generally acquired from infected mothers or during a nursery outbreak.

Coxsackievirus A24 (Ca24V) variant is the first human enterovirus known to cause a disease which has the eyes as the primary site of clinical manifestations. Since its discovery in Singapore in 1970, CA24V continues to give rise to sporadic and extensive epidemics of acute hemorrhagic conjunctivitis (AHC) world over. The conjunctivitis is characterized by a short incubation period and high secondary attack rate. Lacrimation, chemosis, edema and hyperemia of the conjunctiva, and preauricular gland enlargement also occur. Follicular hypertrophy of the conjunctiva is more prominent in the upper than lower fornix. Small petechiae to large blotches of subconjunctival hemorrhage, although striking, are seen in only a few cases. Anterior uveitis is common. Corneal lesions cause pain and blurring of vision. Recovery occurs within 1 to 2 weeks without sequelae. Clinically, it is not possible to distinguish conjunctivitis caused by CA24V from conjunctivitis caused by Enterovirus 70. Headaches, respiratory and gastrointestinal complaints may accompany conjunctivitis.

Diagnosis

Virus isolation is often used for diagnosis. Serodiagnosis is used to confirm a suspected case of coxsackievirus B myocarditis, because by the time the cardiac involvement is recognized, virus excretion has usually ceased. The diagnostic four-fold or greater rise in neutralizing antibody titer between paired sera or high antibody titers to a single serotype is commonly registered in children. In adults, antibody to more than one serotype is frequently observed. It is recommended that in the absence of a fourfold or greater rise in antibody titer, unchanging titers of 512 and above be regarded as suggestive of recent

infection. Some patients maintain high antibody titers for years, which suggests that chronic infections do occur.

Recently, a molecular approach using oligo-primers designed for PCR amplification of viral cDNA and analysis of amplified products by gel electrophoresis has been shown to provide a rapid diagnostic tool for AHC and allows differentiation between CA24V and EV70.

Echoviruses

The echoviruses (enteric, cytopathic, human, and orphan viruses) are grouped together because they produce cytopathogenic effects in cell cultures but generally are not pathogenic for mice, and they differ antigenically from the polioviruses. They were first named "orphan viruses" because their relationship with disease was obscure. Echoviruses are identified by neutralization tests as serotypes 1 to 9, 11 to 27, and 29 to 33 (Table 53-2). Echovirus 1 and 8 show antigenic sharing. Echovirus 22 is distinctive in its genomic sequence, which shows little or no identity to other picornavirus. Nevertheless, its biophysical properties, disease manifestations, epidemiology and pathogenesis support its remaining as a member of Enterovirus.

Arboviruses are viruses that are maintained in nature principally, or to an important extent, through biological transmission between susceptible vertebrate hosts by hematophagous (blood-sucking) arthropods. There are more than 500 known arboviruses of which approximately 100 are capable of causing disease in humans. The major arthropod vectors of arboviruses are mosquitoes, ticks, sandflies, and biting midges. Arboviruses are comprised of a diverse group of viruses belonging to many different taxonomic families and have a worldwide distribution. Prevention and control of arbovirus infections requires surveillance to determine virus activity combined with vaccination, health education, and vector control strategies. Arthropod-transmitted viruses (arboviruses) pose important public health challenges worldwide, and continue to do so even while the world is contending with the 2019 coronavirus disease (COVID-19) pandemic. The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is spread by contact with respiratory droplets from infected individuals. Arboviruses pose a different threat to humanity because of their efficient transmission by our formidable health adversary, the mosquito. There is no evidence that mosquitoes are vectors for SARS-CoV-2 or the two structurally related viruses causing SARS or Middle East respiratory syndrome. There are >500 recognized arboviruses worldwide, 150 of which are known to cause human disease.1 This figure may only represent <1% of all arboviruses, as most are zoonotic infections among hosts other than humans.1 Worldwide, the most prevalent arboviral diseases per year are dengue fever (DENV; 96 million cases), chikungunya virus (CHIKV; 693,000 cases), Zika virus (ZIKV; 500,000 cases), yellow fever (130,000 cases), Japanese encephalitis (42,500 cases), and West Nile virus (2,588 cases).2 Other emergent or reemergent arboviral diseases are Eastern equine encephalitis, St Louis encephalitis, La Crosse encephalitis, Rift Valley fever, Spondweni, Mayaro, Usutu, O'nyong-nyong, and Sindbis. As such, arboviral diseases also must remain a clinical focus for physicians beyond the overwhelming concern for COVID-19. In fact, these diseases may complicate efforts to identify COVID-19, especially in underresourced environments, as they share some clinical and laboratory features. This is exemplified by a recent report of a patient in Thailand who was initially diagnosed as having dengue fever, but was later confirmed to be co-infected with SARS-CoV-2.3 Concurrent outbreaks of influenza and dengue viruses also have been reported to cause challenges in underlying pathogen identification and delayed recognition of outbreaks of either of the diseases in the community.DENV, CHIKV, and ZIKV viruses are of current concern because of rising incidence, expanding geographic range, clinically important disease spectrum, and public health burden. These viruses share epidemiology, transmission pathways, and clinical expressions, although their complications vary. The clinical signs associated with infection from these arboviruses are often inapparent, mild, or nonspecific, but they may include serious complications. Definitive diagnoses of DENV, CHIKV, and ZIKV may be made with enzyme-linked immunosorbent assay or reverse transcriptase-polymerase chain reaction, but these tests may not be readily available in many underresourced laboratory settings.

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Lecture 12

Pathogenic and conditionally pathogenic corynebacterium. Bordetella. Algorithm for laboratory diagnosis of diphtheria, pertussis and pertussis. Features of microbiological diagnosis in connection with the pathogenesis of diseases. Formulation of the Ouchterlony reaction. Interpretation of the results. Principles of treatment, prevention.

Plan of the lecture:
Corynebacterium and bordetella
Laboratory diagnosis of diphtheria and pertussis
Pathogenesis
Ouchterlony reaction
Treatment and prevention

Learning Outcomes:
differentiate causative agents of diphtheria and pertussis, their properties, explain pathogenesis of the development of diseases,
justify features of microbiological diagnosis in connection with the pathogenesis of diseases,
justify principles of prevention and treatment
explain a concept of toxinemic infections

The causative agent of diphtheria - Corynebacterium diphtheriae and a large group of microorganisms of the genus corynebacteria, similar in morphological and biochemical properties, are called coryneform bacteria or diphtheroids. They are represented by gram-positive immobile rods, often with thickenings at the ends resembling a club (coryne - a club). Diphtheroids are widespread in soil, air, and food (milk). Among them, three ecological groups can be distinguished:

- human and animal pathogens;

- plant pathogens;

- non-pathogenic corynebacteria.

Many types of diphtheroids are normal inhabitants of the skin, mucous membranes of the pharynx, nasopharynx, eyes, respiratory tract, urethra, and genitals.
Diphtheria.
Diphtheria is an acute infectious disease, predominantly of childhood, which is characterized by intoxication of the body with diphtheria toxin and characteristic fibrinous (diphtheria) inflammation at the site of localization of the pathogen (phther - film).
Morphological and tinctorial properties. C.diphtheriae are thin, polymorphic rods with club-shaped ends, often containing volutin inclusions, detected by methylene blue or Neisser staining. With the latter, the sticks are colored yellow - straw color, grains of volutin (polymetaphosphate) - dark brown. In cultures, the sticks are at an angle to each other (features of division), forming various shapes - spread fingers, V, Y, L, etc. They have a microcapsule, as well as fimbriae, which facilitate adhesion to the epithelium of the mucous membranes.
Cultural properties. On simple media, diphtheria root bacteria do not grow. They require media with blood or blood serum (Leffler media, Ru), on which growth is noted after 10-12 hours, during which time the accompanying (contaminating samples) microflora does not have time to fully develop.

Bordetella - small coccobacilli, have the shape of an ovoid rod, gram-negative, unstable in the external environment. Three types are of primary importance.
1. B. pertussis - the causative agent of whooping cough - an acute infectious disease accompanied by inflammation of the larynx, trachea and bronchi and paroxysmal cough.
2. B.parapertussis - the causative agent of parapertussis.
3. B. bronchiseptica - the causative agent of whooping cough-like disease in dogs, cats and rabbits, can cause respiratory diseases in humans like ARVI (relatively rare).
Cultural features. Bordetellae are demanding on environments, especially whooping cough. For the primary isolation of these hemophilic microorganisms, potato-glycerin agar with the addition of blood (Bordet-Zhangu medium) or casein-charcoal agar (AMC) is used. On blood media, the pertussis causative agent causes the formation of small colonies of a metallic shade with darkening of the media, on AMC - brownish-brown coloration of the colonies. The main forms of colonies are smooth (S) - the so-called I phase (virulent cultures) through intermediate forms pass into rough (R) - phase IV, which is accompanied by a change in cultural, biochemical and antigenic properties, loss of virulence.
Doctors may suspect diphtheria in a sick child who has a sore throat with a gray membrane covering the tonsils and throat. Growth of C. diphtheriae in a laboratory culture of material from the throat membrane pins down the diagnosis. Doctors can also take a sample of tissue from an infected wound and have it tested in a laboratory to check for the type of diphtheria that affects the skin (cutaneous diphtheria).
If a doctor suspects diphtheria, treatment begins immediately, even before the results of bacterial tests are available.
Clinicians commonly use several types of laboratory tests to diagnose Bordetella pertussis. Scientists consider culture the gold standard because it is the only 100% specific method for identification. Other tests that can be performed include polymerase chain reaction (PCR) and serology.
The causative agent at the site of introduction causes fibrinous inflammation with the formation of a fibrinous film tightly adhered to the tissues. The action of exotoxin (described in the section “factors of pathogenicity”) is essential in the caused pathology. By localization, diphtheria of the oropharynx (most often), respiratory tract, nose and rare localization (eyes, external genital organs, skin, wound surface) is isolated. Pharyngeal diphtheria can cause croup and asphyxia.
The main factor is a thermolabile exotoxin of a protein nature, which has a tropism to the nervous and vascular systems. There is a thermostable endotoxin with toxic and sensitizing properties. Tracheal cytotoxin causes damage to the ciliated epithelium. Bacteria produce hyaluronidase, lecithinase, plasma coagulase.
Ouchterlony double immunodiffusion (also known as passive double immunodiffusion) is an immunological technique used in the detection, identification and quantification of antibodies and antigens, such as immunoglobulins and extractable nuclear antigens
Diphtheria is a serious illness. Doctors treat it immediately and aggressively. Treatments include:
Antibiotics. Antibiotics, such as penicillin or erythromycin, help kill bacteria in the body, clearing up infections. Antibiotics cut the time that someone with diphtheria is contagious.
An antitoxin. If a doctor suspects diphtheria, he or she will request a medication that counteracts the diphtheria toxin in the body from the Centers for Disease Control and Prevention. Called an antitoxin, this drug is injected into a vein or muscle.
Before giving an antitoxin, doctors may perform skin allergy tests. These are done to make sure that the infected person doesn't have an allergy to the antitoxin.
If someone has an allergy, he or she needs to be desensitized to the antitoxin. Doctors do this by initially giving small doses of the antitoxin and then gradually increasing the dose.
Children and adults who have diphtheria often need to be in the hospital for treatment. They may be isolated in an intensive care unit because diphtheria can spread easily to anyone not immunized against the disease.
Preventive treatments
If you've been exposed to a person infected with diphtheria, see a doctor for testing and possible treatment. Your doctor may give you a prescription for antibiotics to help prevent you from developing the disease. You may also need a booster dose of the diphtheria vaccine.

People found to be carriers of diphtheria are treated with antibiotics to clear their systems of the bacteria, as well.
Treatment for pertussis is easily available and highly encouraged. If started early, it can help reduce severity, duration and the risk of complications, particularly in infants. So, once a diagnosis is made or suspected exposure has been determined, you should start on antibiotics immediately. Several antibiotics are available to treat pertussis. The most popular are azithromycin, clarithromycin and erythromycin.
If you have had pertussis for three weeks or more, antibiotics will not be prescribed because the bacteria are already gone from your body. At this point, your symptoms will slowly improve on their own, but your doctor will want to address any other damage done to your body while you were sick.
Supportive care, such as plenty of rest and fluids, can ease symptoms. Eating small, frequent meals can help prevent vomiting. It may also be helpful to rid your home of any irritants that could trigger coughing, such as smoke, dust and chemical fumes. Unfortunately, not much can be done for the cough, as over-the-counter cough medicine is ineffective, and its use is strongly discouraged.
In severe cases, hospitalization may be needed to treat complications. Infants are at the greatest risk of developing severe complications.
Pertussis Prevention
Childhood immunization reduces the risk of catching pertussis, and universal immunization of all infants can limit exposure by reducing the overall number of cases. Booster shots may be needed throughout life to ensure that your immunity remains intact. They are recommended for all adults 19-65 years, and for older adults who will be in contact with babies less than 12 months old.
Because the risk of pertussis transmission is so high, if you or someone in your family has pertussis, your doctor will likely suggest that everyone in the household is treated with antibiotics.
Like many other illnesses, having good health habits can reduce the spread of pertussis. Properly wash your hands with soap and water often, especially if you come into contact with an infected individual. Always cover your mouth and nose when coughing or sneezing and clean your hands afterward.
Questions for self-control:
Explain pathogenic and conditionally pathogenic corynebacterium, bordetella.
Analyze algorithm for laboratory and microbiological diagnosis of diphtheria, pertussis.
Formulate the principle of an Ouchterlony reaction.
Explain the principles of treatment, prevention.

Recommended reading:
Levinson, Warren. Review of Medical Microbiology and Immunology [Electronic resource] : monograph / W. Levinson. - 13th ed. - New York ; Chicago ; San Francisco : McGraw Hill, 2014. - 1950 p. - ISBN 978-0-07-181812-4 : W. p.
Maheshwari, Nanda. Clinical Microbiology and Pathology [Text] : for DMLT Students / N. Maheshwari ; Damyanti DMLT Institute. - 3rd ed. - New Delhi ; London ; Philadelphia : Jaypee, 2016. - 498 p. : il. - ISBN 978-93-5250-018-5 : Ind.: p. 489-498.

Lecture 13
Pathogenic and opportunistic mycobacteria. Tuberculosis. Features of microbiological diagnosis in connection with the pathogenesis of diseases. Algorithm for laboratory diagnosis of tuberculosis. Principles of treatment, prevention
Leprosy. Features of microbiological diagnosis in connection with the pathogenesis of diseases. Principles of treatment, prevention
Plan of lecture:
Mycobacteria
Leprosy
Tuberculosis
Laboratory diagnosis
Pathogenesis
Treatment and prevention

Learning Outcomes:
differentiate causative agent of tuberculosis and leprosy, its properties, explain pathogenesis of the development of the disease,
justify features of microbiological diagnosis in connection with the pathogenesis of the diseases,
justify principles of prevention and treatment
explain vaccination rules for the prevention of tuberculosis
discuss general principles of DOTS treatment of tuberculosis
Mycobacteria belong to the Mycobacteriaceae family, the Mycobacterium genus (from the Greek myces - fungus and bacteria - bacillus), which includes more than 160 species of mycobacteria. These are polymorphic microorganisms that form straight or slightly curved rods 0.2-0.7x1-10 microns in size, sometimes branching; possible the formation of filaments like mycelium, easily disintegrating into sticks or cocci. The generic sign of mycobacteria is acid-, alcohol- and alkali resistance, which is due to the presence of a large amount of lipids in the cell wall. They poorly perceive aniline dyes, according to Gram they are stained with difficulty, and are usually weakly positive. Immobile, do not form spores and capsules, aerobes and chemoorganotrophs. They grow slowly or very slowly. Catalase- and arylsulfotase-positive, resistant to lysozyme
Mycobacteria can be divided into three groups:
Mycobacterium tuberculosis complex – causative pathogen of tuberculosis
Nontuberculous mycobacteria (NTM)
Mycobacterium leprae – causative pathogen of leprosy
Leprosy is a chronic infectious disease caused by Mycobacterium leprae. It damages peripheral nerves and can affect the skin, eyes, nose and muscles. Nerve injury in leprosy can cause severe disabling deformities.
Although it is often thought of as a disease of ancient times, it still occurs today and the World Health Organization recorded 3.8 million new cases of leprosy from 105 different countries in the last decade. Leprosy is only rarely reported in Europe today, but it was once prevalent throughout the region and may still occur among people who live or work abroad in endemic countries. People with leprosy often suffer profound social stigma on account of their disease, and leprosy imposes tremendous economic and psychological burdens on individuals and healthcare systems.
Leprosy (also known as Hansen's Disease) is considered a Neglected Tropical Disease. It is a rare infection, usually found in fewer than 1:10,000 people in most populations, and often associated with poverty. The largest numbers of new cases today originate in South-east Asia, the Americas and Africa. Leprosy is curable with multiple antibiotic therapy, usually consisting of rifampin, dapsone and clofazimine. Early detection and treatment can help avoid many of the disabling complications of leprosy. Although several prototype assays are in development, there are no current laboratory screening tests to aid early detection of leprosy, and the disease must be diagnosed clinically.
The pathogens that cause tuberculosis are mycobacteria that belong to the M. tuberculosis complex. This complex comprises the following species:
M. tuberculosis
M. bovis (subsp. bovis and caprae)
vaccine strain M. bovis BCG (Bacille Calmette-Guérin)
M. africanum
M. canettii
M. microti
M. pinnipedii
These species are, with the exception of M. bovis BCG, considered to cause tuberculosis (TB) in humans and animals. Despite their close genetic similarity, these organisms differ considerably with regard to epidemiology, pathogenicity and their host spectrum.
M. tuberculosis is considered to be the main cause of TB in humans.
In 1882 the German physician and microbiologist Robert Koch discovered M. tuberculosis to be the causative pathogen of phthisis. Based on this discovery, diagnosis of the disease could considerably be improved. Koch published his findings on March 24th 1882 in the Berlin Society of Physiology.

Therefore, March 24th is now known to be World Tuberculosis Day, initiated by the World Health Organization (WHO).
Tuberculosis infections usually arise from patients, who suffer from active and thus infectious pulmonary tuberculosis. The pathogens are transmitted via droplet infection through the air by coughing or sneezing. The risk of infection is increased by bad hygiene conditions and in densely populated areas. As the pathogens infect cells of the immune system, so-called macrophages, especially infants and immunocompromised persons are at risk. In most cases the immune system succeeds in fighting the bacteria or in encapsulating them. Mycobacteria can then persist in the body for several years as latent tuberculosis without causing any symptoms. It cannot be predicted when and if reactivation occurs. Even though every organ can be affected, the disease is manifested as pulmonary tuberculosis in 80% of the patients.
M. bovis is the major cause of bovine tuberculosis. It can be transmitted to humans by the consumption of unpasteurised milk or in rare cases via inhalation of dust in barns. Nowadays this infection is quite rare in central Europe as the cattle population is largely free of tuberculosis.
M. bovis can be divided into two subspecies, M. bovis subsp. bovis and M. bovis subsp. caprae. While the latter is sensitive to pyrazinamide (PZA), M. bovis subsp. bovis is resistant.
The BCG vaccine strain, which was developed from M. bovis, is rarely used nowadays in most European countries because its effectiveness is unclear, side effects are frequent and the epidemiologic situation does not require vaccination. Nevertheless, the WHO still recommends BCG vaccination for children under one year of age in high risk countries.
A heterogeneous group of strains that can mainly be found in Africa and which exclusively causes TB in humans, is called M. africanum. M. canettii was mainly isolated from small rodents, whereas M. pinnipedii was detected in seals. On very rare occasions these pathogens were found to cause TB in humans.
TB can be found all around the world and other than HIV/AIDS and malaria it is one of the most frequent infectious diseases. Recent estimations suggest that one third of the world's population is infected with tuberculosis. According to the WHO, each year more than nine million people are newly infected with TB and about two million die from it. About 95% of all newly infected patients live in developing countries. The facts that more and more resistant mycobacteria emerge and that co-infections with HIV are frequent make it even more difficult to fight TB.
There are four important parameters for the containment of TB:
Early diagnosis
Prevention of disease spreading
Effective treatment with antituberculotics
Prevention of resistance development
A skin biopsy is commonly used to diagnose leprosy. A skin biopsy involves removing a small section of skin for laboratory testing. If you have the symptoms of leprosy, a lepromin skin test may be ordered along with a biopsy to confirm both the presence and type of leprosy.
A complete medical evaluation for tuberculosis (TB) must include a medical history, a physical examination, a chest X-ray and microbiological examination (of sputum or some other appropriate sample). It may also include a tuberculin skin test, other scans and X-rays, surgical biopsy.
Studies indicate that leprosy pathogenesis is a two-step process in which a group of genes controls susceptibility to infection per se while different genes control the clinical manifestation of disease.
Infection occurs when a person inhales droplet nuclei containing tubercle bacilli that reach the alveoli of the lungs. These tubercle bacilli are ingested by alveolar macrophages; the majority of these bacilli are destroyed or inhibited. A small number may multiply intracellularly and are released when the macrophages die. If alive, these bacilli may spread by way of lymphatic channels or through the bloodstream to more distant tissues and organs (including areas of the body in which TB disease is most likely to develop: regional lymph nodes, apex of the lung, kidneys, brain, and bone). This process of dissemination primes the immune system for a systemic response.

Hansen's disease is treated with a combination of antibiotics. Typically, 2 or 3 antibiotics are used at the same time. These are dapsone with rifampicin, and clofazimine is added for some types of the disease. This is called multidrug therapy.
Prevention of leprosy through chemoprophylaxis Studies that evaluate the effectiveness of alternatives to SDR for chemoprophylaxis (e.g. regimens that use drugs other than rifampicin or multiple doses) are needed. In addition, research is needed to understand the effectiveness of chemoprophylaxis provided through a "blanket/high-risk population" approach rather than through identification of contacts, since the former might increase feasibility and reduce the risk of stigma compared to contact tracing-based approaches.
Prevention of leprosy through vaccines Trials are needed on new and existing vaccines, including studies on LepVax, a new subunit vaccine currently in stage 1a studies. Trials are also needed on the effects of combined postexposure immunoprophylaxis and chemoprophylaxis. The GDG recommends that any new TB vaccine be evaluated for the prevention of other mycobacterial diseases such as leprosy and Buruli ulcer and vice versa.
The preferred regimen for treating adults with TB remains a regimen consisting of an intensive phase of 2 months of isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB) followed by a continuation phase of 4 months of INH and RIF.
The risk of infection can be reduced by using a few simple precautions:
good ventilation: as TB can remain suspended in the air for several hours with no ventilation.
natural light: UV light kills off TB bacteria.
good hygiene: covering the mouth and nose when coughing or sneezing reduces the spread of TB bacteria.
Questions for self-control:
Explain pathogenic mycobacteria
Describe leprosy and tuberculosis diseases
Analyze algorithm for laboratory and microbiological diagnosis of leprosy and tuberculosis
Explain the principles of treatment, prevention.
Recommended reading:
Levinson, Warren. Review of Medical Microbiology and Immunology [Electronic resource] : monograph / W. Levinson. - 13th ed. - New York ; Chicago ; San Francisco : McGraw Hill, 2014. - 1950 p. - ISBN 978-0-07-181812-4 : W. p.
Maheshwari, Nanda. Clinical Microbiology and Pathology [Text] : for DMLT Students / N. Maheshwari ; Damyanti DMLT Institute. - 3rd ed. - New Delhi ; London ; Philadelphia : Jaypee, 2016. - 498 p. : il. - ISBN 978-93-5250-018-5 : Ind.: p. 489-498.

Lecture 14
Fungal infections or mycoses. Candidiasis, Cryptococcosis, Aspergillosis, Blastomycosis. Laboratory diagnostic, treatment principles, prevention.
Plan of the lecture:
1) Fungal infections or mycoses.
2) Candidiasis, Cryptococcosis, Aspergillosis, Blastomycosis.
3) Laboratory diagnostic, treatment principles, prevention.
Learning Outcomes:
1. differentiate causative agent of mycoses, its properties,
2. explain their role in the development of pathological conditions,
3. justify principles of laboratory diagnosis and prevention and treatment

Classification of Mycoses
The clinical nomenclatures used for the mycoses are based on the (1) site of the infection, (2) route of acquisition of the pathogen, and (3) type of virulence exhibited by the fungus.
Classification Based on Site

Mycoses are classified as superficial, cutaneous, subcutaneous, or systemic (deep) infections depending on the type and degree of tissue involvement and the host response to the pathogen.

Classification Based on Route of Acquisition

Infecting fungi may be either exogenous or endogenous. Routes of entry for exogenous fungi include airborne, cutaneous or percutaneous. Endogenous infection involves colonization by a member of the normal flora or reactivation of a previous infection.

Classification Based on Virulence

Primary pathogens can establish infections in normal hosts. Opportunistic pathogens cause disease in individuals with compromised host defense mechanisms.

Epidemiology

The primary pathogens have relatively well-defined geographic ranges; the opportunistic fungi are ubiquitous.

Introduction

Current magnitude and problems of mycoses

Fungal infections or mycoses cause a wide range of diseases in humans. Mycoses range in extent from superficial infections involving the outer layer of the stratum corneum of the skin to disseminated infection involving the brain, heart, lungs, liver, spleen, and kidneys. The range of patients at risk for invasive fungal infections continues to expand beyond the normal host to encompass patients with the acquired immunodeficiency syndrome; those immunosuppressed due to therapy for cancer and organ transplantation, and those undergoing major surgical procedures. Each of these patient populations has a high risk of developing invasive fungal infections. As the population at risk continues to expand so also does the spectrum of opportunistic fungal pathogens infecting these patients also continue to increase. Many of the deeply invasive mycoses are difficult to diagnose early and often difficult to treat effectively. The development of new approaches to diagnosis and treatment of invasive fungal infections is the subject of intensive research.

Concepts of classification

Fungal infections may be classified according to the site of infection, route of acquisition, and type of virulence. When classified according to the site of infection, fungal infections are designated as superficial, cutaneous, subcutaneous, and deep. Superficial mycoses are limited to the stratum corneum and essentially elicit no inflammation. Cutaneous infections involve the integument and its appendages, including hair and nails. Infection may involve the stratum corneum or deeper layers of the epidermis. Inflammation of the skin is elicited by the organism or its products. Subcutaneous mycoses include a range of different infections characterized by infection of the subcutaneous tissues usually at the point of traumatic inoculation. An inflammatory response develops in the subcutaneous tissue frequently with extension into the epidermis. Deep mycoses involve the lungs, abdominal viscera, bones and or central nervous system. The most common portals of entry are the respiratory tract, gastrointestinal tract, and blood vessels.

Primary Mycoses

Most cases of primary deep mycoses are asymptomatic or clinically mild infections occurring in normal patients living or traveling in endemic areas. However, patients exposed to a high inoculum of organisms or those with altered host defenses may suffer life-threatening progression or reactivation of latent foci of infection.

The arthroconidia of C immitis are inhaled and convert in the lung to spherules. Most cases of coccidioidomycosis are clinically occult or mild infections in patients who inhale infective arthroconidia. However, some patients have progressive pulmonary infection and also may suffer dissemination to the brain, bone, and other sites. Coccidioides meningitis is a life-threatening infection requiring lifelong treatment.

Histoplasmosis is a primary pulmonary infection resulting from inhalation of conidia of Histoplasma capsulatum which convert in vivo into the blastoconidial (budding yeast) form. Dissemination to the hilar and mediastinal lymph nodes, spleen, liver, bone marrow, and brain may be life-threatening in infants and other immunocompromised patients. Histoplasmosis (like tuberculosis) is characterized by intracellular growth of the pathogen in macrophages and a granulomatous reaction in tissue. These granulomatous foci

may reactivate and cause dissemination of fungi to other tissues. These patterns of primary infection and reactivation are similar to those of Mycobacterium tuberculosis (see Chapter 33). Histoplasmosis also may be associated with a chronic inflammatory process known as fibrosing mediastinitis, where scar tissue (formed in response to H capsulatum) encroaches on vital structures in the mediastinum.

Blastomycosis, similar to histoplasmosis, is a primary pulmonary infection resulting from inhalation of conidia from the mycelial phase of Blastomyces dermatitidis which convert in vivo to the parasitic yeast phase. Blastomycosis (due to B dermatitidis) in the blastoconidial phase also causes a primary pulmonary infection. The organism elicits a granulomatous reaction often associated with a marked fibrotic reaction. The clinical pattern of pulmonary blastomycosis is one of chronic pneumonia. Dissemination occurs most commonly to the skin, bone, and, in males, prostate.

Opportunistic Mycoses

Candidiasis

Candidiasis (due to C albicans and other Candida spp.) is the most common opportunistic fungal infection. Candida albicans is the most common cause of candidiasis. Candidiasis may be classified as superficial or deep. Superficial candidiasis may involve the epidermal and mucosal surfaces, including those of the oral cavity, pharynx, esophagus, intestines, urinary bladder, and vagina. The alimentary tract and intravascular catheters are the major portals of entry for deep (or visceral) candidiasis. The kidneys, liver, spleen, brain, eyes, heart, and other tissues are the major organ sites involved in deep or visceral candidiasis. The principal risk factors predisposing to deeply invasive candidiasis are protracted courses of broad spectrum antibiotics, cytotoxic chemotherapy, corticosteroids, and vascular catheters.

Aspergillosis

Invasive aspergillosis most frequently involves the lungs and paranasal sinuses. This fungus may disseminate from the lungs to involve the brain, kidneys, liver, heart, and bones. The main portal of entry for aspergillosis is the respiratory tract, however, injuries to the skin may also introduce the organism into susceptible hosts. Quantitative and functional defects in circulating neutrophils are key risk factors for development of invasive aspergillosis. For example, neutropenia due to cytotoxic chemotherapy and systemic corticosteroids are common predisposing factors for invasive aspergillosis.

Zygomycosis

Zygomycosis due to Rhizopus, Rhizomucor, Absidia, Mucor species, or other members of the class of Zygomycetes, also causes invasive sinopulmonary infections. An especially life-threatening form of zygomycosis (also known as mucormycosis), is known as the rhinocerebral syndrome, which occurs in diabetics with ketoacidosis. In addition to diabetic ketoacidosis, neutropenia and corticosteroids are other major risk factors for zygomycosis. Aspergillus spp and the Zygomycetes have a strong propensity for invading blood vessels.

Cryptococcosis

Cryptococcosis is most typically an opportunistic fungal infection that most frequently causes pneumonia and/or meningitis. Defective cellular immunity, especially that associated with the acquired immune deficiency syndrome, is the most common risk factor for developing cryptococcosis.

Phaeohyphomycosis

Phaeohyphomycosis is an infection by brown to black pigmented fungi of the cutaneous, superficial, and deep tissues, especially brain. These infections are uncommon, life-threatening, and occur in various immunocompromised states.

Hyalohyphomycosis

Hyalohyphomycosis is an opportunistic fungal infection caused by any of a variety of normally saprophytic fungi with hyaline hyphal elements. For example, Fusarium spp. infect neutropenic patients to cause pneumonia, fungemia, and disseminated infection with cutaneous lesions.

Basic Concepts of Environmental Epidemiology

The epidemiology of dimorphic primary pathogens may be contrasted with that of the opportunistic fungal pathogens. The primary pathogens have a relatively well-defined geographic range of endemic infection in immunocompromised hosts. By comparison, the opportunistic fungi (e.g. Aspergillus spp.) are ubiquitously distributed with the frequency of infection being dependent upon a population of

immunocompromised hosts. Penicillium marneffei, an opportunistic pathogen, appears to be geographically restricted to the East Asia, particularly Thailand and China.
Control and Treatment
Hospital-acquired fungal infections may be reduced by maintaining the lowest possible concentration of fungal spores in the ambient air of the institution. Ideally, a “spore-free” environment should be sought.

References:
Walsh TJ, Dixon DM. Spectrum of Mycoses. In: Baron S, editor. Medical Microbiology. 4th edition. Galveston (TX): University of Texas Medical Branch at Galveston; 1996. Chapter 75. Available from: https://www.ncbi.nlm.nih.gov/books/NBK7902/

Lecture 15
Nosocomial diseases. Classification, risks, prevention, clinical cases
Plan of the lecture:
1) Nosocomial diseases.
2) Classification, risks, prevention, clinical cases
Learning Outcomes:
1. explain the role of popular nosocomial infections in the development of pathological conditions,
2. justify features of microbiological diagnosis in connection with the pathogenesis of the disease,
3. justify principles of prevention and treatment

A nosocomial infection is contracted because of an infection or toxin that exists in a certain location, such as a hospital. People now use nosocomial infections interchangeably with the terms health-care associated infections (HAIs) and hospital-acquired infections. For a HAI, the infection must not be present before someone has been under medical care.

One of the most common wards where HAIs occur is the intensive care unit (ICU), where doctors treat serious diseases. About 1 in 10 of the people admitted to a hospital will contract a HAI. They’re also associated with significant morbidity, mortality, and hospital costs.
As medical care becomes more complex and antibiotic resistance increases, the cases of HAIs will grow. The good news is that HAIs can be prevented in a lot of healthcare situations. Read on to learn more about HAIs and what they may mean for you.
What are symptoms of nosocomial infections?
For a HAI, the infection must occur:
up to 48 hours after hospital admission
up to 3 days after discharge
up to 30 days after an operation
in a healthcare facility when someone was admitted for reasons other than the infection
Symptoms of HAIs will vary by type. The most common types of HAIs are:
urinary tract infections (UTIs)
surgical site infections
gastroenteritis
meningitis
pneumonia
The symptoms for these infections may include:
discharge from a wound
fever
cough, shortness of breathing
burning with urination or difficulty urinating
headache
nausea, vomiting, diarrhea

People who develop new symptoms during their stay may also experience pain and irritation at the infection site. Many will experience visible symptoms.

What causes nosocomial infections?

Bacteria, fungus, and viruses can cause HAIs. Bacteria alone cause about 90 percent of these cases. Many people have compromised immune systems during their hospital stay, so they're more likely to contract an infection.

Of the HAIs, P. aeruginosa accounts for 11 percent and has a high mortality and morbidity rate.

Bacteria, fungi, and viruses spread mainly through person-to-person contact. This includes unclean hands, and medical instruments such as catheters, respiratory machines, and other hospital tools. HAI cases also increase when there's excessive and improper use of antibiotics. This can lead to bacteria that are resistant to multiple antibiotics. Who is at risk for nosocomial infections?

Anyone admitted to a healthcare facility is at risk for contracting a HAI. For some bacteria, your risks may also depend on:

your hospital roommate
age, especially if you're more than 70 years old
how long you've been using antibiotics
whether or not you have a urinary catheter
prolonged ICU stay
if you've been in a coma
if you've experienced shock
any trauma you've experienced
your compromised immune system

Your risk also increases if you're admitted to the ICU. The chance of contracting a HAI in pediatric ICUs is 6.1 to 29.6 percent. A studyTrusted Source found that nearly 11 percent of roughly 300 people who underwent operations contracted a HAI. Contaminated areas can increase your risk for HAIs by almost 10 percent.

HAIs are also more common in developing countries. Studies show that five to 10 percent of hospitalizations in Europe and North America result in HAIs. In areas such as Latin America, Sub-Saharan Africa, and Asia, it's more than 40 percent.

How are nosocomial infections diagnosed?

Many doctors can diagnose a HAI by sight and symptoms alone. Inflammation and/or a rash at the site of infection can also be an indication. Infections prior to your stay that become complicated don't count as HAIs. But you should still tell your doctor if any new symptoms appear during your stay.

You also may be required to talk a blood and urine test as to identify the infection.

How are nosocomial infections treated?

Treatments for these infections depend on the infection type. Your doctor will likely recommend antibiotics and bed rest. Also, they'll remove any foreign devices such as catheters as soon as medically appropriate.

To encourage a natural healing process and prevent dehydration, your doctor will encourage a healthy diet, fluid intake, and rest.

What is the outlook for nosocomial infections?

Early detection and treatment are vital for HAIs. Many people are able to make a full recovery with treatment. But people who get HAIs usually spend 2.5 times longer in the hospital.

In some cases, a HAI can seriously increase your risk for life-threatening situations. The Centers for Disease Control and Prevention (CDC)Trusted Source estimate that around 2 million people contract HAIs. About 100,000 of those cases result in death.

Preventing nosocomial infections

The responsibility of HAI prevention is with the healthcare facility. Hospitals and healthcare staff should follow the recommended guidelines for sterilization and disinfection. Taking steps to prevent HAIs can decrease your risk of contracting them by 70 percentTrusted Source or more. However, due to the nature of healthcare facilities, it's impossible to eliminate 100 percent of nosocomial infections.

Some general measures for infection control include:

Screening the ICU to see if people with HIAs need to be isolated.
Identifying the type of isolation needed, which can help to protect others or reduce chances of further infection.
Observing hand hygiene, which involves washing hands before and after touching people in the hospital.
Wearing appropriate gear, including gloves, gowns, and face protection.
Cleaning surfaces properly, with recommended frequency.
Making sure rooms are well ventilated.
To reduce the risk of UTIs, your healthcare provider can:
Follow the aseptic insertion technique to minimize infection.
Insert catheters only when needed and remove when no longer needed.
Change catheters or bags only when medically indicated.
Make sure the urinary catheter is secured above the thigh and hanging below the bladder for unobstructed urine flow.
Keep a closed drainage system.
Talk to your doctor about any concerns you have during a procedure.
Takeaway
Nosocomial infections, or healthcare associated infections occur when a person develops an infection during their time at a healthcare facility. Infections that appear after your hospital stay must meet certain criteria in order for it to qualify as a HAI.
If new symptoms appear within 48 hours of admission, three days after discharge, or 30 days after an operation, talk to your doctor. New inflammation, discharge, or diarrhea could be a symptom of a HAI. Visit the CDC websiteTrusted Source to see what your state's healthcare facilities do to prevent HAIs.

References:

https://www.healthline.com/health/hospital-acquired-nosocomial-infections#takeaway