1.10 Prolonged fever in the adult

Ville Valtonen

Principles

♦ Diagnose common diseases (pneumonia, sinusitis, urinary tract infection) before ordering a large number of tests.
♦ Decide on the urgency of tests according to the patient’s general condition, risk factors (immunosuppression) and local signs.
♦ Repeat history and physical examination before repeating tests.

Diagnostic strategy

♦ Exclude the following common diseases before further investigations:
  ● Pneumonia (chest x-ray and auscultation)
  ─ Chest x-ray may also show tuberculosis, sarcoidosis, alveolitis, pulmonary infarction or lymphoma.
  ● Urinary tract infection (urine test and culture)
  ─ Urine test may even also suggest epidemic nephropathy or renal tumour.
  ● Maxillary sinusitis (ultrasound or x-ray).
♦ Important questions on the history include
  ● Occurrence (measuring!) and duration of fever
  ● Travelling, place (country) of birth, living
  ● Past diseases, particularly tuberculosis and valvular defects
  ● Drug therapy, including over-the-counter drugs
  ● Use of alcohol
  ● Systematic review of organ systems for symptoms
♦ Diagnostic clues and possible aetiologies
  ● See Table 1.10.1
♦ Tests
  ● Primary investigations
    ─ Urine test and culture
    ─ CRP and ESR
    ─ Haemoglobin, WBC count (WBC differential and platelet count)
    ─ AST and ALT
    ─ Option: serum sample to be frozen for eventual serology
    ─ Chest x-ray
    ─ Maxillary sinus ultrasound or x-ray
  ● Secondary investigations
    ─ Abdominal ultrasonography
    ─ Bone marrow aspiration
    ─ Serology (Yersinia, tularaemia, HIV, Borrelia burgdorferi, viral antibodies, serum HBs-Ag, serum HCV-Ab, antinuclear antibodies)
  ─ Blood bacterial culture
♦ Consider your tactics before continuing with investigations
  ● See Table 1.10.2.
♦ Browse a list of causes for fever to see what may have escaped your notice.

Causes of prolonged fever

♦ Tuberculosis (any organ)
♦ Bacterial infections
  ● Sinusitis
  ● Urinary tract infection
  ● Intra-abdominal infections (cholecystitis, appendicitis, abscesses)
  ● Perianal abscess
  ● Abscesses of the chest cavity (lungs, mediastinum)
  ● Bronchiectasis
  ● Salmonellosis, Shigellosis
  ● Osteomyelitis
♦ Bacteraemia without focus (more often an acute disease rather than prolonged fever)
♦ Intravascular infections
  ● Endocarditis
  ● Infections of vascular prostheses
♦ Generalized viral or bacterial infections
  ● Mononucleosis
  ● Adeno-, Cytomegalio- or Coxsackie B viral infections
  ● Hepatitis
  ● HIV
  ● Chlamydial infection (Psittacosis, Ornithosis)
  ● Toxoplasmosis
  ● Lyme disease
  ● Tularaemia
  ● Malaria
♦ Benign temperature elevation after an infectious disease
♦ Chronic fatigue syndrome
♦ Sarcoïdosis
♦ Atrial myxoma
♦ Subacute thyreoiditis
♦ Thyreotoxicosis
♦ Hemolytic diseases
♦ Post-traumatic tissue damage and haematoma
♦ Vascular thrombosis, pulmonary embolism
♦ Kawasaki disease
♦ Erythema nodosum
♦ Drug fever
♦ Malignant neuroleptic syndrome
♦ Allergic alveolitis
  ● Farmer’s lung
♦ Connective tissue diseases
  ● Polymyalgia rheumatica, temporal arteritis
  ● Ankylosing spondylitis
  ● Rheumatoid arthritis
  ● Systemic lupus erythematosus (SLE)
Table 1.10.1  Prolonged fever in the adult – diagnostic clues

<table>
<thead>
<tr>
<th>Clue</th>
<th>Possible causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection parameters (ESR, CRP) are normal</td>
<td>Chronic fatigue syndrome, minor temperature elevation after an infectious disease, drug fever, self-induced fever</td>
</tr>
<tr>
<td>Already cured viral or bacterial infection</td>
<td>Mild “vegetative” temperature elevation after an infectious disease lasting for up to 1–2 months is a functional disorder (“thermostatic temperature elevation”). The thermoregulatory system is temporarily reset by high fever, and body temperature remains elevated. Stress and fatigue may contribute to the disorder</td>
</tr>
<tr>
<td>Erythema</td>
<td>See 31.3. Meningococcaemia, drug fever</td>
</tr>
<tr>
<td>Throat or neck pain</td>
<td>Subacute thyreoiditis, retropharyngeal abscess, mononucleosis</td>
</tr>
<tr>
<td>Confusion</td>
<td>In elderly confusion is associated with the fever itself, in younger patients remember encephalitis and any possible septic infection (1.70)</td>
</tr>
<tr>
<td>Known valvular defect or murmur suggesting one</td>
<td>Endocarditis</td>
</tr>
<tr>
<td>GI symptoms</td>
<td>Crohn’s disease, ulcerative colitis, periappendicular abscess, other peritoneal abscesses, yersiniosis</td>
</tr>
<tr>
<td>Abnormal urinary findings</td>
<td>UTI, epidemic nephritis, renal cancer, endocarditis</td>
</tr>
<tr>
<td>History of stay in the tropics</td>
<td>See article on suspected tropical disease 2.30</td>
</tr>
<tr>
<td>Farmer</td>
<td>Tularaemia</td>
</tr>
<tr>
<td>Suppurative mosquito bite or ulcer</td>
<td>Mononucleosis, Hodgkin’s disease, lymphoma</td>
</tr>
<tr>
<td>Lymph nodes felt on palpation</td>
<td>Neuroleptic malignant syndrome</td>
</tr>
<tr>
<td>Neuroleptic medication</td>
<td>Drug fever, Clostridium difficile</td>
</tr>
<tr>
<td>Long-term antimicrobial medication</td>
<td>See 1.71</td>
</tr>
<tr>
<td>Immunosuppression patient</td>
<td>Temporal arteritis</td>
</tr>
<tr>
<td>Headache</td>
<td>Polymyalgia rheumaticia (may be associated with the fever itself)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>Myeloma, metastasis</td>
</tr>
<tr>
<td>Bone pains</td>
<td>Ankylosing spondylitis, several infections</td>
</tr>
<tr>
<td>Back pain</td>
<td>Infection focus</td>
</tr>
<tr>
<td>Back pain on tapping</td>
<td>Endocarditis, deep infectious foci</td>
</tr>
<tr>
<td>Recurring fever</td>
<td>Self-induced fever</td>
</tr>
<tr>
<td>Discrepancy between findings and history</td>
<td></td>
</tr>
</tbody>
</table>

1) The diagnosis of diseases marked with bold must not be delayed.

Table 1.10.2  Diagnostic tactics in prolonged fever

<table>
<thead>
<tr>
<th>Right</th>
<th>Wrong</th>
</tr>
</thead>
<tbody>
<tr>
<td>Take history again</td>
<td>Repeat laboratory and radiologic investigations</td>
</tr>
<tr>
<td>Repeat the physical examination</td>
<td>Start drug therapy or increase dosage</td>
</tr>
<tr>
<td>Read the journal again</td>
<td>Suggest a surgical intervention</td>
</tr>
<tr>
<td>Take time to reflect upon the case</td>
<td></td>
</tr>
</tbody>
</table>

♦ Malignant diseases
  - Leukaemia
  - Cancer of the pancreatic and biliary ducts
  - Renal carcinoma (hypernephroma)
  - Sarcomas
  - Hodgkin’s disease, other lymphomas
  - Metastases (renal carcinoma, melanoma, sarcoma)

**FUO**

♦ The diagnosis Febris e causa ignota (fever of undetermined origin, FUO) is used when a fever above 38°C has lasted longer than 2–3 weeks.

♦ Usually the cause is a serious disease, which can often be treated. An aetiological diagnosis should be pursued intensively, preferably in the hospital.

♦ The final diagnosis is infection in about 35% of the patients, malignant disease in 20%, collagenosis in 15% and some other disease in 15%. In about 15% of the patients the cause remains unknown.

- Still’s disease of the adult
- Rheumatic fever
- Vasculitides
- Periarteritis nodosa
- Wegener’s granulomatosis

♦ Inflammatory bowel diseases
  - Regional enteritis (Crohn’s disease)
  - Ulcerative colitis

♦ Cirrhosis of the liver, alcoholic hepatitis
1.20 Yersiniosis

Rauli Leino

Basic rules

- Consider yersiniosis in patients with
  - acute abdominal pain
  - acute diarrhoea
  - fever of unknown origin
  - Reiter’s disease
    - arthritis
    - urethritis
    - iritis, conjunctivitis
  - erythema nodosum
  - abnormal results in urine test, liver function tests or tests for pancreatitis
  - hypersedimentation.

Causative agents

- Yersinia enterocolitica 3 and 9, Y. pseudotuberculosis IA and 3.
- The causative agent cannot be identified on the basis of the clinical symptoms.

Symptoms and clinical picture

Symptoms of acute infection

- Fever
- Diarrhoea: children often have blood and mucus in the stools.
- Abdominal pain: in children often in the right lower quadrant. If the patient is operated on, mesenteric lymphadenopathy, terminal ileitis, or true appendicitis may be detected.

Post-infectious symptoms

- Reactive arthritis
  - 1–3 weeks after enteritis
  - The symptoms vary from mild arthralgia to severe polyarthritis, sometimes Reiter’s syndrome.
  - A small proportion of the patients develop chronic arthritis.
  - The disease is strongly associated with HLA-B27.
- Ocular symptoms
  - Iritis
  - Conjunctivitis
- Urinary symptoms
  - Urethritis
  - Balanitis
  - Glomerulonephritis
- Skin symptoms
  - Erythema nodosum is the most common skin manifestation (about 10% of cases are caused by Yersinia); it can be the only symptom of yersiniosis.
- Cardiac findings
  - Transient ECG abnormalities
  - Valvular disease is not associated with yersiniosis.
- Other symptoms
  - Hepatitis, pancreatitis or thyroiditis

Diagnosis

Faecal bacterial culture

- Useful in acute disease
- The sensitivity decreases rapidly after the symptoms of enteritis have disappeared.

Serology

- The primary diagnostic method in post-infectious symptoms (arthritis)
- The ELISA method is the most specific.
  - A recent infection can be diagnosed on the basis of one serum sample.
  - Class IgM antibodies appear in a few days and disappear after a few months.
  - Class IgG antibodies can be detected for years.
  - Class IgA antibodies are particularly associated with arthritis.
  - A cross-reaction occurs between Y. enterocolitica 9 and Brucella, but an ELISA inhibition test confirming the diagnosis is automatically performed in positive cases.

Treatment

- The disease is usually cured spontaneously.
- Chronic carriers have not been detected.
- There is little evidence on the effect of antibiotic treatment; its effect on the occurrence of post-infectious symptoms is not known.

Indications for antibiotics

- Septicaemia
- Fulminant disease or severe post-infective symptoms (such as arthritis) are relative indications for antibiotics.

Selection and dosage

- Quinolones, e.g. ciprofloxacin 500 mg × 2 × 7–10 days
- Tetracyclines are a good alternative.
- Trimethoprim-sulpha is the drug of choice for children.
Indications for specialist referral

♦ Acute appendicitis
♦ Severe post-infectious symptoms

1.21 Tularaemia

Janne Laine

Aims

♦ Suspect tularaemia in patients with fever, lymphadenopathy and an ulcerated skin lesion (Figure 1.21.1) at the site of a mosquito bite or a scratch.
♦ Begin treatment on the basis of the clinical picture if the symptoms are typical. Diagnosis can be confirmed with serology.

Transmission

♦ The most important reservoir host is the mole.
♦ The infection is transmitted by
  • mosquitoes (most important)
  • other blood-sucking arthropods (horse-flies, black flies, ticks)
  • bites or scratches of a sick animal
  • inhalation of infected aerosols

Symptoms

♦ Varying clinical manifestations:
  • The ulceroglandular form (75–85% of the cases) causes fever, a small infected skin lesion as well as swelling and tenderness of regional lymph nodes.
  • The glandular form (5–10% of the cases) causes fever and lymphadenopathy but no skin lesions.
  • The typhoidal form (5–15% of the cases) causes severe systemic symptoms (fever, fatigue and weight loss) and possibly enlargement of the liver and spleen.
  • The oculoglandular form causes granulomatous conjunctivitis with regional lymphadenopathy.
  • The oropharyngeal form causes tonsillitis, pharyngitis and cervical lymphadenopathy.

♦ Symptomless infection is common (about 50% of the cases).
♦ Rash has been reported in up to 20% of the patients.
♦ Pneumonia is seen in 15% of the ulceroglandular cases and in nearly all patients with other forms of the disease.
♦ Elevated liver enzyme values, enlarged liver
♦ Peritonitis, meningitis and osteomyelitis are rare.
♦ CRP increases moderately, ESR to a lesser extent.
♦ Anaemia

Diagnosis

♦ Treatment is begun on the basis of the clinical picture.
♦ Diagnosis is confirmed by serology. The antibody titre rises first 10–14 days after onset of fever. The blood samples are taken 2–3 times, at 2 week intervals. A rise in the antibody titre is an indication of a recent infection. A 4-fold rise of the titre, or a single clearly elevated titre (1:160 with agglutination technique, 1:128 with microagglutination technique), is considered diagnostic.
♦ Bacterial culture of the secreting lesion can also be performed.

Treatment

♦ Fluoroquinolones are the recommended antibiotic therapy in mild and moderate cases (the dose of ciprofloxacin is 500 mg b.d. for adults). Alternatively, doxycycline (100 mg b.d. for 10 to 14 days, or 2–3 weeks after onset of symptoms), or streptomycin or aminoglycosides for 1–2 weeks can be used depending on the severity of the disease.
♦ If the patient has severe symptoms, an infectious disease physician should be consulted.
♦ Beta-lactam antibiotics are ineffective.
♦ Children are managed under the supervision of a paediatrician. Ciprofloxacin has been used for children in verified cases of tularaemia. The dose is 15–20 mg/kg daily divided into two doses.
Prevention

♦ A live attenuated vaccine has been developed, but is not currently available.
♦ Recommendations have been issued in the United States for measures to be taken in case tularemia is used as a biological weapon. Doxycycline and ciprofloxacin are recommended for exposed individuals during an epidemic.

1.22 Erysipeloid

Petteri Carlson

Epidemiology

♦ The bacterium that causes erysipeloid (Erysipelothrix rhusiopathiae) can be found in many animals (pigs, fish, birds).
♦ Humans can be infected through skin erosions.
♦ Occurs as a rare occupational disease among animal farmers, butchers, fishermen, veterinarians etc.

Symptoms

♦ Swollen, bluish, well-demarcated skin lesions usually in the hands (Figure 1.22.1). There is no suppuration.
♦ There is usually intense pain, and itching and a prickling sensations are also common.
♦ Local lymph nodes often swell, but otherwise systemic symptoms are rare. Septicaemia and endocarditis may sometimes occur.

♦ The disease is self-limiting within a few weeks. The skin remains brown and often scaly.

Diagnosis

♦ The diagnosis can be made on the basis of history and the typical clinical picture. Staining and culture from a biopsy sample or tissue fluid obtained by aspiration can be performed but is rarely indicated.

Treatment

♦ Penicillin 1.5 million units × 2 × 10 shortens the duration of the disease. Also cephalosporins, macrolides, and fluoroquinolones are probably effective.

Prevention

♦ Good occupational practice, covering hand wounds and erosions

References


1.23 Listeriosis

Kirsi Skogberg

Epidemiology

♦ Listeria monocytogenes, a gram-positive rod, has been isolated from soil, animals and stools of asymptomatic individuals; food, dairy products in particular, has also been implicated as a source of infection.
♦ Pregnant women, foetuses and newborns as well as those with impaired cell-mediated immunity are more susceptible to the infection.

Symptoms

♦ Sepsis or meningitis are the most common clinical presentations, seen mostly in those with impaired immunity.
♦ In foetal infection the result is abortion, intrauterine death or sepsis of the newborn (early infection).
♦ Newborn may also be infected through genital tract or the infection can be hospital born. Meningitis may develop days of weeks after delivery (late infection).
♦ Listeriosis in individuals with no underlying risk factors may present as a flu like illness or gastroenteritis, rarely as meningitis or sepsis.

Diagnosis
♦ Bacterial staining and culture. Listeria is grown from normal blood and CSF samples. Special request is needed in order to inform the laboratory of the use of specific conditions for culture from other locations.
♦ Serology is of little use.

Treatment
♦ The first drug of choice is ampicillin or G penicillin intravenously in large doses. Synergism with aminoglycosides may prove clinically useful.
♦ In penicillin allergy, trimethoprim-sulphamethoxazole or in mild cases, erythromycin may be used.
♦ Cephalosporins are not effective against listeria.
♦ Antimicrobial therapy should continue for at least 2 weeks.

Prevention
♦ Measures for reducing the risk of listeriosis.
  - General recommendations
    – Cook or roast all meat thoroughly.
    – Wash raw vegetables carefully before eating them.
    – Store uncooked meat away from vegetables, cooked food and convenience foods.
    – Avoid unpasteurized milk and products prepared from such milk.
    – Wash your hands and all knives and chopping boards that you have used for preparing the above-mentioned uncooked foods.
  - Recommendations for persons at risk
    – Avoid soft, (mould-)ripened cheeses.
    – Avoid vacuum-packed raw-pickled or raw-smoked fish products.
    – Before eating leftover foods and convenience foods warm the food until it is steaming hot.

1.24 Tetanus

Janne Mikkola

Aims
♦ Prevention by vaccination and careful treatment of contaminated wounds
♦ Early identification of the disease in unvaccinated patients

Definition
♦ Tetanus is a severe systemic infection in the unvaccinated individual caused by Clostridium tetani, which can be found in high concentrations in the soil and in normal intestinal flora.

Symptoms
♦ First, a local wound infection in which the bacteria multiply and produce toxin.
♦ Within days or weeks, a generalized systemic infection with muscle spasms most often beginning at the mandibular joint (trismus)
♦ Localized tetanus consists of muscle rigidity and painful spasms close to the site of injury.
♦ In spite of intensive care, mortality is high.

Diagnosis
♦ Depends mostly on history and clinical features. The usefulness of aspirate gram-stain and culture is limited.

Treatment
♦ Making the airway secure, supportive care with anticonvulsive medications and sedation require intensive care in most cases.
♦ Human antitetanus immunoglobulin and debridement of the wound are the cornerstones of treatment.
♦ Metronidazole orally or i.v. is the drug of choice. The dose for adults is 500 mg × 3 and for children 30 mg/kg daily in three doses. G penicillin is an alternative.
♦ Active immunization should be initiated during convalescence.

Prevention
♦ In most developed countries, a universal immunization is effective and the boosters are given every ten years.
  - Td vaccine gives protection also against diphtheria.
♦ Prevention when treating dirty wounds
  - Booster vaccination
    – A booster is given if it is more than 10 years since the previous vaccination.
    – With a big contaminated wound, the booster is given after 5 years.
    – Patients who have not received the primary series of vaccinations are both immunized and given tetanus immunoglobulin.
  - Frequent vaccinations increase the probability of local reactions.
1.25 Diphtheria

Petri Ruutu

Epidemiology

♦ An infectious disease with potential for causing serious epidemics, preventable by vaccination.
♦ The disease spreads via respiratory secretions (nasal secretions, saliva), but also via direct contact with wounds and other secretions.
♦ The incubation period is 1–7 days.
♦ A number of cases have been diagnosed in Europe since 1990. Nearly all patients were infected in the countries of the former Soviet Union.
♦ All new cases should be reported to the WHO.

Symptoms

1. Local inflammation with copious pharyngeal exudates, grey or dark mucosal adhering exudates and soft tissue oedema. In children this phase of the disease may result in the obstruction of the airway.
2. The systemic disease caused by bacterial toxin starts 1–2 weeks after the local symptoms. The toxin affects the heart (myocarditis, arrhythmias particularly during the second week of the disease) and the nervous system (paralyses, neuritis 2–7 weeks after disease onset). If the patient survives the acute phase of the disease he/she usually recovers without sequelae.

Diagnosis

♦ The need for treatment is decided on the basis of the history and clinical picture (severe, exudative pharyngitis, particularly in a patient who has visited an endemic country 1–7 days before the onset of the disease).
♦ The diagnosis is confirmed by bacterial culture taken from the exudate into a standard transport tube for bacterial specimens. The specimen should be cultured on special media (inform the laboratory in advance).

Treatment

♦ Symptomatic patients should be treated in a hospital under the supervision of a specialist in infectious diseases and under isolation to prevent further transmission. Asymptomatic individuals can be treated at home.
♦ In children, the patency of the airway must be ensured in the initial phase.
♦ All patients should be treated with antibiotics (penicillin, roxithromycin, erythromycin). The drug should be administered intravenously at first. Diphtheria antitoxin should be administered as early as possible according to the instructions of a specialist in infectious diseases.
♦ Take throat bacterial cultures from close contacts, treat them with antibiotics (benzathine penicillin, 600 000–1.2 million units as a single dose intramuscularly or erythromycin at a standard dose for 7–10 days), and vaccinate them.

Prevention

♦ Vaccination prevents complications caused by the toxin but it does not prevent infection.
♦ If the basic vaccinations have been given, the protection is over 90%. In people over 30 years of age without a booster the protection is not as good. A booster vaccination should be given every 10 years. The booster often contains a combination of tetanus and diphtheria vaccinations.
♦ Travellers to epidemic areas should be given the basic series of three vaccinations, if they have not been vaccinated previously. A booster vaccination is sufficient in adults if they are over 30 years of age and have previously received a full basic series of three vaccinations.

1.28 Methicillin-resistant Staphylococcus aureus (MRSA)

Jaana Vuopio-Varkila, Pirkko Kotilainen

Definition

♦ MRSA strains are S. aureus isolates, which are not susceptible to beta-lactamase resistant staphylococcal antibiotics (cloxacillin and dicloxacillin) or other beta-lactam antibiotics (such as cephalosporins and imipenem).
♦ In addition, MRSA strains are often multi-resistant in which case, for example, clindamycin, aminoglycosides and fluoroquinolones are not effective for treatment.
♦ This guideline applies in Scandinavia and in other areas where MRSA is not common.

Epidemiology

♦ The majority of the cases are asymptomatic carriers. Only 10% of the cases are clinical infections.
♦ In many hospitals in Central and Southern Europe, USA, Asia or Middle East up to 50% of all S. aureus isolates are methicillin-resistant.

Diseases

♦ MRSA usually causes hospital-acquired surgical site and bone infections or septic systemic infections.
MRSA infections are rare among outpatients.
- The spectrum and severity of infections caused by MRSA are similar to those caused by methicillin-susceptible S. aureus.

Why is prevention important?
- Treatment of MRSA is difficult as the only drugs of choice for severe systemic infections are intravenously administered vancomycin or teicoplanin. Increased use of vancomycin may lead to bacterial strains resistant to vancomycin. This has already been shown to be the case with enterococci.
- It is important to prevent MRSA epidemics and the spread of MRSA by blocking the route of transmission.
- Each new MRSA case means significant cost for the hospital.
  - Isolation precautions
  - Wide-scale screening for MRSA colonization
  - Prolonged hospitalization of patients with MRSA
  - Increased work load of healthcare personnel

Diagnostics
- In order to prevent spread of MRSA, patients who are infected or colonized by MRSA should be identified as soon as possible after admission to the hospital.
  - A patient, who has been hospitalized in an area where MRSA is common, should be treated in contact isolation, until his/her MRSA screening culture has been shown to be negative.
  - The clinical microbiology laboratory should be requested to screen specifically for MRSA from the samples.
- Bacterial cultures for MRSA screening and follow-up are performed on an individual basis. It is recommendable to consult a specialist in infectious diseases or a clinical microbiologist about the timing and technique of taking the MRSA cultures.
  - Nasal swab is performed by rotating a cotton swab in both nostrils, and applying the swab directly in to enrichment broth or into a transportation culture tube.

Ways of transmission
- The most important way of transmission is through MRSA-infected or colonized patients.
- In the hospital, patient-to-patient transmission of MRSA strains may occur rapidly through direct contact, often via healthcare personnel.
- Healthcare workers may become colonized with MRSA while taking care of MRSA-positive patients. This type of colonization is a significant source of transmission only when the person has a skin disease or a defective skin area.
- Among hospitalized patients MRSA acquisition usually first leads to asymptomatic colonization. The most common areas of colonization are the nostrils, throat, perineum, groin, armpits and skin lesions (for example skin eruptions).

Prevention of transmission
- Careful hand disinfection after all contact with patients is the most important means of preventing the spread of MRSA in hospitals.
- An MRSA patient must be isolated from other patients. Type of isolation may vary, depending on the situation. In hospital settings the patients should be placed in contact isolation.
- When a patient is found to be MRSA-culture positive, it is advisable to screen at least his/her roommates for MRSA colonization.
- If a second MRSA case is detected from the same hospital ward within a short time period, it is necessary to consider screening also other patients or healthcare personnel for MRSA colonization. If resources available for surveillance cultures are limited, it is better to direct them for detection of colonized patients.
- The patient records of those patients who are known to have been colonized or infected by MRSA previously, should be labelled accordingly.
- In case a patient is transferred to another healthcare facility, it is necessary to inform the receiving unit of his/her MRSA-status.

Treatment and follow-up
- During hospitalization, patients who are infected or colonized by MRSA are treated in contact isolation.
- MRSA acquisition often prolongs hospitalization. The patient should be discharged from the hospital as soon as it is possible without compromising patient care.
- Treatment of MRSA infections and MRSA colonization is performed in collaboration with a physician responsible for infection control or an infectious diseases specialist. MRSA must not prevent the patient from receiving any care or treatment he/she needs.

Colonization
- MRSA colonization of an outpatient is not treated.
- Among hospitalized patients treatment of asymptomatic MRSA colonization may be indicated.
- An MRSA-colonized healthcare worker is usually treated.
- If colonization is restricted for example to the nostrils, the bacterium can be eradicated by local treatment with mupirocin
  - A small amount of ointment containing mupirocin is applied three times daily to the nostrils during 5 days.
- If colonization is widespread or the patient has a severe skin disease, eradication of the bacterium will usually not be successful. Also foreign bodies (a urinary catheter, a tracheotomy tube, a nasogastric tube and different drainage tubes) may prevent successful eradication.
- Systemic antimicrobial agents have little effect on colonization, because they are secreted to the mucosal surfaces only in a limited degree. Their usage should be considered if MRSA colonization is very large-scale or affects areas of the body where local treatment cannot be administered. Systemic treatment of colonization is reasonable only in exceptional cases.
♦ Washing the patient with disinfectants (for example liquid soaps containing chlorhexidine) aims at diminishing the amount of bacteria on the skin and mucosal surfaces. There is no definite proof of its effect on treatment of colonization.

♦ The patient is considered cleared from colonization if three consecutive MRSA-surveillance cultures taken at 1-week intervals are negative.

♦ Relapses are, however, common especially if the patient has received antimicrobial treatment because of an infection. As relapses are possible even after several years, it is advisable to perform MRSA cultures from previously colonized patients every time they are readmitted to hospital.

♦ The decision of whether MRSA carrier personnel should be removed from patient care is made by the Infection Control Doctor of the hospital or medical district. Staff who are solely nasal carriers are commonly allowed to continue work whilst being treated with mupirocin. Staff who are employed in intensive care units or on wards, where immunocompromised patients are cared for, are usually removed from duty until the MRSA colonization has been successfully treated.

Infections

♦ At present, the only drug of choice is vancomycin, which is used for treatment of all severe MRSA infections.

♦ Rifampin, fluoroquinolones, fusidic acid and sulphatrimethoprim can be used on the basis of susceptibility pattern for the treatment of less severe infections.

♦ Apart from the choice of the antimicrobial treatment, MRSA infections are treated following the common principles of treatment of staphylococcal infections.

National guidelines for prevention of MRSA

♦ Many countries have developed national guidelines for control of MRSA.

Reference


To remain alert to the late symptoms and signs of Lyme disease as a diagnostic possibility, and to avoid overdiagnosis.

Causative agent

♦ The disease is caused by the tick-borne spirochete Borrelia burgdorferi sensu lato including at least three human-pathogenic species. The borrelia species causing human disease in Europe are B. afzelii, B. garinii and B. burgdorferi sensu stricto. In USA, B. burgdorferi s.s. is almost the sole cause of Lyme disease.

♦ Spirochetes may be transmitted by all stages of the tick, also the small larvae and nymphs, which may be difficult to observe.

Geographical distribution

♦ The tick Ixodes ricinus is the common vector of the disease in Europe. In Eastern Europe and in Asia, Ixodes persulcatus has also been reported to function as a vector. Lyme disease was originally observed in the USA, and has now been diagnosed all over Europe and in parts of Asia.

♦ The infection has now been reported from all parts of Europe. The spectrum of Borrelia species and subspecies and incidence of infection varies from country to country, from region to region and even between local areas within the same region. In heavily endemic regions, the incidence of infection may be as high as 1500/100 000, whereas in other areas it may be below 1/100 000. Because of travelling and the sometimes long latency period of the late stages of the disease, doctors almost everywhere may see patients with Lyme borreliosis.

♦ In Northern Europe, the risk of a tick bite is greatest in moist, grassy terrain.

♦ The seroconversion rate in healthy inhabitants of a highly endemic area may be over 1000/100 000/year, and the prevalence of seropositivity in the population of such highly endemic regions varies between 15% and 45% increasing with age.

Symptoms and Signs

Primary Infection (Stage I)

♦ The most common form of primary LB is Erythema migrans (EM) (Figures 1.29.1 and 1.29.2) at the site of the tick bite. It begins at or continues for about 1 week after the bite, and if untreated, disappears within 2–4 weeks, but may also stay on for a much longer time. The erythema varies in appearance. Often, but not always, it spreads centrifugally as a ring around the bite (“bull’s eye lesion”), but it may also form an enlarging patch or even become multiple. Multiple erythematous are usually regarded to belong to disseminated borreliosis.

♦ The lesion must not be confused with the common small erythema around the bite that is caused by irritants and subsides within a few days.
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Figure 1.29.1  An unusually wide Erythema migrans, affecting almost the whole left lower extremity. The positive IgG- serology, positive PCR to Borrelia and rapid and complete response to amoxicillin therapy confirmed the diagnosis. Photo © R. Suhonen.

♦ As a rule, if an erythema around a tick bite is more than 5 cm in diameter and starts or persists for more than a week after the bite, it should be regarded as EM.

♦ During the primary stage the patient usually feels well. Sometimes there may be malaise and fatigue, or the patient may run a slight temperature.

♦ Even in the presence of a borrelia infection, the primary lesion may be absent, or it may not be observed because the bite has been on the patient’s back or in a skin fold.

♦ Borrelial lymphocytoma (Figure 1.29.3), or lymphadenosis benigna cutis, is a rarer form of primary borreliosis. It may occur at a tick bite in very soft tissue, often an ear lobe, and consists of a soft local non-tender, often bluish or reddish swelling. It follows approximately the same timetable as EM.

Figure 1.29.2  Erythema (chronicum) migrans, primary borrelial infection in the skin, has a variable outlook. The central skin may be normal, and only the margin is red and spreads peripherally. The whole area may be red, even bullous. IgG antibodies may be negative in early phase. Photo © R. Suhonen.

Figure 1.29.3  Lymphocytoma, induced by infection with Borrelia. The borrelial IgG serum antibody titre was high, but it returned to normal after antibiotic therapy. The patient is a boy of pre-school age. Photo © R. Suhonen.

Disseminated Lyme borreliosis

♦ If the primary infection is not treated, up to 50% of patients may have later manifestations, which may develop weeks, months and even years after the primary lesion.

♦ Some common symptoms and signs of later borreliosis are

- Paresis
  - Cranial nerve pareses, particularly facial nerve paresis, occur frequently. Borrelia antibodies in the serum or CSF should be assayed in all patients with facial nerve paresis if there is the slightest suspicion of borreliosis.

- Central nervous system
  - Lymphocytic meningitis, meningoencephalitis
  - Meningoradiculitis (Bannwarth’s syndrome)
  - Chronic progressive encephalomyelitis
Figure 1.29.4 Acrodermatitis chronica atrophicans (ACA) is a skin manifestation in the late phase of borrelial infection. This elderly female patient had skin atrophy on the back of her right hand. The patient had typical histopathological features and positive IgG borrelial serum antibodies, and borrelial DNA was found in a PCR study of the lesional biopsy specimen. Atrophy was reversed to some degree after appropriate antibiotic therapy. Photo © R. Suhonen.

- Big joints
  - Arthritis and hydrops, especially of big joints
- Heart
  - Myocarditis
  - Conduction disturbances
- Skin: Acrodermatitis atrophicans (Figure 1.29.4)
- Eyes: Ocular inflammatory syndromes

The manifestations of late LB are protean, and this disease must be kept in mind as a possibility if a patient has otherwise unexplained symptoms and signs and the history includes moving about in terrain where ticks may thrive.

Diagnosis

Primary Stage

- Laboratory tests are usually not carried out in primary Lyme borreliosis. If an erythema of more than 5 cm in diameter is still present at the bite site 1 week after the tick bite, the patient is regarded as having EM. Lymphocytoma at the tick bite is diagnostic for primary LB.

Disseminated Lyme borreliosis

- The diagnosis starts from clinical symptoms and signs and a history of tick bite or of having moved about in areas where ticks have been found \(^1\)\(^2\). Lymphocytic pleocytosis of the CSF is a helpful corroborative sign.
- The principal laboratory test is the determination of specific antibodies to borrelia antigens \(^1\)\(^2\). As a screening test, in order to rule out disease, an ELISA-based test is mostly used. In nervous system involvement, elevated titres of antibody and intrathecal antibody production are found in the CSF, sometimes even in the absence of significant elevation of serum antibody. The serological method should ideally be tested and adapted for the local spectrum of borrelia species and antigens.
  - IgM antibodies rise within ca. 3 weeks after the infection and remain high for ca. 6 weeks, after which the titres go down. Not all patients revert to normal levels but expression of IgM antibodies may be seen for a longer time even without active disease.
  - IgG antibody titres rise ca. 6 weeks after the infection and remain high, sometimes for years.
  - A repeated test one month after the first one may help if the first result is borderline or negative. Conversion from IgM to IgG antibody, or a significant rise of IgG antibody titre on repeated testing may support the diagnosis.
  - Intrathecal antibody production is a good criterion for central nervous borrelia infection. For this purpose CSF and serum from the same day must be obtained. Thus, if borrelia infection is strongly suspected it may be advisable to look for intrathecal antibody production even without clear-cut clinical signs of neurological involvement.
  - The diagnosis is usually corroborated with the aid of a blot test. The blot test may be omitted by using such immunoassay methods that give a statistically proven indication of the presence of specific antibodies. The result should be interpreted according to the EUCALB principles.
  - In special cases, where the diagnosis is difficult to reach, nucleic acid amplification techniques may be helpful.

- Patients who have symptoms and signs of possible LB but lack laboratory confirmation should not be diagnosed as having LB.
- In regions where LB infection is common, a substantial part of the healthy population may have elevated titres against borrelia. A diagnosis of active LB in symptomless people who have elevated borrelia antibodies in the serum is therefore not appropriate.
- Culture of the spirochete would be the best laboratory investigation but is difficult to perform and thus restricted to specialized laboratories.
- The most appropriate approach to the interpretation of a positive serology would be the application of Bayesian principles of analysis to the positive respectively the negative predictive values of the test, taking into account both the level of background seropositivity and the pre-test likelihood of disease (Table 1.29).

Treatment

Tick bite without any symptoms or signs of primary borreliosis

- A tick bite without erythema does not call for treatment with antimicrobial agents \(^3\)\(^4\). In pregnancy, prophylaxis with antimicrobial drugs may be considered (consult a specialist in infectious diseases).
Primary stage (Erythema migrans or lymphocytoma)

- The treatment time is usually 15 days. It may be extended to 3 weeks if signs are still present after the first 15 days.
- The drug of choice is amoxicillin 500 mg q.i.d. for children or 1 g b.i.d. for adults.
- If amoxicillin cannot be given because of confirmed allergy, the drug is divided into 2 daily doses.
- Doxycycline is not recommended as the first choice because of its side-effects, especially sensitivity to sunlight, as the infection usually occurs during summertime when people often live an outdoor-life and are exposed to sunlight for long periods of time.
- Pregnancy: The general view is that the infection in pregnant women should be treated. LB has however not been shown to cause damage to the foetus.
- The recommended treatment for primary LB in pregnancy is amoxicillin 500 mg q.i.d. for 30 days. A specialist in infectious diseases should be consulted when a pregnant woman has any form of LB.

Late stages

- The treatment is time-consuming and demanding. Treatment recommendations from USA cannot be directly followed in Europe because of the difference in the spectrum of borrelia subspecies. The choice of treatment, and especially its duration, is a subject of controversy.
- If the attending physician is unfamiliar with patients with LB, the advice of a specialist in infectious diseases or LB should always be sought.
- Reported results vary from country to country, possibly because of differences in borrelia species, but in some cases also because of insufficient follow-up time.
- There are so far no randomized prospective double-blind studies on the treatment of late LB in Europe, and even some semi-official recommendations for treatment are based merely on subjective clinical experience.
- A frequent suggestion for treatment is a 2–3-week course of i.v. ceftriaxone 2 g daily, for children 100 mg/kg daily. Many authors recommend adding a course of an oral antibiotic after the ceftriaxone.
- In Finland, good results have been reported with a regimen of i.v. ceftriaxone 2 g daily for 14 days, followed by either amoxicillin or cephadroxil, for 100 days.
- In Sweden, oral doxycycline 200 mg daily for 8–20 days has been recommended nationally, however without organized trials.
- Clinical experience indicates that early neuroborreliosis tends to react more favourably to antibacterial treatment than other forms of the disease.
- One should distinguish between failure of treatment because the bacteria have not been eradicated, and persistent symptoms and signs due to permanent damage of tissues by the bacteria. This differentiation would require reliable objective laboratory criteria for eradicated infection vs. persistent infection. Such criteria that would be constantly reliable have not been found. A sharp decline in antibodies may serve as indicator of eradication, or the continued presence of borrelia DNA as shown by PCR technique may be an indicator of persistent infection.
- It has been shown that in some patients borrelial proteins may cross-react with human proteins, which helps to explain persistent arthritis after treatment of Lyme borreliosis.
- There is still no totally reliable laboratory method for assessing the success of therapy. Clinical treatment results should be interpreted cautiously, as the disease can flare several months after an apparently successful therapy.

Table 1.29  Bayesian analysis of the post-test probability of disease in relation to the pre-test probability and the endemic serological situation

<table>
<thead>
<tr>
<th>Background seropositivity</th>
<th>Pre-test probability</th>
<th>Post-test probability</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt; 80%&lt;sup&gt;1)&lt;/sup&gt;</td>
<td>20–80%&lt;sup&gt;2)&lt;/sup&gt;</td>
</tr>
<tr>
<td>5%</td>
<td>&gt; 96%</td>
<td>61–96%</td>
</tr>
<tr>
<td>15%</td>
<td>&gt; 94%</td>
<td>49–94%</td>
</tr>
<tr>
<td>30%</td>
<td>&gt; 90%</td>
<td>37–90%</td>
</tr>
<tr>
<td>45%</td>
<td>&gt; 87%</td>
<td>30–87%</td>
</tr>
</tbody>
</table>

- The basis of reasoning is that a serological test with a sensitivity of 0.95 and a specificity of 0.90 is applied on groups of patients with different grades of clinical suspicion of borreliosis (= pre-test probability) and coming from regions with various degrees of background seropositivity.
- A pre-test probability of disease > 80% represents a situation where an observed tick bite is followed by an erythema and lymphocytic meningitis.
- A 20–80% pre-test probability of disease exists in patients from endemic areas showing lymphocytic meningitis or monoarthritis.
- Patients from non-endemic regions without observed tick bites presenting with non-specific symptoms, for example fatigue and diffuse myofascial pain, have a disease probability below 20%.
- In the case of a background seropositivity of 5–15% a positive serology is associated with a moderately positive likelihood for disease whereas higher background seropositivity gives lower likelihood values.

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INF
Prevention of Lyme borreliosis

♦ Obviously, the best prevention is to avoid being bitten by ticks when moving about terrain where ticks thrive.
♦ There is no danger in rocky and dry terrain. The ticks thrive in moist terrain, especially in grass. Use the centre of the footpath when walking in the woods.
♦ Long trousers (light-coloured to help identifying the ticks), tucked into the socks hamper the ticks’ access to the skin.
♦ Every day after moving about in terrain where ticks thrive, the skin should be inspected and any ticks removed. An embedded tick is easily removed by rolling it under a moistened finger tip or by pulling the tick out with pliers. There are special pliers for this purpose for sale in most pharmacies. One should avoid pulling hard on the tick, as its head may remain in the skin and cause local purulent infection. If this should happen, the dislodged tick head will eventually come out spontaneously.
♦ The method of removal of the tick does not influence the possible risk for borrelia infection. An embedded tick should preferably be removed within the first day, as the risk for infection increases with time.
♦ Experiments has been done for developing a vaccine against Lyme borreliosis. Such a vaccine must be tailored to fit the local spectrum of borrelia subspecies. Vaccines based on the outer surface protein A of borrelia burgdorferi sensu stricto were for some time used in the United States but are no longer manufactured. The spectrum of borrelia subspecies and the antigenic composition in Europe are quite different from those in the United States.

References


1.40 Influenza

Terho Heikkinen

Basic rules

♦ Influenza vaccination is recommended to all persons with high-risk medical conditions and the elderly population.
♦ The vaccine should be administered well before the expected influenza epidemic.
♦ It is important to be aware of the local epidemiological situation in the community.
♦ Updated web-based information about the epidemiology of influenza is available in most developed countries.

Cause

♦ Influenza viruses are classified into three distinct types (A, B, and C), of which influenza A viruses are clinically most important.
♦ During the past decades, influenza outbreaks have been caused by subtypes A/H3N2 and A/H1N1 as well as B viruses.
♦ Other subtypes of influenza A viruses (e.g. H5N1 and H7N7) have also caused severe illnesses in humans during the recent years. Extensive preventive measures have so far been successful in preventing large-scale transmission of these “new” subtypes into human population. However, the risk of an influenza pandemic exists all the time.

Epidemiology

♦ Influenza epidemics occur usually during wintertime in temperate regions of the northern hemisphere.
♦ The severity of influenza outbreaks varies between different years depending on the antigenic variation of the circulating virus strains.
♦ Influenza viruses spread mainly via small-particle aerosols, but transmission can also occur through direct contact.
♦ The incubation period ranges between 1 to 7 days, but is most often 2–3 days.
♦ Excretion of the virus may begin already 1–2 days prior to the onset of clinical symptoms.

Clinical presentation

♦ Varies from asymptomatic infection to severe lethal illness (multiple organ failure).
♦ The duration of illness is usually 3–8 days.
♦ Typical initial symptoms in adults include sudden onset of illness, fever, chills, headache, myalgia, malaise, and cough. Rhinitis is not common in the early phase.
In children, the symptoms often overlap with those of other viral respiratory infections. Rhinitis is present in most children already in the early phase of the illness. Also febrile convulsions may occur in young children.

The most frequent complications of influenza in adults are pneumonia, sinusitis, and exacerbation of asthma or chronic bronchitis. Pneumonia is usually caused by bacteria (pneumococci, staphylococci or haemophilus). However, influenza viruses may also cause primary viral pneumonia which is often very severe.

Acute otitis media is the most common complication in children.

Diagnosis

During a verified local influenza outbreak, the sudden onset of fever and a dry hacking cough are indicative of influenza in adults, although distinguishing influenza is usually very difficult on clinical grounds alone.

Several rapid tests are available for the detection of influenza in clinical specimens within 15–30 minutes, but the sensitivity and specificity of these tests vary substantially.

Treatment

Treatment is mainly symptomatic: rest and anti-inflammatory drugs or paracetamol (not acetylsalicylic acid).

Specific antiviral drugs available for the treatment of influenza include oseltamivir and zanamivir and amantadine (plus rimantadine in some countries).

- Oseltamivir and zanamivir are effective against both influenza A and B viruses whereas amantadine is only effective against influenza A viruses.
- Oseltamivir and amantadine are administered orally. Zanamivir is administered by inhalation with the use of a special device.
- All drugs shorten the duration of clinical illness by 1.0–1.5 days when the treatment is initiated within 48 h of the onset of symptoms.
- The effect is inversely correlated with the time lag between the onset of symptoms and treatment initiation.
- Oseltamivir treatment started within 48 h of the onset of symptoms decreases the rate of development of acute otitis media as a complication of influenza by 40% in children.
- Elderly persons may find it difficult to use the inhalation device that is necessary to administer zanamivir into the airways.
- The most important limitation to the use of amantadine is the rapid emergence of resistance to the drug. Resistant viral strains have been isolated from a substantial proportion of patients within 2–3 days of treatment initiation.

Salicylates should not be used for influenza especially in children and adolescents because of increased risk of Reye’s syndrome.

Prevention

- Influenza vaccination is the cornerstone of the prevention of influenza. The antigenic composition of the vaccine is changed every year. Therefore, to maximise the preventive efficacy, the vaccine should be administered annually.
- The vaccine is administered intramuscularly. The inactivated vaccine currently available is safe and well-tolerated but local reactions at the injection site are possible.
- Influenza vaccine can be administered to any person older than 6 months of age to decrease the likelihood of contracting influenza.
- Oseltamivir and amantadine can also be used to prevent influenza. However, the preventive efficacy can only be expected during the medication period, whereby seasonal prevention of influenza with these drugs is rarely a reasonable option.

References

1.41 Herpes zoster

Jaakko Karvonen

Basic rules

♦ Aim at identifying herpes zoster at an early stage to avoid unnecessary diagnostic investigations.
♦ Start antiviral medication immediately for immunosuppressed patients and if the disease is localized in the trigeminal area.
♦ Treat other patients with antiviral drugs if the symptoms are severe and if no more than 3 days have elapsed since the appearance of the rash. For immunosuppressed patients the antiviral medication should be started even if more time has elapsed.

Aetiology

♦ Herpes zoster is caused by the varicella-zoster virus that has remained in the paraspinal ganglia after a varicella infection. Recurrence is not common.

Symptoms and signs

♦ A linear bullous rash is confined to one side of the midline and occurs most often on the trunk or face (Figure 1.41.1), rarely on the extremities.
♦ Local pain may begin days before the rash erupts.
  • Remember herpes zoster in the differential diagnosis of chest pain and examine the patient’s skin.

Antiviral medication

Effect of antiviral drugs on herpes zoster

♦ Antiviral therapy started early
  • shortens the duration of the disease
  • limits ulceration
  • alleviates pain in the acute phase
  • reduces need for analgesics
  • reduces the number of ocular complications
  • probably prevents and alleviates postherpetic neuralgia

Absolute indications

♦ Patients who are immunosuppressed because of the following diseases or medications should always be treated with antiviral drugs:
  • bone marrow depression (leukaemia, granulocytopenia)
• immunodeficiency
• AIDS or HIV carrier
• any severe systemic disease
• poorly controlled diabetes
• antineoplastic drugs
• continuous oral corticosteroid medication.

♦ Herpes zoster in the trigeminus area should always be treated because of the risk for ocular complications.
• The risk is present if the rash is situated on one side of the nose.
• If the eye is clearly red, the sensation of the cornea is impaired when tested with a cotton wool probe or visual acuity is decreased (possible iridocyclitis) the patient should be referred to an ophthalmologist. The referral should not delay the start of antiviral medication.

Relative indications
♦ Persons over 60 years of age frequently need antiviral therapy, because the clinical course is more severe.
♦ Young patients should be given antiviral drugs if the disease is severe enough to warrant hospitalization.

Dosage
♦ Acyclovir 800 mg x 5 x 7 p.o.
♦ Famciclovir 250 mg x 3 x 7 or 500 mg x 2 x 7 p.o.
• The effective agent is penciclovir
♦ Valacyclovir 1 g x 3 x 7 p.o.
• Valacyclovir is metabolized into acyclovir and valine in the gastrointestinal tract
• Absorption is superior to that of acyclovir.
♦ Immunosuppressed patients should be treated with intravenous acyclovir.
♦ Local acyclovir creams have limited efficacy in the treatment of herpes zoster.

Adverse effects
♦ Acyclovir, famciclovir and valacyclovir are well tolerated. Serious adverse effects are rare, but some patients may have
  • gastrointestinal symptoms
  • rashes
  • headache
  • transient increases in liver transaminase concentrations.

Contagiousness and need for isolation
♦ Varicella-zoster virus may be transmitted during the bullous phase.
♦ The patient should avoid contact with children on antineoplastic drug therapy, as the consequences of a herpes infection may be serious for them. If a contact has already occurred, the child should receive zoster-hyperimmunoglobulin.

Postherpetic neuralgia
♦ Nearly all patients have pain or skin hyperaesthesia after the rash has disappeared. In the elderly the neuralgia may last for years.
♦ Antiviral treatment given in the acute phase probably prevents and alleviates postherpetic neuralgia. NSAIDs should first be tried against postherpetic pain. If they are not effective
  • tricyclic antidepressants (e.g. amitriptyline 25–50 mg x 1 in the evening) should be prescribed to patients whose skin is sensitive to contact with clothes (hyperaesthesia) or who are in continuous pain.
  • carbamazepine can be prescribed for stabbing pain sensations. The initial dose is 100 mg x 2. The dose can be increased to 200 mg x 3 over 2 weeks. If no response is obtained within one week on the full dose, the medication should be discontinued.

References
1 INFECTIOUS DISEASES

Epidemiology
- Caused by Epstein-Barr virus (EBV) which spreads by the transfer of saliva (“kissing disease”).
- Incubation time varies from 7 to 50 days.
- In Northern Europe, half of the children under 5 years of age, and nearly all adults have serum antibodies to EBV as a sign of earlier infection or subclinical exposure to the virus.

Symptoms and clinical manifestations
- Symptomless or mild fever in pre-school-aged children and therefore rarely diagnosed
- In older patients the symptoms are more pronounced: high fever, tonsillitis, generally enlarged lymph nodes or spleen, hepatitis; oedema of the eyelids (in 15%) may be a prodromal symptom.
- About one out of ten patients gets a rash with small erythematous macules. It will also be provoked in nearly all patients treated with amoxicillin.
- Spontaneous recovery is often seen within 2 weeks, even though fever may persist for 4–6 weeks.
- Hospitalization may be required in cases with severe symptoms or complications, which are rare: myocarditis, autoimmune haemolytic anaemia (AIHA), bleeding (thrombocytopenia), glomerulonephritis, arthritis, meningitis or encephalitis, neuropa thy and polyradiculitis, psychic disturbances, and spontaneous rupture of the spleen, which is the most common serious complication sometimes resulting in death (1/3000 of hospitalized patients).
- NSAIDs can be used to relieve the throat pain and swelling, if the patient is able to swallow the medicine. Severe swelling (which impairs eating and breathing) can safely be treated with corticosteroids. These patients belong in hospital care.
- The symptoms of mononucleosis may reoccur or become chronic.

Laboratory diagnosis
- Clinical manifestations, blood picture (including differential white cell count) and a quick test for mononucleosis (several commercial alternatives) are sufficient for making a reliable diagnosis.
- If the clinical suspicion is strong but the immediate test is negative, IgM class antibodies to EBV can be detected from a single serum sample.
- A typical finding in the blood picture is an increase of mononuclear cells (over 50% of white blood cells are lymphocytes). Over 10% of all the lymphocytes in peripheral blood are atypical. Thrombocytopenia and granulocytopenia are fairly common.
- Other laboratory tests are needed only for differential diagnosis. Erythrocyte sedimentation rate is slightly elevated, CRP remains nearly normal, liver function tests, such as transaminases, are clearly elevated (by as much as several hundred IU/ml) and the patient may even be icteric. Bacterial culture from the throat should be taken from those with tonsillitis; simultaneous streptococcal colonization (20–30%) or infection is common in mononucleosis.

Mononucleosis in outpatient setting
- In adults the illness often manifests with a vast number of long lasting symptoms; 1 to 2 weeks of sick leave from work to start with.
- Streptococcal tonsillitis, other fevers, hepatitis and even lymphoma have to be remembered in differential diagnosis.
- Spleen and liver should be palpated; the patient has to be warned to avoid physical exercise if the spleen is enlarged (i.e. the spleen can be felt upon palpation or it is larger than 10–12 cm by ultrasonography; risk of spleen rupture).
- In case of throat symptoms along with group A streptococcus in the culture or antigen test, treatment with penicillin is indicated; there is a risk of peritonsillar abscess.
- Isolation of the patient is not necessary (even symptomless persons have generous loads of viruses). One out of ten patients has a symptomatic secondary infection case in the immediate surroundings. It is advisable not to donate blood for 6 months following the infection.

1.43 Nephropathia epidemica (NE)

Jukka Mustonen

Epidemiology
- A mild form of haemorrhagic fever with renal syndrome (HFRS).
- Caused in Northern Europe by Puumala (PUU) hantavirus spread by a bank vole (Clethrionomys glareolus).
- The bank vole exhibits in 3–4-year population cycles. Most human NE cases occur in the peaks of the population cycle.
- 2/3 of the patients are men. NE rarely occurs in children.
- The risk groups are farmers, forestry workers, animal trappers and soldiers.

Clinical picture
- Symptoms and signs found in more than 30% of the patients:
  - High fever with rapid onset
  - Nausea and vomiting
  - Headache
  - Back pains
  - Abdominal pains
  - Decreased diuresis
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 Symptoms and signs found in less than 30% of the patients:
- Transient visual disturbances
- Clinical bleedings: conjunctivae, mucous membranes, skin, nose
- Visible haematuria
- Vertigo
- Hypotension, even shock
- Diarrhoea, obstipation
- Cough
- Throat pain
- Arthralgias
- Oedemas

 Laboratory findings

 Blood samples
- Elevated serum creatinine in 90% of hospital-treated patients
- Thrombocytopenia in 75% of the patients in the acute phase
- Leucocytosis in 50% of the patients (11.0 x 10^9/l)
- Elevated ESR 80% of the patients (mean ESR, 40 mm/h)
- Elevated CRP level in 90% of the patients (mean CRP, 50 mg/l)
- Elevated haemoglobin or haematocrit in some patients (haemoconcentration) due to drying; later on anaemia is common.
- Hypoproteinaemia, hypokalaemia, hyponatraemia, hypocalcaemia
- Slightly elevated liver function tests, e.g. ALT in 80% of the patients

 Urinary findings
- Proteinuria (albuminuria) in most patients during the acute phase
- Haematuria is common as well; usually microscopic
- Pyuria or glucosuria are uncommon.

 Chest x-ray
- Normal in most patients
- Abnormal findings are caused by increased capillary permeability and fluid retention: pleural effusion, atelectasis, parenchymal infiltrates, venous congestion and pulmonary oedema.

 Ultrasonography
- Enlarged kidneys with abnormal echoes are observed.

 ECG
- Nonspecific findings, ST-depression or T-wave inversion, are rather common. Findings are transient.

 Investigations

 Clinical picture
 Laboratory studies
- First-line studies in an outpatient unit include haemoglobin or haematocrit, CRP or ESR, serum creatinine and urinalysis (clearly voided urine).
- Antibodies to Puumala hantavirus
  - Often one serum sample is enough because of the rapid increase in antibodies. The result is found out the same day or the day after that.
  - If the symptoms have lasted less than 6 days and the finding is negative it should be confirmed by another sample.

 Differential diagnosis

- Other viral infections
- Acute bacterial infections (septicaemias, urinary infection)
- Other types of acute nephritis
- Meningitis
- Acute abdomen

 Course of the disease

- There are typical phases in the clinical course; however, they are not seen in all patients.
- Febrile phase (high fever, pains, general symptoms)
- Hypotensive phase (haemoconcentration, shock)
- Oliguric phase (renal failure, fluid retention)
- Polyuric phase (weight loss—on average 3 kg)
- Convalescence phase (days, weeks, or even months)
- About 5% of hospitalized patients need dialysis.

 Treatment

- In mild cases the patient does not need hospitalization, if differential diagnosis has been considered adequately.
- Fluid therapy
- Analgesics
- Send the patient for hospital care, if he/she has
  - Poor general condition
  - Obvious dehydration
  - Fluid retention
  - Renal failure (serum creatinine > 150 µmol/l), anuria
  - Uncertain diagnosis
- Transient dialysis therapy is needed in less than 10% of hospital treated patients. The most severe cases must be treated in an intensive care unit.

 Follow-up

- About one month after the acute phase the clinical picture and the laboratory findings are usually normal or near normal.

 Prognosis

- NE is not known to causes chronic renal disease.
- For most patients, good
- Lifelong immunity
Fatal cases are rare. Causes of death have been severe dehydration or shock associated with increased capillary permeability and severe renal failure on admission.

### 1.44 Pogosta disease

*Satu Kurkela, Olli Vapalahti*

#### Basic rule
- The disease should be identified on the basis of the clinical picture and serology in order to avoid unnecessary investigations and treatment attempts.
- Chronic joint manifestations of Pogosta disease should be considered in the differential diagnosis of undefined joint symptoms.

#### Epidemiology
- The etiological agent is Sindbis-virus (family Togaviridae, genus Alphavirus), which is spread by late summer mosquito species. The disease can be found in most of Finland in August-September.
- Outbreaks of hundreds or thousands of patients have occurred every seventh year in Finland (the last outbreak was in 2002). During the years in between, there are some dozens (up to couple of hundreds) of cases diagnosed.
- Clinically similar diseases in nearby geographical areas are called Ockelbo disease in Sweden and Karelian Fever in Russian Karelia.

#### Symptoms
- The typical clinical manifestation consists of arthritis, itching maculopapular rash in the trunk and limbs (Figure 1.44.1), fatigue, and mild fever.
- Other possible symptoms are headache, muscle pain and nausea.
- Usually polyarthritis (typically 3–5 joints), especially affecting ankle, finger, wrist and knee joints. The joint symptoms usually co-occur with other symptoms.
- Arthritis typically manifests as tenderness in movement, ache and oedema.

#### Diagnosis
- When Pogosta disease is clinically suspected, the diagnosis should be confirmed with serology.
- Serodiagnosis is based on measuring antibodies to Sindbis virus (SINV) using IgG-EIA, IgM-EIA and/or hemagglutination inhibition from a serum sample.
- Positive IgM-result and/or a four-fold rise in SINV antibody titer is decisive for the diagnosis.
- If there is less than a week from the onset of symptoms, a negative antibody result does not rule out the infection, and a second sample is required.
- The majority of cells in synovial fluid are mononuclear – or polynuclear; the total white blood cell count is usually < 10 000.
- Basic blood picture and CRP are usually normal.
- Differential diagnosis: parvovirus infection, rubella, varicella, rheumatoid arthritis.

#### Treatment and prognosis
- Symptomatic treatment. NSAIDs can be prescribed when necessary.
- Rash and fever usually disappear within a few days.
- Joint symptoms generally last for some weeks. However, a considerable proportion of patients feature arthritis for several months or even years.

### 1.45 HIV infection

*Janne Laine, Janne Mikkola*

#### In general
- Suspect HIV infection on clinical grounds
- In patients with a history of high-risk behaviour and who present with symptoms suggesting primary HIV infection
HIV INFECTION

- in patients with unexplained immunosuppression and in young individuals with weight loss, dementia or oesophageal candidiasis, thrombocytopenia or anaemia without a clear cause.
- Serology will become positive 1–4 months after contracting the infection. The patient may manifest primary symptoms 2–6 weeks after infection. Serological diagnosis is usually possible 2–4 weeks after symptom onset or 4–8 weeks after contracting the infection. To exclude the possibility of HIV infection antibody testing should be carried out until four months have elapsed.
- There is no cure for HIV infection, but a combination therapy (HAART – highly active antiretroviral therapy) has greatly improved the patients’ outlook.

Epidemiology

- In 2003, an estimated 5 million new infections with HIV were diagnosed worldwide, a total of 3 million people died of HIV/AIDS-related causes and there were 40 million people living with HIV/AIDS.

Natural course of HIV infection

Primary infection

- Primary HIV infection develops in 30–50% of infected patients, 2–6 weeks after contracting the virus.
- The symptoms may include: fever, tiredness, sore throat, headache, diarrhoea, myalgia, arthralgia and occasionally enlarged lymph nodes as well as an eruption of small papules on the body (Figure 1.45.1). Primary infection often resembles mononucleosis.
- The symptoms resolve within a month.
- Diagnosis is made difficult by the fact that during primary infection over 50% of the patients will be HIV antibody negative when tested with ELISA serology. The HIV antigen test and PCR assay become positive at an earlier stage. A positive PCR assay warrants confirmation with other test methods at a later stage.

Asymptomatic phase

- Lasts for several years, in some cases over 10 years.
- A high viral load will hasten the disease progression.

Symptomatic HIV infection

- CD4 cell count has often decreased to below $0.35 \times 10^{9}/l$.
- An increasing viral load is often predictive of symptom emergence.
- Symptoms are non-specific, such as weight loss, fever and persistent diarrhoea.
- Herpes zoster (shingles), oropharyngeal candidiasis and seborrhoeic eczema are also indicative of reduced immune response, but do not warrant the diagnosis of AIDS.

AIDS

- AIDS is defined as an HIV infection with at least one of the officially listed opportunistic diseases.
- The introduction of HAART has significantly reduced the occurrence of opportunistic diseases.
- The most common opportunistic diseases in Western Europe are:
  - fungal oesophagitis or stomatitis
  - infections caused by atypical mycobacteria (M. avium-intracellulare)
  - Pneumocystis carinii pneumonia
  - Kaposi’s sarcoma.
- Tuberculosis is common in the rest of the world.

Indications for an HIV test

- An HIV test may be indicated particularly in the following clinical conditions:
  - fever, diarrhoea, weight loss or dementia of unknown origin
  - history of intravenous drug use
  - unexplained thrombocytopenia
  - sexually transmitted diseases
  - tuberculosis in a young or middle-aged person
  - atypical pneumonia or fever with exertional dyspnoea (Pneumocystis carinii)
  - widespread oral candidiasis associated with dysphagia or pain on swallowing (oesophageal candidiasis)
  - Kaposi’s sarcoma (wine-red or violet spots or tumours in the palate, gums or skin)
  - HIV serology should always be tested on the patient’s request.
- The need to test the HIV status must be discussed with the patient. If the patient declines the test, the problems and possible harm caused by the delayed diagnosis, both for the patient himself/herself, the treating personnel (extra
investigations and prolonged treatment time) and other people (infection risk), should be further explored with the patient.

Diagnosis

♦ HIV antibody test. A positive sample is retested; if it remains positive the laboratory will request a further sample before submitting a result.
♦ The test will become positive 2–4 weeks after symptom onset or 1–4 months after contracting the virus.
♦ HIV nucleic acid test should be considered when strong suspicion of the infection exists in a patient with primary symptoms and if urgent diagnosis is required and the antibody test is negative.

Investigations and patient education in primary care

♦ Adequate time must be allocated for breaking the news of a positive test result. The patient should also be given contact details of how to obtain more information or moral support (AIDS help lines are available 24 hours a day).
♦ If the result is negative the patient should be given advice regarding high-risk behaviour and the possible need of a repeat test.
♦ Any unit carrying out HIV testing should be able to provide a patient whose HIV test result is positive with general information regarding the mode of HIV transmission, course of the disease and the treatment choices available. The unit should also be prepared to answer any questions relating to daily hygiene needs etc. B 5 6.
♦ The disease staging and the assessment of an individual patient’s prognosis, as well as the decision on specific drug therapies, are carried out by a specialist team.
♦ As soon as a positive test result is obtained every effort should be made to identify and inform the patient’s past contacts, who should be encouraged to agree to be tested.
♦ An official notification of an infectious disease should be made.
♦ If the patient is an intravenous drug user the following blood tests should be carried out: HCVAb, HBsAg, HBeAb. A hepatitis B vaccination programme should also be instigated, unless the patient has had the disease.
♦ The follow-up of the patient is usually undertaken by an infectious disease team.

Treatment

Specific treatment with HIV drugs

♦ Treatment of an HIV infection requires specialist skills, and the prescription and implementation of drug therapies should be undertaken only by those experienced in their use.

♦ The development of HIV drugs has significantly improved the prognosis of an HIV infection. No cure exists, but it may be possible to add several tens of years to the life expectancy of an HIV positive patient A 1 2. Quality of life has also improved significantly as has the patients’ ability to continue in working life.
♦ Indications for starting drug therapy for an HIV infection are:
  • symptomatic disease (particularly if AIDS is diagnosed)
  • asymptomatic disease, if CD4 cell count falls below 0.35 \times 10^9/l.
  • an HIV positive pregnant mother (to prevent vertical transmission) A 7.
♦ The treatment is carried out with the combination of at least three antiviral drugs (HAART) A 8.
♦ The drugs that are available today are divided into four groups:
  • nucleoside reverse transcriptase inhibitors (NRTI)
  • non-nucleoside reverse transcriptase inhibitors (NNRTI)
  • protease inhibitors (PI)
  • HIV entry inhibitors.
♦ Once antiviral drug therapy has been started, its uninterupted continuation is of vital importance.
  • Development of drug resistance and loss of efficacy may follow irregular adherence to therapy.
  • The treatment must not be interrupted without prior consultation with the treating physician.
  • HIV drugs interact with several other drugs. There is potential for too high or too low concentrations of either drug. Specialist consultation should always be sought in unclear cases.
♦ Patient compliance is the most important factor in successful drug therapy for HIV infection.
  • The patient is expected to take a large number of tablets and adverse effects are common, particularly in the beginning.
  • To facilitate dosing at the same time every day may involve some lifestyle changes.
♦ In some countries all pregnant mothers are tested for HIV antibodies. An HIV positive pregnant mother should be referred to the care of a specialist team with expertise in HIV management.

HIV and the general practitioner

♦ The asymptomatic phase lasts for a long time, and the correct timing of the specific antiviral drugs effectively reduces the occurrence of opportunistic diseases. These patients will visit their GP more often than before with common infections, skin or dental problems or with problems totally unrelated to their positive HIV status.
  • When an HIV positive patient presents with a febrile illness the treating specialist unit should be consulted over the telephone in all unclear cases, particularly if antiretroviral medication has been introduced.
  • Abnormal headache, paralysis, impaired consciousness or visual disturbances in an HIV positive patient always
warrant an immediate referral to specialist care for further investigations.

- HIV is not curable with current drug therapies and the introduction of terminal care may have to be broached at some stage. The options include home nursing services, hospices or general hospital wards. The situation should be anticipated in good time to allow the appropriate staff time to undertake any additional training.

**The working capacity of HIV carriers**

- During the asymptomatic phase the working capacity of the patient remains normal in most occupations.
- The decreased working capacity during primary infection is transient. AIDS often causes permanent loss of working capacity, but its degree varies according to the occurrence of opportunistic diseases. Working capacity may be restored by antiviral treatment. In some cases the patient can continue to work even after AIDS has been diagnosed.
- Infection risk does not usually contribute towards the patient’s inability to work.

**Guidelines for health care professionals**

- When exposure to blood is a possibility, gloves and a facial shield should be worn.
- Gloves should be worn when taking blood samples, but there is no need to wear a facial shield (if vacuum tubes are used).
- Particular attention should be paid to following recommended procedures in order to avoid needle stick injuries.

**Post-exposure prophylaxis in an occupational setting**

- In percutaneous exposure, where the source patient is known to be HIV positive, prophylaxis is recommended with a combination of three drugs for four weeks. The treatment should be started within two hours of the exposure. Post-exposure prophylaxis has been found to be highly effective but should be reserved for cases where the potential for infection transmission exists. Prophylaxis after mucous membrane exposure is discretionary. An infectious disease physician should be consulted in uncertain cases and in order to obtain assistance in risk assessment.
- The decision about initiating post-exposure prophylaxis must be made by a physician with HIV experience. Health care staff must have access to post-exposure prophylaxis 24 hours a day.
- An HIV antibody test should be taken without delay and again after (1), 3 and 6 months.
- If antiviral medication was prescribed for prophylaxis, antibody testing may be continued for even longer.
- Official notification must always be made of a needle stick injury.
- During the follow-up period, a condom must be used during sexual intercourse B 9.

**References**

• is spread via saliva (either from a bite or through mucous membrane contact)
• will lead, after an average incubation period of 20–90 days, to encephalomyelitis which is always fatal unless early prophylactic treatment has been administered
• causes an estimated 100 000 human deaths annually, mostly in underdeveloped countries.

♦ Treatment with vaccine and rabies immunoglobulin will always prevent the development of clinical disease, provided that
  • it is started early (< 24 hours) after exposure
  • it is carried out appropriately.

Human infection
♦ Rabies is transmitted via saliva. A rabid animal can transmit the disease to a human through
  • a bite or
  • a lick on mucous membrane or broken skin
♦ Species of possible reservoir include:
  • Wild animals: fox, wolf, raccoon, badger and bat
  • Domestic animals: dog, cat and cattle.

Establish the following
1. When and where the exposure occurred?
2. Was the contact a bite, a lick or other type of contact (nibbling, scratching etc.)?
3. What type of animal was involved?
4. Does the animal appear rabid, for example abnormal aggressiveness or other symptoms suggesting central nervous system involvement?
5. If the animal is a domestic animal, what is the vaccination status?
6. Was the animal caught and will it be possible to keep it for observation?
7. Has a veterinarian been consulted regarding the rabies status of the animal?

Post-exposure treatment
Local treatment of the wound
♦ The following measures should be undertaken as soon as possible, preferably at the scene of exposure:
  • Remove any dirt or debris from the wound.
  • Rinse the wound with running water. Wash the wound with soap and water.
♦ At a Health Centre
  • Repeat the cleaning if necessary.
  • Disinfect the wound, for example with an alcohol solution.
  • Remove any dead tissue, but leave the wound open, i.e. no suturing.
♦ Early, effective local treatment can reduce the risk of rabies by 90%.

Vaccination therapy
♦ Should be started as soon as possible, preferably within 24 hours of exposure.
  • In some cases it may be justified to initiate vaccination therapy even after a considerable time delay.
♦ Administered at a Health Centre or hospital.
♦ The dose for individuals not previously vaccinated (unimmunized)
  • consists of five 1 ml (2.5 IU/ml) injections on days 0, 3, 7, 14 and 28
  • should be injected into the deltoid muscle. In infants, into the upper region of the outer thigh muscle.

Rabies immunoglobulin
♦ Rabies immunoglobulin is usually available from specialist microbiology laboratories; check the availability in your country.
♦ When immunoglobulin administration is indicated it should be administered
  • preferably within 24 hours of exposure
  • no later than on the day of the third injection (on day 7).
♦ The dose is 20 IU/kg (150 IU/ml) and it is administered as a single dose. Rabies immunoglobulin should be infiltrated into the depth of the wound(s) and injected into surrounding tissues.
♦ Both the vaccine and immunoglobulin may be administered at the same time provided that the injection sites are not anatomically adjacent;
  • i.e., if immunoglobulin is infiltrated into the left upper arm give the vaccine into the right upper arm.

Note
♦ Always consider consulting the appropriate rabies advisory centre of your country.
♦ Rabies is a notifiable disease.
♦ Remember the need for tetanus prophylaxis. Prophylactic antibiotic treatment is often warranted in cases of animal bites (for example oral amoxicillin + clavulanic acid orally).

Indication for vaccine therapy and rabies immunoglobulin
No indication for vaccination therapy or rabies immunoglobulin
♦ The contact only involved touching the animal or minor scratches.
♦ The animal has only licked unbroken skin and no animal saliva has been in contact with broken skin or mucous membranes.
♦ A bite or mucous membrane exposure caused by a vaccinated domestic animal.
• with no direct signs of rabies
• the health status of which can be monitored.
• Note. The animal must be observed for 10 days! If it shows any signs of rabies, the exposed individual should be treated with vaccine therapy and rabies immunoglobulin.

**Indication for vaccination therapy**

♦ A wild animal or a (possibly) non-vaccinated domestic animal
  • has licked broken skin or
  • has caused a small superficial cut to body parts other than the head, neck or a peripheral part of a limb.
♦ Treatment can be interrupted if the animal does not show any signs of rabies during the 10-day observation period.
♦ If the animal shows signs of rabies at the time of contact or during the observation period, the treatment of the exposed individual should consist of both vaccination therapy and rabies immunoglobulin.

**Indication for both vaccination therapy and rabies immunoglobulin**

♦ A wild animal or a (possibly) non-vaccinated domestic animal has caused one of the following (high risk exposure):
  • a serious and deep bite
  • several bites
  • a bite to the head, neck or a peripheral part of a limb
  • a mucous membrane exposure.
♦ In cases where it is possible to observe the animal clinically, or to carry out laboratory examination of the brain tissue of a dead animal, it is possible to withdraw the vaccination therapy if
  • the animal shows no clinical symptoms signs of rabies during the 10-day observation period or
  • the brain reveals no histopathological changes consistent with rabies.

**Symptoms**

♦ A papular, itching rash particularly on the feet (after wading).

**Diagnosis**

♦ Based on a typical history.
♦ A cercaria may sometimes be detected from a papule by microscopy.
♦ No serological test is available.

**Treatment**

♦ Itching can be alleviated with ointments and oral antihistamines. The disease is cured spontaneously.

**Prevention**

♦ Drying the skin thoroughly after swimming.

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### 1.51 Echinococcosis

*Kirsi Skogberg*

**Basic rules**

♦ Cystic echinococcosis is caused by Echinococcus granulosus, a canine helmint parasite. Alveolar echinococcosis, a less frequent form of echinococcosis, is caused by Echinococcus multilocularis.

**Course of the disease**

♦ Echinococci (Echinococcus granulosus and the more rare Echinococcus multilocularis) are tapeworms. The adult worm is 3–9 mm long. Dogs and other canines act as the final host and the eggs are excreted in their faeces. Intermediate hosts include humans, sheep, reindeer and moose.
♦ Infection to humans is transmitted by ingestion of food that has been contaminated with faeces of the final host. The parasite eggs are transported through the intestinal wall, usually into the liver and lungs, where they form a hydatid cyst. The cyst is filled with infectious larvae and may grow to a diameter of several centimetres. Symptoms usually reflect the size of the cyst and may become evident only several years after infestation.
**Symptoms**

♦ The cysts cause no symptoms for a long time and are often found accidentally, e.g. in ultrasonography of the liver.
♦ The cysts may cause compression symptoms depending on their location (most often in the liver or lungs but also in the central nervous system, bones etc.)
♦ A cyst rupture may result in anaphylactic reaction or haemoptysis (pulmonary cyst).

**Diagnosis**

♦ The diagnosis is based on finding a typical echinococcus cyst with radiographic imaging (ultrasound, chest radiograph, CT or MRI) in a patient with a history of exposure.
♦ The presence of echinococcus antibodies confirms the diagnosis, but does not rule out echinococcosis. Even false positive antibodies can be present.
♦ If a suspected cyst is removed, the diagnosis of echinococcosis can be made in a parasitologic laboratory. Even puncture with albendazole protection (to prevent spreading) is a possible, but rarely used, procedure.
♦ Inspection of a faecal sample for the presence of parasites is of no value.

**Treatment**

♦ Surgical excision of the intact cyst
♦ Albendazole 10 mg/kg/day for 28 days is the drug of choice. The course is repeated after an interval of 2 weeks.

**Prevention**

♦ Dogs must be wormed (praziquantel).
♦ Dogs and predators must not be allowed access to offal and carcasses.

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1.52 Tapeworm disease

*Sakari Jokiranta*

**The infectious agents**

*Diphyllobothrium sp.*

♦ Caused most frequently by *Diphyllobothrium latum*, *D. dendriticum*, or *D. ursi*.
♦ Crustaceans and fish are intermediate hosts.
♦ The larvae that infest fish are frequently found in muscles and a coiled larva can be seen as a white mass.

♦ An adult tapeworm infesting the small bowel is 0.5–2 cm wide and may be more than 10 m long.
♦ Endemic in Scandinavia, North America, Russia, Eastern Europe, Uganda, and Chile.

**Taenia sp.**

♦ Intestinal taeniasis can be caused by *Taenia saginata* and *T. solium*. In addition to the intestinal infestation *T. solium* may cause more severe disease, cysticercosis, characterised by tissue larvae.
♦ The larvae are acquired from poorly cooked beef (*T. saginata*) or pork (*T. solium*).
♦ An adult *Taenia* worm is 2–7 m long and 5–7 mm wide.
♦ Both *Taenia* species are worldwide in distribution. *T. saginata* is common in parts of the Middle East, Central Africa, and South America while *T. solium* is rare in Muslim countries.

**Other tapeworms**

♦ *Hymenolepis nana*, *H. diminuta*, and *Dipylidium caninum* are tapeworms of mouse, rat, and dog, respectively, but may also cause human tapeworm disease.
♦ The infections are obtained by accidental ingestion of beetles (*Hymenolepis*) or fleas (*Dipylidium*).

**Clinical picture**

♦ Infestations are usually asymptomatic but mild intestinal discomfort, abdominal pain, and nausea may occur. Intestinal obstruction is a rare complication.
♦ Due to vitamin B12 adsorption by *Diphyllobothrium*, B12 deficiency may develop and is characterised by
  - macrocytic anaemia (15.24)
  - smooth tongue
  - neurological abnormalities (paraesthesias of the limbs, ataxia).
♦ Patients often become aware of the infestation when worm segments are passed in faeces.

**Diagnosis**

♦ Identification of eggs or worm segments from a faecal sample is diagnostic.
♦ Due to sequential release of ova from proglottids several faecal samples may be necessary for diagnosis. Sensitivity of the faecal ova analysis can be enhanced by concentration methods.
♦ Eosinophilia may occur in taeniasis but does not help in diagnosis.

**Treatment**

♦ The drug of choice is Praziquantel as a single dose of 5–10 mg/kg. For treatment of *Hymenolepis nana* higher dose is used (25 mg/kg).
Niclosamide is an alternative as a single dose of 2 g for adults. The pediatric dose is 50 mg/kg.
Niclosamide can be administered in conjunction with a laxative to facilitate expulsion of the worms.
To verify treatment efficacy the stools are re-examined for eggs three months after the treatment.

Prevention
Fish, roe and meat should be well cooked, salted or frozen (for a minimum of 24 hours at −18°C or −0.4°F).
Meat inspection helps to prevent Taenia infections.

1.53 Trichinosis

Editors

The infectious agent
The trichin is a parasite of predators. Humans are infected from uninspected, infested meat. The most common sources of infection are poorly cooked pork, sausage, or bear meat.
The larvae are released in the gut and invade muscles via the bloodstream.
Once inside a muscle the larvae develop into a cyst that becomes calcified and remains viable for years.

Symptoms
In the intestinal phase symptoms are mild or non-existent.
One week after inoculation, in the migration phase, the patient has fever, eosinophilia, myalgia, vasculitis, oedema around the eyes, urticaria, increased blood concentrations of aminotransferases and occasionally a cough.
During the third week, in the muscle-infestation phase, the patient has myalgia, ocular pain, and haemorrhages under the nails and in the conjunctivae.

Diagnosis
The diagnosis is based on history and the clinical picture.
Consumption of uninspected meat (home-slaughtered pork, bear meat) is usually disclosed by history.
Eosinophilia can be observed about 10 days after inoculation, and antibody levels rise after 2–3 weeks. The concentrations of muscle enzymes creatine kinase and lactate dehydrogenase may be increased.
Larvae can be found in muscle biopsy samples (deltoid, gastrocnemius) most easily on the fourth week after inoculation.

Treatment
Consult a specialist on infectious diseases.
If ingestion of infected meat is strongly suspected, give the patient thiabendazole 25 mg × 2 × 7, starting within 24 hours. In later stages of the disease give large doses of mebendazole as a long course (e.g. 400 mg × 3 × 14).
Initial treatment of the acute phase also consists of rest, NSAIDs, and (for severe symptoms) corticosteroids.

Prevention
Inspection of meat (regular, thorough).
Cooking (over 77°C) or freezing meat (−15°C for at least 20 days). Smoking fish or meat is not sufficient.

1.54 Ascariasis

Sakari Jokiranta

The infectious agent
Ascaris lumbricoides is a 15–35 cm long and 0.3-0.6 cm wide intestinal roundworm.
Ascariasis is worldwide in distribution and is very common in developing countries (estimated 1–1.5 × 10⁹ cases).
The inoculation occurs by ingestion of eggs from the soil. The larvae hatch in the gastrointestinal tract and invade the bloodstream. They migrate through lungs to the pharynx from where they are again swallowed into the gut where the adult cream-coloured worms live.
The eggs are transported to soil with faeces. They then mature in the soil for a couple of weeks until they are infective. A female worm produces massive amounts of eggs (2 × 10⁵–10⁶ per day) and this explains the wide distribution of ascariasis.

Clinical picture
Most infestations are asymptomatic or the symptoms are very mild.
Vague abdominal discomfort or pain is the most usual intestinal symptom followed by nausea and colic.
During the migratory stage of the larvae cough and fever may occur in association with pneumonitis; urticaria may also develop.
Large amounts of worms cause malnutrition and may cause intestinal obstruction.
Since the adults are actively motile nematodes they may enter the biliary tract followed by symptoms of biliary
obstruction or may even penetrate the intestinal wall and cause peritonitis.

**Diagnosis**

- Identification of eggs or a worm from a faecal sample is diagnostic.
- Sensitivity of the faecal ova analysis can be enhanced by concentration methods.
- During the migratory stage of the larvae eosinophilia and an increase in the serum IgE concentration can be detected and occasionally the larvae can be detected in sputum.

**Treatment**

- Ascariasis should always be treated. Treatment for ascariasis should precede treatment of other intestinal worms.
- The drug of choice is a single dose of albendazole 400 mg (for children < 2 years 200 mg). Alternatively, for adults and children > 2 years, mebendazole 100 mg b.i.d for three days (or as a 500 mg single dose) can be used. Also pyrantel pamoate (11 mg/kg single dose) can be used.
- In intestinal or biliary duct obstruction piperazine citrate is given as a single daily dose of 50–75 mg/kg (maximum of 3.5 g) on two consecutive days to cause flaccid paralysis of the worms.
- During pregnancy piperazine or pyrantel pamoate is usually given.

### 1.55 Pinworm (enterobiasis)

**Sakari Jokiranta**

#### The infectious agent

- The causative agent, *Enterobius vermicularis* (pinworm, threadworm), is a white nematode worm. It is exclusively a human parasite.
- The infestation is obtained by ingestion of mature eggs. The adults live in colon and are frequently found in coecum.
- The female worms (8–13 mm long and less than 1 mm wide) come out through the anus, often during sleep, to lay eggs onto the perianal skin.
- Distribution is worldwide and pinworm is the most common helminthic infection in several industrialized countries. The infections are mostly found in children at the age of 3 to 10.

#### Clinical picture

- The most usual symptom is perianal pruritus, particularly at night.

- Secondary bacterial dermatitis of the perianal region may develop.
- Anorexia or irritability may occur.
- Rarely, the worms invade the female genital tract followed by vulvovaginitis, peritoneal granulomas, or urethritis.

#### Diagnosis

- For diagnostic detection of eggs, samples should be taken from the perianal skin in the morning before defecation or shower.
- The most frequently used methods for sampling are adhesive tape and a cotton swab.
- Sensitivity of the perianal sampling is increased by taking several samples over a few days.
- Adult worms are diagnostic when visible on the perianal skin or motile on the surface of the stools.
- The eggs can sometimes be identified from faecal samples (successful only in 10% of cases).

#### Treatment

- The drug of choice is a single dose of pyrantel pamoate (11 mg/kg, max. 1 g), mebendazole (100 mg, 50 mg for children under 2 years of age), or albendazole (400 mg).
- Pyrvine as a single dose (7.5–10 mg/kg) is also effective.
- The treatment should be repeated after 2 weeks.
- The bedlinen are usually changed on the day after the treatment and children’s fingernails are trimmed.
- The whole family is often treated at the same time, including asymptomatic family members.
- If many children in a day care facility are infected it should be considered if the whole group needs to be sampled or treated.

#### Prevention

- The most effective preventive act seems to be more careful hand washing and improved toilet hygiene.
- It might be beneficial to keep children’s fingernails short.
- Sleeping in the same bedlinen as a pinworm carrier should be avoided.

### 1.60 Giardiasis

**Sakari Jokiranta**

#### The infectious agent

- *Giardia lamblia* (G. intestinalis, G. duodenalis) is a protozoan flagellate that lives attached to the mucosa of the duodenum and jejunum.
Transmission
- from stools of an infected individual by ingestion of cysts in food or water or through hand contact
- adding chlorine to water does not reduce infection risk; however, filtering does
- cysts can remain viable in cold water for 2 to 3 months
- several species of wild animals may transmit the disease
- high risk of transmission among children for example in day-care centers
- Giardia is found worldwide with prevalence varying from abundant (5 to 50% in developing countries) to moderate (0.5 to 7% in industrialized areas).

Clinical picture
- Varies from symptomless cases to severe acute gastroenteritis and chronic malabsorption. Abdominal cramps and diarrhoea are dominant features.
- Specific diagnosis cannot be based on clinical picture.
- Symptoms of acute giardiasis
  - Symptoms usually begin 1–3 weeks from infection.
  - Epigastric cramps, nausea.
  - Stools may vary from watery to more solid, and they may be profuse, foul smelling, pale and may float.
  - Tenesmus is present especially in the mornings and after meals.
  - Bloating, flatulence, anorexia, weight loss.
- Symptoms of chronic giardiasis
  - Similar to the acute form but milder and periodic.
  - Recurrent diarrhoea and abdominal discomf ort and distention are dominant features.
- The following complications are possible: secondary malabsorption, for example lactose intolerance, even subtotal villus atrophy, pancreatitis, cholangitis, rarely growth retardation in children and possibly also reactive arthritis, urticaria and uveitis.
- Differential diagnosis

Diagnosis
- Based on detection of protozoa cysts, antigen or trophozoites.
- Stool is preserved in formalin, concentrated and microscoped for cysts.
- Usually at least three stool samples are collected 2 to 3 days apart for faecal parasite examination.
- If the laboratory test for faecal parasites is repeatedly negative, the more sensitive method of antigen detection (ELISA or immunofluorescence assay) can be used to reveal Giardia. Unlike the faecal microscopy test, antigen detection does not reveal other faecal parasites.
- Giardiasis is characterized by a so-called prepatental period, which means that the protozoa may be detected in stools rather late after the transmission. Incubation period is often shorter which may lead to false negative stool samples at the onset of the disease.

In chronic giardiasis the protozoa are few, and detection of cysts or Giardia antigens in stools is sporadic.
- Trophozoites may be searched from duodenal mucus or intestinal wash. Mucosal biopsies should be the so-called touch preps, i.e. a clean microscopic slide is touched with the villus biopsy and allowed to dry before subjecting to staining of the trophozoites.
- Differential diagnosis
  - Other intestinal infections—finding one does not rule out another.
  - Bile disorders, ulcus, gastritis, lactose intolerance
  - Coeliac disease, impairment of pancreatic function and other causes of malabsorption

Treatment, follow-up, prognosis
- The aim is to eradicate both symptoms and the protozoa. Treating symptomless individuals is indicated in order
  - to eliminate the source of transmission
  - to prevent development of further disorders associated with giardiasis.
- The most effective drugs are metronidazole as a 5-day course (the usual dose is 250 mg × 3 for adults and for children 15 mg/kg/day divided into three doses) and tinidazole, taken as a single dose of 1.5–2 g; these drugs provide cure for over 90% of the patients.
- Alternatively albendazole (po 400 mg daily, for 5 days) or quinacrine (po 100 mg × 3 after meals, for 5 days) may be used. Recently the Food and Drug Administration (FDA) has approved nitazoxanide for treatment of giardiasis in 1–11 year-old patients.
- In relapses a longer course of metronidazole with a higher dose is often efficient (up to 750 mg × 3, for 2 to 3 weeks). That can be combined with quinacrine (100 mg × 3, for 2 to 3 weeks) in refractory patients.
- During pregnancy, a case of giardiasis with mild symptoms may be temporally left untreated; in an infection with severe symptoms non-absorbable paromomycin po (25–35 mg/kg/day) divided into four doses for 7 days is preferable. There is, however, no evidence of any relationship between metronidazole exposure during the first trimester of pregnancy and birth defects.
- Relapses occur in most cases 2 weeks after treatment, although they may be seen even after 2 months.
- Relapses can also be symptomless. Control specimens are useful at least 1 and 2 months after treatment.
- It is useful to examine and, if necessary, treat all persons in contact with the patient. In relapse.
- Prognosis is good, and after the protozoan is eliminated, all the complications will also be cured, with perhaps the exception of reactive arthritis.

References
A 1
1.61 Cryptosporidiosis

Sakari Jokiranta

The infectious agent

- Cryptosporidium parvum is a protozoan of the Apicomplexa phylum and it can infect many animal species (e.g. pigs, calves, sheep, horses, mice, chickens, dogs, cats) in addition to man.  
- Transmission occurs readily by ingestion of oocysts in food or water or via fecal-oral route; as low as 10–100 oocysts can cause an infection.  
- The parasite lives in the intestinal epithelial cells in small bowel and the infection leads to excretion of oocysts in faeces. The whole life cycle is completed in one individual causing an autoinfective stage and huge production of oocysts.  
- Cryptosporidium infects both immunocompetent and immunocompromised individuals and is found worldwide.  
- Cryptosporidium infection has been estimated to account for 2 to 6% of cases of diarrhoea.  
- Several local and large outbreaks have been reported, largest being an outbreak in Milwaukee and Georgia in 1993 with estimated 403 000 affected persons.  
- Two other protozoans, Cyclospora cayetanensis and Isospora belli, can cause Cryptosporidium-like infections.

Clinical picture

- The incubation period is 7 to 10 days.  
- In immunocompetent patients  
  - more than 90% of infected patients present with watery diarrhoea and epigastric cramps.  
  - one third of the patients have a short fever period.  
  - nausea is common, vomiting less frequent.  
  - symptoms last on average 12 days, varying from 2 days to 1 month.  
  - the disease is cured spontaneously.  
  - asymptomatic carriage occurs.  
- In immunocompromised patients  
  - severe watery diarrhoea develops (up to 6 litres/day).  
  - the disease persist for several weeks to years and may even be fatal.  
  - in HIV patients the infection may be self-limiting if CD4 cell count is 180 mm$^3$ or more.  
- Cryptosporidium can infect epithelial cells of biliary tree and respiratory tract, mainly in patients with AIDS.

Diagnosis

- Cryptosporidium should be considered as the cause of prolonged or acute diarrhoea, especially in immunocompromised patients.  
- The diagnosis is based on detection of the causative organism.  
- Oocysts are excreted most abundantly and are thus best detected in the early phase of the disease, which is when two samples may be sufficient.  
- After the symptoms have disappeared oocysts continue to be excreted in the faeces for about 1 week, sometimes for up to 2 weeks.  
- Cryptosporidium can be identified from stool samples using modified acid-fast stains or immunoassay reagents. The acid-fast stain can be performed from the same formalin-fixed stool sample as the routine parasitological examination ("ova and parasites") or from non-fixed faeces.  
- Sometimes Cryptosporidium is detected accidentally when faeces is examined for other parasites; however, when Cryptosporidium is suspected the more sensitive acid-fast staining or an antigen detection assay should be used. The staining is also sensitive for the oocysts of the diarrhoea-causing protozoans, Cyclospora cayetanensis and Isospora belli.  
- Antigen detection assay (ELISA or immunofluorescence technique) is an alternative for the traditional acid-fast staining. At least most of the commercially available immunoassays are more sensitive in detecting Cryptosporidium. They fail, however, to detect Cyclospora and Isospora.

Treatment and prevention

- Because the disease is self-limiting in immunocompetent patients, the treatment is usually symptomatic.  
- In immunocompromised patients no therapy has been proven efficacious. Cryptosporidiosis may be treated p.o. with a long course of oral roxithromycin ($1^1$), azithromycin (600 mg × 1, for 4 weeks), and/or paromomycin (500–750 mg × 3–4, for at least 4 weeks). There is, however, only limited and partly controversial scientific evidence on the benefits of these drugs.  
- In treatment of cryptosporidiosis in immunocompetent or malnourished pediatric patients nitazoxanide (2000 mg/day) has been shown to be effective. The Food and Drug Administration (FDA) has approved nitazoxanide for the treatment of diarrhea caused by cryptosporidiosis in 1–11 year-old patients.  
- Prevention is based on avoiding contamination, which requires identification of the possible sources of infection, i.e. diagnosing Cryptosporidium infections in human and domestic animals.
Cryptosporidium is easily transmitted and can, therefore, cause epidemics spread by water, food or person-to-person contact.

Cyclospora cayetanensis and Isospora belli infections that cause Cryptosporidium-like manifestations can be treated with trimethoprim-sulfamethoxazole. In addition, pyrimethamine can be used in Isospora infections.

Reference


1.62 Toxoplasmosis

Maija Lappalainen, Klaus Hedman

Causative agent

♦ The most common latent protozoan infection
♦ The transmission is usually from cat faeces, soil, or inadequately cooked meat.
♦ Symptomatic disease is the consequence of a primary infection or the reactivation of a latent infection.

Epidemiology

♦ The seroprevalence increases with age, and there is no significant difference between men and women.

There are considerable geographic differences. The reasons are explained by differences in the cat population, climatic conditions, farming methods, hygiene, and cultural habits in regard to cooking food.

In the Nordic countries and the USA, approximately 80% of fertile-aged women are seronegative and thus at risk for primary toxoplasma infection during pregnancy. In countries with a high number of seronegative women and a low infection rate the actual number of primary infections might be the same as in a country with a low number of seronegative women and a high infection rate.

Estimates of incidences of primary toxoplasma infection during pregnancy and congenital toxoplasma infection in various parts of the world are presented in Table 1.62.

Source of infection

♦ Tissue cysts
  * Food (uncooked or inadequately cooked meat)
  * Organ transplantation

♦ Oocysts occur in the intestines of members of the cat family. It is estimated that approximately 1% of cats in Central and Northern Europe excrete oocysts.
  * Cat faeces
  * Soil
  * Unwashed and unpeeled fruit and vegetables
  * The oocysts may remain viable for months in warm and moist surroundings.

♦ Tachyzoites
  * Blood and tissue transplantation
  * Infected secretions

The tachyzoite form may traverse the placenta during parasitaemia so that the foetus becomes infected. Primary infection in the mother poses a danger to the foetus, but a reactivation does not.

Table 1.62 The seroprevalence of toxoplasma-specific antibodies, incidence of primary toxoplasma infections among seronegative pregnant women, and congenital toxoplasma infections in different countries.

<table>
<thead>
<tr>
<th>Country</th>
<th>Seroprevalence (%)</th>
<th>Incidence per 1000 seronegative pregnancies</th>
<th>Incidence of congenital toxoplasma infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td>37</td>
<td>1–2</td>
<td>&lt;1/1000</td>
</tr>
<tr>
<td>France</td>
<td>71</td>
<td>2.3</td>
<td>no data</td>
</tr>
<tr>
<td>Belgium</td>
<td>56</td>
<td>9.5</td>
<td>2/1000</td>
</tr>
<tr>
<td>Germany</td>
<td>68</td>
<td>2.5</td>
<td>0.7/1000</td>
</tr>
<tr>
<td>UK</td>
<td>13</td>
<td>1–5</td>
<td>1/13 000</td>
</tr>
<tr>
<td>Sweden</td>
<td>21</td>
<td>4–6</td>
<td>1.4/1000</td>
</tr>
<tr>
<td>Norway</td>
<td>13</td>
<td>2</td>
<td>1/1000</td>
</tr>
<tr>
<td>Denmark</td>
<td>27</td>
<td>6.5</td>
<td>3.3/1000</td>
</tr>
<tr>
<td>Japan</td>
<td>30</td>
<td>no data</td>
<td>no data</td>
</tr>
<tr>
<td>USA</td>
<td>15</td>
<td>1–6</td>
<td>&lt; 1/1000</td>
</tr>
<tr>
<td>Australia</td>
<td>35</td>
<td>0.3–0.5</td>
<td>2.3/1000</td>
</tr>
<tr>
<td>Finland</td>
<td>20</td>
<td>2.4</td>
<td>0.3–0.5/1000</td>
</tr>
<tr>
<td>Slovenia</td>
<td>no data</td>
<td>no data</td>
<td>3/1000</td>
</tr>
<tr>
<td>Scotland</td>
<td>no data</td>
<td>no data</td>
<td>0.5/1000</td>
</tr>
</tbody>
</table>

1 seroprevalence among native born inhabitants
2 only manifest cases included
Symptoms and signs

♦ Acquired infection is often either asymptomatic or the symptoms are ignored.
♦ The usual incubation period is 10–14 days.
♦ When symptoms exist, lymphadenopathy is the most common manifestation in non-pregnant and pregnant individuals, causing 3–7% of cases of clinically significant lymphadenopathy.
♦ Fever, fatigue, muscle pain and dermatologic manifestations may also occur.
♦ Even without known immune defects, patients with primary toxoplasma infection can develop severe manifestations, such as encephalitis, pneumonia or myocarditis.
♦ The term chronic active toxoplasmosis refers to patients whose symptoms and signs have persisted for months or years. In these patients the parasite or its DNA can be detected in blood.
♦ Immunocompromised patients have often serious sequela: encephalitis, pneumonia or myocarditis. Antiparasitic treatment is indicated in these patients.
♦ Congenital toxoplasmosis results from primary infection of the mother during pregnancy, but as a rule, not from reactivation of her latent infection.
  • The rate of transmission from mother to foetus increases from less than 10% to 80% with gestational age.
  • Infection early in pregnancy usually results in severe disease, while foetal infection following third-trimester infection is usually subclinical.
  • Most children with intrauterine infection are initially asymptomatic. However, by early adulthood 80–90% develop late manifestations such as retinochoroiditis or neurologic defects. The clinical manifestations of congenital toxoplasmosis range extremely widely from a normal appearance to encephalitis.
♦ Retinochoroiditis is the most common lesion in ocular toxoplasmosis.
♦ Toxoplasmic retinochoroiditis is usually considered to be the result of congenital infection rather than of acquired infection, although retinochoroiditis related to acquired infection has been reported.

Diagnosis

♦ The diagnosis of primary infection is usually serological.
  • Toxoplasma-specific IgG and IgM antibodies are first determined from one serum sample.
  • According to the result of the IgM test the avidity of IgG may be determined, and in infants also IgA.
♦ PCR examinations from the blood, cerebrospinal fluid, amniotic fluid or tissues can be determined if there are special indications.
♦ Diagnosis of congenital toxoplasmosis after birth requires several serum samples.

Diagnosis of primary toxoplasma infection during pregnancy

♦ Irrespective of the toxoplasma-IgM result, high avidity of specific IgG during the first trimester is a strong indicator against maternal primary infection; the foetuses of such women are at a very low risk for congenital toxoplasmosis.
♦ Low avidity of IgG, on the other hand, suggests recent primary infection, and further investigations are indicated.
♦ Follow-up of the seronegative women could be based primarily on IgG serology. The mothers with verified primary infection during pregnancy should be referred to the central hospital for further investigations and treatment.

Treatment

♦ Treatment of the immunocompetent patients is in most cases unnecessary.
♦ Treatment is indicated in
  • patients with severe infection
  • immunocompromised patients
  • pregnant women
  • infants with congenital toxoplasma infection.
♦ Spiramycin or a combination of pyrimethamine and sulphonamide is the treatment of choice in toxoplasmosis during pregnancy.
♦ Pregnancy need not be interrupted if repeated foetal ultrasound is normal, toxoplasma-PCR from amniotic fluid is negative and antiparasitic treatment is given.

Prevention

Advice for pregnant women on avoiding toxoplasma infection

♦ Clean cat litter trays daily (if it is you who has to do it) and wear gloves and wash hands afterwards.
♦ Wear gloves when gardening, and wash hands afterwards, as well as after contact with children’s sandpits.
♦ Peel or at least wash vegetables that have been in contact with soil. Peel fruit.
♦ Do not eat undercooked meat (especially on holidays abroad) and wash hands after handling raw meat.
♦ Do not drink unpasteurized milk or eat raw eggs.
♦ A common piece of advice for tourists is valid also in this context: “Peel it, boil it, cook it—or forget it”.

Screening for primary toxoplasmosis during pregnancy

♦ Arguments for and against the screening of pregnant women have been voiced.

Reference

1. Cook AJC, Gilbert RE, Buffolano W, Zufferey J, Petersen E, Jenum PA, Foulon F, Semprini AE, Dunn DT on behalf of
1.63 Amoebiasis

Sakari Jokiranta

The infectious agent

♦ The causative agent of amoebiasis is a pathogenic protozoa (amoeba) called Entamoeba histolytica. Entamoeba histolytica is now recognized as a separate species from the closely related non-pathogenic Entamoeba dispar.
♦ E. histolytica invades the large intestine and feeds on the host’s dead cells, red blood cells and bacteria.
♦ E. histolytica may penetrate the intestinal mucous layer, destroy epithelial cells, cause crater-shaped ulcers, invade the peritoneum via the intestinal wall and disseminate through the venous circulation into the liver and other organs leading to development of amoebic abscesses.
♦ Contamination occurs when cysts are ingested via faecally contaminated food or drink.
♦ Adding chlorine to drinking water does not destroy the cysts of E. histolytica, but good filtering systems, treating water with iodine tablets, freezing it to –20°C or heating it (5 min +50°C) will eliminate the cysts.
♦ Its distribution is worldwide with a higher prevalence in tropical and subtropical regions. The WHO estimates that the annual number of patients with amoebic colitis or amoebic abscesses is approximately 40–50 million, with associated mortality around 0.1%.

Clinical picture

♦ The most common manifestations of the pathogenic E. histolytica are amoebic colitis and liver abscesses. Other manifestations include:
  ● intestinal region: peritonitis, toxic megacolon, amoeboma
  ● extraintestinal: skin fistula and amoebiasis cutis, amoebic abscess in the spleen/lungs/brain, pericarditis, amoebic empyema.
♦ Specific diagnosis is not possible on clinical manifestation alone.
♦ The incubation period from contracting the infection until symptom onset is from 1 week to 4 months.
♦ It was previously thought that 90% of patients with E. histolytica cysts in their faeces were asymptomatic carriers. However, over the past few years differentiation has been made between E. histolytica and the non-pathogenic E. dispar which, according to current knowledge, does not induce symptomatic illness. Of the combined E. histolytica/dispar laboratory findings up to 90% are in fact positive to E. dispar only. It appears that most of the patients previously considered to be asymptomatic carriers of E. histolytica are in fact infected with the non-pathogenic E. dispar. Nevertheless, some patients infected with E. histolytica still appear to remain asymptomatic or only have mild symptoms.

Amoebic colitis

♦ The clinical picture varies from very slight diarrhoea to bloody diarrhoea, i.e. dysentery, which, if left untreated, may be life threatening.
♦ In addition to diarrhoea, the symptoms may include abdominal pain, cramps, lethargy, low grade fever, loss of appetite, headache and lower back pain.
♦ On examination the patient usually has a tender abdomen and fever (38%).
♦ Complications include intestinal bleeding as well as peritonitis or amoeboma following intestinal perforation. Amoeboma is a granulomatous colonic tumour-pretending lesion which may cause local intestinal obstruction.

Amoebic abscess

♦ The most common is a liver abscess which manifests itself as upper abdominal pain, diarrhoea (in recent past) and weight loss.
♦ On examination the patient usually has a tender upper abdomen, fever and enlarged liver.
♦ Leucocytosis as well as increased alkaline phosphatase and CRP values are common.

Differential diagnosis

♦ In amoebic colitis: other intestinal infections, particularly those causing bloody diarrhoea, as well as ulcerative colitis and irritable bowel syndrome
♦ Sometimes a stool or intestinal sample for E. histolytica may reveal the presence of other amoebae. Entamoeba coli, E. hartmanni, E. dispar, Endolimax nana and Iodamoeba buetschlii are all non-pathogenic and do not therefore require treatment with antibiotics.
♦ In amoebic abscess: bacterial abscesses, tumours, echinococcosis, cysts.
♦ Dientamoeba fragilis is an amoeba flagellate, which may cause an intestinal infection with associated diarrhoea. It can only be detected from a stool sample with the use of trichrome staining or another amoeba staining.

Specific diagnosis

♦ Diagnosis is based on detecting the protozoa from a stool sample or a colonic biopsy.
The stool sample may be examined after it has been fixed with formalin or with polyvinyl alcohol (PVA), or Schaudinn’s fixative. An untreated sample may also be used. Only the cysts may be isolated from samples fixed with formalin whereas, in addition to the cysts, trophozoites may be isolated from samples fixed with the other fixatives. These morphological studies are not sufficient to distinguish between the pathogenic E. histolytica and non-pathogenic E. dispar.

Antigen detection may be carried out on untreated stool samples to distinguish between the pathogenic E. histolytica and non-pathogenic E. dispar. Differentiation may also be carried out using methods based on a polymerase chain reaction (PCR).

In severe diarrhoea, no cysts are formed but the majority of the amoebae will be shed as trophozoites. Therefore, a PVA-fixed sample or an untreated sample (for antigen testing) are recommended for diagnosis. In cases of suspected chronic amoebiasis or suspected amoebic abscess a formalin-fixed sample can be used. A minimum of three samples should be collected with an interval of 2–3 days to accommodate for the periodic shedding of cysts.

Samples (biopsies) taken during colonoscopy can be examined either immediately for the presence of characteristically moving trophozoites or the samples can be subsequently stained and examined for the presence of trophozoites.

The significance of stool and colonic samples is small in the diagnosis of amoebic abscess, since in most cases the amoebae are no longer present in the intestines. In these cases, the detection of amoebic antibodies in the serum, imaging of the abdominal and hepatic regions and, where necessary, the examination of percutaneous aspirates of suspicious abscesses are beneficial. A specific diagnosis is usually achieved with antigen detection studies or microscopic examination of the aspirate. However, due to the associated complications this procedure cannot always be recommended.

**Treatment, monitoring, prognosis**

The aim of the treatment is to eliminate both the symptoms and the amoebae.

The most effective treatment of amoebic colitis and extraintestinal amoebiasis is metronidazole 750–800 mg t.d.s., for 7–10 days (children: 10–16 mg/kg t.d.s.). For the elimination of the intestinal cysts diloxanide furoate should be administered 500 mg t.d.s., for 10 days (children: 6.5 mg/kg t.d.s.) or iodoquinol 650 mg t.d.s., for 20 days (children: 10–13 mg/kg t.d.s., up to 2 g/day).

In amoebic abscesses, percutaneous aspiration of the abscess could be attempted as an adjunct to the metronidazole treatment. Metronidazole may also be substituted with chloroquine.

During pregnancy, if the illness is asymptomatic or the patient only has mild symptoms, it is recommended that paromomycin (8–12 mg/kg t.d.s., for 7 days) is used rather than metronidazole.

The aim of treating asymptomatic carriers of E. histolytica is to eliminate the source of infection and to prevent the development of a subsequent symptomatic illness. The first line treatment of asymptomatic infection is usually metronidazole. However, if diloxanide furoate or iodoquinol are available they might be better justified for the eradication of an asymptomatic infection since they both are effective against the cysts. Carriers of E. dispar do not need to be treated.

Relapses do sometimes occur and 2–3 repeat stool samples should therefore be submitted 3–12 weeks after the treatment.

1.70 Septicaemia

**Veli-Jukka Anttila**

**Basic rules**

- A severe microbe-induced systemic infection with usually, but not always, positive blood culture results
- Suspect septicaemia in all patients who are very unwell and manifest severe symptoms.
- Check serum CRP without delay in patients who are not to be admitted to hospital immediately.
- Consider the possibility of streptococcal and staphylococcal sepsis in patients with a skin infection.
- Petechiae and extensive haematoma: meningococcus, pneumococcus or Capnocytophaga canimorsus (for example, following a dog bite)
- Check for nuchal rigidity, and assess the level of consciousness, to diagnose meningitis in all suspected cases of severe infection.

**Symptoms suggesting septicaemia**

- General malaise
- Fever
- Generalized or local pain
- Chills
- Fatigue, weakness
- Nausea
- Vomiting
- Rapid pulse rate
- Increased respiratory rate
- Skin symptoms (often petechiae, haematoma)
- Low blood pressure
- Confusion
- Unexplained worsening of an underlying illness

**Investigations**

- Clinical examination: vital signs, auscultate heart and lungs, examine skin, auscultate and palpate abdomen, examine mouth and throat, palpate lymph nodes, inspect anal area.
A high serum CRP is a good indicator of a septic infection provided that the symptoms have lasted for at least 12 hours, before which time CRP may be normal even in the presence of septicemia.

Leucocyte count may increase earlier than the CRP concentration (and should therefore be measured if the symptoms have been present for less than 12 hours). However, a low leucocyte count does not exclude a septic infection.

A low platelet count supports the diagnosis of septicemia or other severe infectious disease (consider the possibility of epidemic nephropathia, see 1.73).

Blood cultures should be taken twice before antibiotic treatment is instigated. In septic shock, samples are taken simultaneously from both arms. The samples need not be taken during a peak in the patient’s temperature. If high temperature persists, blood cultures should be repeated during antibiotic treatment.

The most common causative agents of septicaemia in a previously healthy individual

- Staphylococcus aureus
- Pneumococcus
- Meningococcus
- Group A beta-haemolytic streptococcus
- E.coli

Treatment

- Intravenous fluids (normal saline) should be started as soon as possible (before transportation to the hospital) to treat the shock. The patient may need several litres. If hypotension cannot be corrected, plasma expanders and gradually increasing doses of dopamine can be attempted.
- If the clinical picture suggests meningococcal sepsis or if the patient’s general condition is poor and transportation to an intensive care unit will take more than one hour:
  - start antibiotics (e.g. penicillin G, cefuroxime or a third generation cephalosporin)
  - consult the hospital and take blood cultures before starting antibiotics (if blood culture bottles are not available transport a syringe full of blood in a warm place, e.g. jacket pocket along with the patient). A delay in antibiotic therapy will worsen the patient’s prognosis.
- Serum CRP concentration is usually high in immunosuppressed patients with a bacterial infection, but can be near normal right at the very beginning of the infection. High fever is therefore the only certain sign of infection in a neutropenic patient, because e.g. imaging findings are often scarce during severe neutropenia. If the fever has lasted at least for 12 hours a normal serum CRP concentration almost rules out a serious bacterial infection.
- The blood granulocyte count is more important than serum CRP for the decision on hospital admission.

Causes of infection in patients with cancer

- Neutropenia (after cytostatic therapy)
- Gram-negative rod bacteria (enterobacteria, Pseudomonas)

Diseases and drugs causing immunosuppression

- Malignant haematological diseases
- HIV infection
- Congenital immunodeficiencies (hypogammaglobulinaemia, impaired phagocytosis, disorders of cell-mediated immunity)
- Organ transplantations
- Prematurity (infants)
- Cytotoxic drugs (including azathioprine and methotrexate prescribed for rheumatoid arthritis)
- Cyclosporin, mycophenolate, tacrolimus
- Prednisolone in doses exceeding 0.3 mg/kg
- TNF-α inhibitors
- Antilymphocyte globuline

Fever in the immunosuppressed patient

- The blood granulocyte count is determined immediately. If the count exceeds 1 × 10⁹/l and the general condition is good or fair, the patient can be treated as a normal patient with fever, but if the count is below 1 × 10⁹/l the patient should be admitted to hospital and a septic infection should be suspected. In severely immunodeficient patients an empiric broad-spectrum antibiotic should always be started immediately after taking blood culture samples because the course of the disease is often violent and difficult to predict. The antibiotic therapy can later be changed after receiving answers from blood culture and sensitivity studies.
- Staphylococcus aureus
- Staphylococcus epidermidis (central venous catheter)
- Yeasts (Candida species)
- Aspergillus moulds (especially in severe and prolonged, i.e. lasting for several weeks, neutropenia)
- Disorders of humoral immunity (myeloma, chronic lymphocytic leukaemia)
  - Bacteria with a capsule (pneumococci, Haemophilus influenzae, meningococcus)
- Splenectomized patients
  - Pneumococci, Haemophilus influenzae, meningococcus
- Disorders of cell-mediated immunity (HIV infection, lymphomas, organ transplantsations)
  - Mycobacteria
  - Listeria
  - Salmonella
  - Herpes
  - Cytomegalovirus
  - Toxoplasma
  - Pneumocystis carinii
  - Cryptococcus
  - Candida yeasts
  - Aspergillus moulds

**Infections in cancer patients without severe granulocytopenia**

- The granulocyte count is above $1.0 \times 10^9/l$.
- The infections are often associated with obstruction, interruption of anatomical borders caused by tumours, invasive procedures, and tumour necroses.
- The causative agents are ordinary virulent bacteria.
- Longlasting hospitalization exposes the patient to colonization caused especially by intestinal bacteria and therefore exposes the patient to severe infections.
- The infections should be treated like infections in other immunosuppressed hospital patients.
- Local radiation can increase the risk of infection by damaging the mucosal lining of the gastrointestinal tract.

**Prevention of bacterial infections in neutropenic patients or patients who have received stem cell transplantation**

- The key to preventing hospital-acquired infections is properly functioning hospital hygiene which prevents the transmission of infections via hands. In addition, it is important to shorten the duration of neutropenia (leucocyte growth factors).
- Even though prophylactic antimicrobial treatments have in some studies been shown to reduce the occurrence of bacterial infections, most experts find the routine use of prophylactic treatment to bring more harm than benefit.

**Herpes zoster**

- Acyclovir treatment (1.41) is indicated in patients with cancer with the exception of cases where more than 3 days has elapsed since the emergence of the first vesicles and several days since the emergence of new skin lesions.
- Herpes zoster may be more violent and widespread in severely immunodeficient patients (especially during severe neutropenia) than normal, so it is important to begin antiviral therapy (acyclovir or valaciclovir) immediately after emergence of the first vesicles.

**Cytomegalovirus (CMV)**

- CMV is a significant cause of infection in patients who have received stem cell or organ transplantation. The virus may reactivate during longlasting immunosuppressive therapy in patients who are themselves positive for CMV antibodies and those who are negative for CMV antibodies, but who have received a transplant from a CMV antibody positive person. These patients are given either prophylactic or preemptive therapy with ganciclovir or foscarnet. The initiation of pre-emptive treatment is based on follow-up of CMV-pp65-antigen or CMV-DNA-PCR.
- CMV infection can be treated with ganciclovir, foscarnet or cidofovir.
- The mortality rate of CMV pneumonia is especially high. It is treated with antiviral drugs combined with intravenous immunoglobulin.

**Tuberculosis**

- Remember the possibility of reactivation of tuberculosis in immunosuppressed patients.
- Prophylactic treatment is considered if
  - earlier tuberculosis has not been treated by chemotherapy
  - tuberculosis was treated before the year 1970 (before the time of effective combination chemotherapy)
  - the patient was exposed to a case of pulmonary tuberculosis in the family as a child.

**Pneumocystis carinii**

- Secondary or primary prevention is indicated according to the aetiology of immunosuppression. Prophylactic medication is given to all patients who have received allogeneic stem cell transplantation and patients with HIV whose CD4 level is below $0.2 \times 10^9/l$.
- Prophylactic therapy consists of either sulphaphenazole, given three times a week, or inhaled pentamidine, given once a month. The prophylactic therapy is continued for 6 months after allogeneic stem cell transplantation, even longer if the patient receives other potently immunosuppressant drugs e.g. corticosteroids or ciclosporin. In patients with HIV the prophylaxis is continued until the CD4 level has permanently risen to $0.2 \times 10^9/l$. 

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**Cytomegalovirus (CMV)**

- CMV is a significant cause of infection in patients who have received stem cell or organ transplantation. The virus may reactivate during longlasting immunosuppressive therapy in patients who are themselves positive for CMV antibodies and those who are negative for CMV antibodies, but who have received a transplant from a CMV antibody positive person. These patients are given either prophylactic or preemptive therapy with ganciclovir or foscarnet. The initiation of pre-emptive treatment is based on follow-up of CMV-pp65-antigen or CMV-DNA-PCR.
- CMV infection can be treated with ganciclovir, foscarnet or cidofovir.
- The mortality rate of CMV pneumonia is especially high. It is treated with antiviral drugs combined with intravenous immunoglobulin.

**Tuberculosis**

- Remember the possibility of reactivation of tuberculosis in immunosuppressed patients.
- Prophylactic treatment is considered if
  - earlier tuberculosis has not been treated by chemotherapy
  - tuberculosis was treated before the year 1970 (before the time of effective combination chemotherapy)
  - the patient was exposed to a case of pulmonary tuberculosis in the family as a child.

**Pneumocystis carinii**

- Secondary or primary prevention is indicated according to the aetiology of immunosuppression. Prophylactic medication is given to all patients who have received allogeneic stem cell transplantation and patients with HIV whose CD4 level is below $0.2 \times 10^9/l$.
- Prophylactic therapy consists of either sulphatherapimethoprim, given three times a week, or inhaled pentamidine, given once a month. The prophylactic therapy is continued for 6 months after allogeneic stem cell transplantation, even longer if the patient receives other potently immunosuppressant drugs e.g. corticosteroids or ciclosporin. In patients with HIV the prophylaxis is continued until the CD4 level has permanently risen to $0.2 \times 10^9/l$. 

**Herpes zoster**

- Acyclovir treatment (1.41) is indicated in patients with cancer with the exception of cases where more than 3 days has elapsed since the emergence of the first vesicles and several days since the emergence of new skin lesions.
- Herpes zoster may be more violent and widespread in severely immunodeficient patients (especially during severe neutropenia) than normal, so it is important to begin antiviral therapy (acyclovir or valaciclovir) immediately after emergence of the first vesicles.

**Cytomegalovirus (CMV)**

- CMV is a significant cause of infection in patients who have received stem cell or organ transplantation. The virus may reactivate during longlasting immunosuppressive therapy in patients who are themselves positive for CMV antibodies and those who are negative for CMV antibodies, but who have received a transplant from a CMV antibody positive person. These patients are given either prophylactic or preemptive therapy with ganciclovir or foscarnet. The initiation of pre-emptive treatment is based on follow-up of CMV-pp65-antigen or CMV-DNA-PCR.
- CMV infection can be treated with ganciclovir, foscarnet or cidofovir.
- The mortality rate of CMV pneumonia is especially high. It is treated with antiviral drugs combined with intravenous immunoglobulin.
The drug of choice for treatment of Pneumocystis carinii infection is intravenous sulphamethoxazole in large doses. For allergic patients the alternative drug is intravenous pentamidine. In severe infections corticosteroids are added to the regimen.

**Fungal infections**

During prolonged and severe neutropenia patients are usually given empiric antifungal medication, if they still have fever after 3–5 days of broad-spectrum antibacterial medication. The drug of first choice is amphotericin B. There are also newer and better tolerated drugs, e.g. liposomal amphotericin B, caspofungin and voriconazole. These new drugs have been shown to be at least as effective as traditional amphotericin B in empiric antifungal treatment, but their high treatment costs limit their extensive use. Fluconazole may in some cases be appropriate for empiric antifungal therapy, but its problems include poor effect in mould fungal infections and the increasing resistance of yeast fungi.

Antifungal prophylaxis has been shown to reduce superficial oropharyngeal yeast infections. The prevention of deep fungal infections is most effective in patients who have received allogenic stem cell transplantation. According to current opinion, routine antifungal prophylaxis is therefore indicated only for these patients. The dose of fluconazole is 400 mg/day. Extensive prophylaxis with fluconazole in other immunodeficient patients may lead to increase of resistant yeast species.

**Chickenpox and measles**

Chickenpox can be prevented by administering varicella-zoster hyperimmunoglobulin within 3 days from exposure. Measles can be prevented by administering ordinary immunoglobulin intramuscularly soon after exposure.

**Vaccinations**

Absence of the spleen is not a contraindication for vaccinations.

**Pneumococcal vaccine**

- Recommended for all splenectomized patients.
- The vaccination should be performed 2 weeks before elective splenectomy.
- A booster is indicated every 5 years.

**Vaccine against Haemophilus influenzae B**

- Recommended for patients who have not been vaccinated when they were children.
- The vaccine is given only once.

**Meningococcal vaccine**

- The vaccine does not protect from infections caused by type B meningococci. The protective effect against meningococci types A and C is rather short-lived. According to British guidelines meningococcal vaccination should be given to all patients after splenectomy, and before travelling to epidemic areas.

**Influenza vaccine**

- Vaccination against influenza should be performed annually because the vaccination decreases the risk of secondary bacterial infections.

**Guidelines in suspected infections**

- The patients should carry a note about their splenectomy to inform health care personnel in emergencies.
- In case of fever and chills or nausea the patient should contact a doctor immediately.
- A 5-day course of amoxicillin is indicated after animal bites.
- If a serious infection is suspected in a splenectomized patient a parenteral dose of penicillin can be administered before transportation to a hospital. A blood sample for culture should be taken before giving penicillin if this can be carried out without delay.
- People travelling to areas where malaria is endemic should be informed about the increased risk of severe malaria, and they should be provided with proper prophylaxis.
1.80 Ecology of the use of antimicrobial drugs

Pentti Huovinen

Introduction

- The first true antimicrobial drugs were introduced in 1935 (sulphonamides) and 1942 (penicillin). Since then, hundreds of new antimicrobials have been launched into the market.
- Most antibiotics are prescribed in outpatient care. Some 80% of the antimicrobials used in outpatient care are prescribed for the treatment of respiratory tract infections, e.g. otitis media and sinusitis. The next most common indications for antimicrobial drug therapy are infections of the urinary tract and skin. In hospitals, the most frequent indication is surgical prophylaxis.

Development of resistance

- Bacteria have been present on the earth for 3.8 billion years. Depending on the manner of calculation, the human species is a few million years old. Bacteria are able to multiply every 20 minutes in optimal circumstances, and they have an excellent capacity of adaptation to changes in their environment. Some bacteria are known to withstand temperatures of several hundred degrees or survive the hydrostatic pressure at thousands of meters below the sea surface. Thanks to their DNA repair mechanism, some bacteria are even resistant to radioactive radiation.
- During the past 60 years, man’s own bacteria and those in his immediate surroundings have been subjected to an unparalleled selection pressure. The use of antimicrobial drugs favours bacteria with a natural resistance to drugs. Susceptible bacteria die and the most resistant ones survive, whereby man may already have altered the species composition or relative frequencies of species in his bacterial flora. As the composition of man’s normal microbial flora has so far been beyond study, it is impossible to estimate the changes that may have taken place, let alone appraise their consequences for human health.
- Hundreds of different resistance genes have been discovered in bacteria. They have been surmised to originate from within or without the normal bacterial flora, but bacteria are also able to compile new resistance genes. The pneumococcal penicillin resistance genes, for instance, are a compilation from other bacteria of the oral flora.
- The most worrying feature of bacteria is multiple resistance, i.e. the ability to withstand several antimicrobial drugs at the same time. Many resistant bacteria of clinical relevance possess multiple resistance. Bacteria are able to collect resistance-coding genes into gene cassettes that are transferred from one bacterium to another. On the other hand, resistance may also be encoded by mutations in chromosomal genes.

Control of resistance

- Resistance poses problems for everyday clinical work within primary care and especially in hospitals. As the use of antimicrobial drugs is a necessity, bacterial resistance will remain a permanent problem. Although there is a constant effort to reduce the use of antimicrobial drugs, it appears instead that their use is increasing all the time, resulting in further aggravation of the resistance problem.
- New antimicrobial drugs do not present a solution to the problem. Although there is continual drug development, new drugs are likely to offer only short-term remediation. The development of a new drug takes at least 5–12 years.
- Bacterial resistance can be controlled by reducing the use of antimicrobials and by preventing bacteria from spreading.
  - Always try to reach a precise diagnosis. Use laboratory tests and radiography according to recommendations.
  - Use antimicrobial drugs only when needed. Do not deviate from the therapeutic recommendations for the various indications, unless you have a valid reason for doing so.
  - If you decide not to start antimicrobial drug therapy, ensure careful follow-up of the patient.
  - Adhere to stringent hand hygiene. Alcohol-based hand rubs are clearly better than regular soap in reducing hand contamination.
- It is probable that the level of hygiene influences the spread of resistant bacteria. In hospitals the hands of staff and patients are the most important factor in spreading microbes. In many countries, an optimal climate maintains an abundant flora, which in turn contributes to the problem of resistance.
- In the future, in all countries and especially in ambulatory care there is a need to improve hygiene. For example, day care centres are important in spreading infections among children.

The importance of normal flora increases

- It is in the patient’s interest that antimicrobial drugs be used only when clearly necessary. Several studies have found that antimicrobial treatment increases the patient’s risk of being colonised by new resistant bacteria. Animal experiments have shown that 1000 to 100 000 times less bacteria are needed for colonisation during antimicrobial treatment than without such treatment.
- Antimicrobial drugs destroy bacteria of the normal flora, and the resultant vacuum is easily occupied by foreign resistant bacteria that now have room to proliferate. The patient then starts shedding these resistant bacteria, thereby facilitating their spreading.
- In young women, antimicrobial treatment of any infection involves a two- to fivefold risk of urinary infection. This is probably due to the suppression of normal bacterial flora, which favours colonisation by pathogenic bacteria two to four weeks after the treatment.
- Preliminary studies suggest that correction of the disturbance in bacterial flora by means of oral and oropharyngeal alpha-haemolytic streptococci after antimicrobial treatment affords...
Diarrhoea caused by antibiotics

- Suppression of the normal intestinal flora allows Clostridium difficile to grow in the intestine. C. difficile produces diarrhoeagenic toxins. Its significance has increased, especially with the increased use of cephalosporins. Wide-spectrum antibiotics together with repeated treatments are important risk factors for antibiotic-associated diarrhoea.
- Prevention of antibiotic-associated diarrhoea: Avoid unnecessary use of antimicrobial drugs. Isolate patients with antibiotic-associated diarrhoea in hospitals. Adhere to good hand hygiene. In children, the administration of Lactobacillus GG capsules brings about a statistically significant prevention of antibiotic-associated diarrhoea. In addition, Saccharomyces boulardii yeast product can help to reduce recurrent episodes of antibiotic-associated diarrhoea.

Successful and safe treatment

- Preserving the efficacy in the future requires the avoidance of unnecessary use of antimicrobial drugs and the correction of biased treatment practices.
- Efficacy and safety are not independent of each other. The use of new broad-spectrum antimicrobial drugs in outpatient care is very rarely justified in the changed resistance situation. On the contrary, over-enthusiastic use of wide-spectrum drugs causes unnecessary suppression of normal flora and promotes development of resistance to these drugs that are not intended for first-line therapy.
- By following up the development of bacterial resistance situation and the consumption of antimicrobial drugs, guidelines promoting efficient and safe antimicrobial treatment can be drafted and issued.

Table 1.81

<table>
<thead>
<tr>
<th>Indication</th>
<th>Drug</th>
<th>Dosage</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tonsillitis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Penicillin V</td>
<td>adults: 1–1.5 million IU × 2 × 10</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>children: 50 000–100 000 IU/kg/day/2 × 10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Cephalexin/Cefadroxil</td>
<td>adults: 750/500 mg × 2–3 × 10</td>
<td>children: 50 mg/kg/day/2 × 10</td>
<td>In penicillin allergy without anaphylaxis</td>
</tr>
<tr>
<td>3. Clindamycin</td>
<td>adults: 150 mg × 4 or 300 mg × 2–3 × 10</td>
<td>children: 20 mg/kg/day/3 × 10</td>
<td>For patients with anaphylactic penicillin allergy</td>
</tr>
<tr>
<td><strong>Sinusitis or otitis media in the adult</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Amoxicillin</td>
<td>500–750 mg × 2 × 5–7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Doxycycline</td>
<td>150 mg × 1 × 5–7 or 100 mg × 2 one day, then 100 mg × 1 × 5–7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Amoxicillin clavulanate</td>
<td>750 mg × 2 × 5–7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Cefaclor</td>
<td>500 mg × 2 × 7</td>
<td></td>
<td>Only if allergic to other drugs</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>500 mg, 250 mg × 1 × 4</td>
<td></td>
<td>Only if allergic to other drugs</td>
</tr>
<tr>
<td>Roxithromycin</td>
<td>150 mg × 2 × 7</td>
<td></td>
<td>Only if allergic to other drugs</td>
</tr>
<tr>
<td><strong>Otitis media or sinusitis in the child</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Amoxicillin</td>
<td>40 mg/kg/day/2 × 5–7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penicillin V</td>
<td>100 000 IU/kg/day/2 × 5–7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Amoxicillin clavulanate</td>
<td>40–45 mg/kg/day/2 × 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Cefaclor</td>
<td>40 mg/kg/day/2 × 7</td>
<td></td>
<td>Only if allergic to other drugs</td>
</tr>
<tr>
<td>Cefuroxime axetil</td>
<td>40 mg/kg/day/2 × 7</td>
<td></td>
<td>Only if allergic to other drugs</td>
</tr>
</tbody>
</table>

Reference


1.81 Guidelines for antimicrobial therapy

Editors

- These guidelines (Table 1.81) have been collected from other guidelines in the EBMG. The numbers indicate priority of the drugs. Careful clinical and laboratory investigations are essential to proper diagnosis. Local resistance patterns should always be considered before making decisions on individual patients.
Table 1.81  (continued)

<table>
<thead>
<tr>
<th>Indication, drug</th>
<th>Dosage</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pneumonia in ambulatory care</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Penicillin V</td>
<td>1 mill. IU × 4 × 10</td>
<td>Suspected pneumococcal pneumonia: rapid onset, chills, increased blood leucocyte count and serum CRP, consider hospital care</td>
</tr>
<tr>
<td>Roxithromycin</td>
<td>150 mg × 2 × 10</td>
<td>Or some other macrolide</td>
</tr>
<tr>
<td>2. Doxycycline</td>
<td>100 mg × 2 × 10</td>
<td></td>
</tr>
<tr>
<td><strong>Community-acquired pneumonia in the hospital</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Penicillin G</td>
<td>1–2 mill. IU × 4 i.v.</td>
<td>Strong suspicion of pneumococcal pneumonia</td>
</tr>
<tr>
<td>2. Cefuroxime</td>
<td>1.5 g × 3 i.v.</td>
<td>Severe pneumonia (respirations &gt; 30/min, hypoxia), unknown aetiology. Consider also in combination with macrolide drugs.</td>
</tr>
<tr>
<td><strong>Pneumonia in children</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Amoxicillin</td>
<td>40 mg/kg/day × 7–10</td>
<td>Children under 4 years of age</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>40 mg/kg/day × 3 × 10</td>
<td>Children above 4 years of age, and in penicillin allergy</td>
</tr>
<tr>
<td><strong>Urinary tract infection in the adult in ambulatory care</strong> (the local resistance pattern should guide the choice of drug)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Trimethoprim</td>
<td>160 mg × 2 × 5 or 300 mg × 1 × 5</td>
<td>Varying resistance especially in aged patients</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>75 mg × 2 × 5</td>
<td>Not in renal insufficiency</td>
</tr>
<tr>
<td>Pivmecillinam</td>
<td>200 mg × 3 × 5</td>
<td>Not effective against Staphylococcus saprophyticus</td>
</tr>
<tr>
<td>2. Norfloxacin</td>
<td>400 mg × 2 × 3–7</td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>100–250 mg × 2 × 3</td>
<td>Complicated infections and pyelonephritis: 250–500 mg × 2 × 7–14</td>
</tr>
<tr>
<td>Levofoxacin</td>
<td>250 mg × 1 × 3–7</td>
<td></td>
</tr>
<tr>
<td>Cephalexin</td>
<td>500 mg × 2 × 5–7</td>
<td></td>
</tr>
<tr>
<td>Cefadroxil</td>
<td>500 mg × 1 × 5–7</td>
<td></td>
</tr>
<tr>
<td>Fosfomycin</td>
<td>3 g × 1 × 1</td>
<td></td>
</tr>
<tr>
<td><strong>Renal insufficiency:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Cephalexin, cefadroxil, amoxicillin, pivmecillinam</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pregnancy:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pivmecillinam, nitrofurantoin, cephalexin, cefadroxil, amoxicillin according to the antibiogram</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Urinary tract infection with fever in the hospital</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Cefuroxime</td>
<td>1.5 g × 3 i.v.</td>
<td></td>
</tr>
<tr>
<td><strong>Urinary tract infection in a child</strong> (treat infants for 10 days, cystitis in older children for 5 days)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Nitrofurantoin</td>
<td>5 mg/kg/day × 2</td>
<td></td>
</tr>
<tr>
<td>2. Cephalexin</td>
<td>40 mg/kg/day × 2</td>
<td></td>
</tr>
<tr>
<td>3. Trimethoprim</td>
<td>8 mg/kg/day × 2</td>
<td></td>
</tr>
<tr>
<td>4. Pivmecillinam</td>
<td>20–40 mg/kg/day × 3</td>
<td></td>
</tr>
<tr>
<td><strong>Mastitis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Cephalexin</td>
<td>500 mg × 3 × 7</td>
<td></td>
</tr>
<tr>
<td>Cefadroxil</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Roxithromycin</td>
<td>150 mg × 2 × 7</td>
<td>Or some other macrolide</td>
</tr>
<tr>
<td><strong>Erysipelas</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Penicillin G</td>
<td>1–3 mill. IU × 4 i.v.</td>
<td>Followed by penicillin V orally for at least three weeks</td>
</tr>
<tr>
<td>Procaine penicillin</td>
<td>1.2–1.5 (–2.4) mill. IU × 1</td>
<td>Followed by penicillin V orally for at least three weeks</td>
</tr>
</tbody>
</table>

(continued overleaf)
Table 1.81 (continued)

<table>
<thead>
<tr>
<th>Indication, drug</th>
<th>Dosage</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Cefuroxime</td>
<td>750–1 500 mg × 3 i.v.</td>
<td>For patients with allergy for penicillin</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>300–600 mg × 4 i.v.</td>
<td></td>
</tr>
<tr>
<td>Further treatment: Penicillin V 1.5 mill. IU × 2 or cephalexin 750 mg × 2 or cefadroxil 1 g × 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prophylactic medication: Penicillin V 1.2–1.4 mill. IU i.m. every 3rd-4th week</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Impetigo in children</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cephalexin</td>
<td>50 mg/kg/day/3 × 7</td>
<td></td>
</tr>
<tr>
<td>Cefadroxil</td>
<td>50 mg/kg/day/3 × 7</td>
<td></td>
</tr>
<tr>
<td><strong>Purulent skin infection caused by staphylococci in adults</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cephalexin</td>
<td>500 mg × 3 × 7</td>
<td></td>
</tr>
<tr>
<td>Cefadroxil</td>
<td>500 mg × 2 × 7</td>
<td></td>
</tr>
<tr>
<td><strong>Eradication of Helicobacter pylori</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amoxicillin and</td>
<td>1000 mg × 2 × 7</td>
<td>Recurrent infection, see 8.32.</td>
</tr>
<tr>
<td>Clarithromycin and</td>
<td>500 mg × 2 × 7</td>
<td></td>
</tr>
<tr>
<td>Proton pump inhibitor</td>
<td>Normal doses</td>
<td></td>
</tr>
<tr>
<td><strong>Campylobacter</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roxithromycin</td>
<td>150 mg × 2 × 10 (or some other macrolide)</td>
<td></td>
</tr>
<tr>
<td><strong>Salmonella gastroenteritis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin (or some other fluoroquinolone)</td>
<td>500–750 mg × 2 × 14</td>
<td>Always assess the need for antimicrobial treatment individually</td>
</tr>
<tr>
<td><strong>Gonorrhoea</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Ciprofloxacin</td>
<td>500 mg as a single dose</td>
<td></td>
</tr>
<tr>
<td>2. Ceftriaxone</td>
<td>250 mg i.m. single dose</td>
<td></td>
</tr>
<tr>
<td><strong>Chlamydial urethritis or cervicitis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Azithromycin</td>
<td>1000 mg as a single dose</td>
<td>Complicated or recurrent disease</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>100 mg × 2 × 7–10, 100–150 mg × 2 × 21</td>
<td>During pregnancy</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>500 mg × 3 × 10</td>
<td></td>
</tr>
</tbody>
</table>

### 1.93 Streptococcal epidemics

*Marjukka Mäkelä*

#### Basic rule

- Identify and control epidemics quickly.

#### Aetiology

- Group A streptococci are the most common cause of epidemics, but group C and G may also cause them.
- The epidemics can be food-borne (particularly if the epidemic is severe).

#### Diagnosis

- Epidemics commonly occur in day-care institutions, schools and military units.

- Suspect an epidemic if
  - several patients come from one family or other unit in a short time, or
  - the same patient has recurrent streptococcal disease.

#### Treatment

- A nurse should visit the site of the epidemic and take streptococcal culture both from symptomatic and asymptomatic people.
- All persons with positive cultures are treated simultaneously, and kept away from day care, school or work for one day after starting treatment whether they have symptoms or not. Symptomatic patients may need a longer sick leave. Control samples need not be taken after treatment.
- Consider also taking cultures from and treating family members of symptomatic patients.
- Food-borne epidemics
  - The disease usually manifests as tonsillitis.
  - All kitchen personnel should be cultured and treated as usual.
- Treat with penicillin V or a first generation cephalosporin for ten days (38.20).