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Various infections with fever including those of tropical origin

Differential diagnostics and management of fever of unknown, but possibly infectious origin, in patients coming from non-European countries and so possibly having an infection that is imported

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1. Fever with suspicion for infection – global survey

Fever with or without other symptoms is a common symptom of many diseases, both infectious and non-infectious. The aim of this material is not to cover all of them, but just to indicate some possible differential diagnostic procedures and management of such diseases.

When a patient of non-European origin, or a traveller that visited non-European countries, comes with fever (and usually also headache, fatigue, maybe muscle pain, maybe short breathing and other symptoms) comes, we have to think about:

- An infection that is not common in Europe
- An infection that is common worldwide, or even in Europe only (as the person might get infected *after* coming to Europe)
- A non-infectious reason for the fever (e. g. a tumour)

When a foreigner, especially a non-European one, comes to a doctor, we have to take into account:

- Possible communication problems (language, non-verbal language, cultural differences).
- Administrative problems, especially health insurance. In the Czech Republic, a person that is not an EU citizen and has no special conditions (e. g. working in Czechia, being a family member of somebody working in Czechia or being from a country that has a special bilateral agreement with Czechia) should have commercial health insurance, otherwise, the person is not insured. Even the insurance does not necessarily cover all types of care, especially if the care is not urgent. Exceptions exist, e. g. for asylum seekers.
- The possibility that the patient might refuse the treatment because of cultural or religious reasons.

When a foreigner, but also a traveller coming back from non-European, especially tropical or subtropical countries, comes to a doctor, a typical set of actions should be taken:

(a) Personal history

We should never forget to ask the questions given to any patient (subdued diseases, surgeries, allergies, used drugs, abuses, family history), as in practice we can never be sure if the patient has an infection or not, and if yes, where the infection has been acquired.

We have to put special attention to the momentary disease (when it developed, it had been suddenly or step by step, what are the problems of the patient).

The special topic is the **traveller's anamnesis**. It is not sufficient to know what country the patient comes from or where the traveller did travel, but also more facts: did the person stay in a big city? In a village? In the wild nature? Which part of the country? (It is important – for example, in Zimbabwe, you may catch malaria in the lowlands around the rivers, but hardly in the highlands.) For foreigners: did the patient work in her/his country? What was her/his occupation? For travellers: what was the reason for the visit? (Tourism, business, work with local people – e. g. missionaries, work in nature – e. g. scientists).

(b) Examination

The examination should be performed as usual, which means, a complete routine examination of the patient. Apart from that, the examination should concentrate on organs or parts of the body where the patient refers for pain or any other problems.

(c) Imaging tests

Imaging tests are often important, as they can show a focus of infection. X-rays of the chest can show existing pneumonia or an active TB, but we should never forget, that some forms of TB may be hidden. Other imaging tests (abdominal X-rays, ultrasound examination, CT, MR) are usually indicated just if we already have a specific suspicion.

(d) Endoscopy, biopsy

Endoscopy is quite invasive and complicated procedure, so it is usually indicated only if there is a reason for it coming for it, either because we expect to see some changes in the mucosa of a given organ, or we wish to take a biopsy from that organ. A biopsy can be also performed through the skin, especially for lymph nodes, if they are enlarged. Thin needle aspiration might be required for such a case. It is less invasive than the excision of a lymph node, which is only recommended if it has also a supposed therapeutical effect.

(e) Biochemical, haematological and immunological markers

Basic biochemical markers (in English-speaking countries often "urea and electrolytes" or just U&E) are a good tool for the first moment when we do not know anything about the origin of the infection. The combination with **liver function tests** can inform us about a risk of viral hepatitis, but also some other diseases concerning the liver (malaria, some flukes, cysticercosis localised in the liver etc.). **Inflammation markers** (C-reactive protein, procalcitonin, presepsin) can inform us about infection and its severity at the moment.

A full blood count (including the differential count) is a very important marker. Bacterial diseases are mostly characterised by neutrophilia, while viral diseases are characterised by elevated levels of lymphocytes. Some other abnormalities can be also typical for haemoblastoses (in differential diagnostics) or some other diseases (anaemia).

Immunological markers can inform us about changed rations between lymphocyte subpopulations, that are typical for HIV infections. Some more immunological markers might be also followed.

(f) Microbiology tests

In case of fever and suspicion of infection, the most important test is the **blood culture**. Nevertheless, we should know, that the examination takes 5–7 days, although first results are usually available already after 24–48 hours. Even if the infection does not have characteristics of sepsis, we can still find signs of bacteriaemia connected with organ diseases like pyelonephritis or bacterial pneumonia. We should understand that blood culture can be only positive for bacterial and fungal pathogens. In viral or parasitic fevers, it would be negative. It can be also negative if the causative agent is a bacterium or fungus that cannot be cultivated (spirochetes, fungus *Pneumocystis jirovecii*).

Apart from blood cultures, we can also **take a specimen** for bacteriology and yeast examination from any site depending on the patient's problems: sputum, if respiratory problems are reported, urine if painful urination or blood in urine is found, stool (rectal swab) in case of diarrhoea.

For viral pathogens, the typical specimen is **clotted blood** as a primary specimen**/blood serum** as a secondary one. We search for antibodies, only sometimes also for antigens (hepatitis B). We should understand that in very fresh infections the tests for antibodies would be negative. On the other hand, the presence of antibodies (especially IgG antibodies) does not always mean active infection, it can be an infection in past.

For parasites, we take different tests according to the expected origin. The most typical parasites are intestinal parasites; typical detection of these contains finding their eggs in the stool. It is very important to understand that a piece of stool must be delivered to the laboratory, not just a rectal swab. The piece must be at least hazelnut-sized. For bloodstream parasites, especially malaria, we have to take a **thin smear and a thick drop**. This requires two slides and fresh capillary blood from the patient.

(g) Complications

All infections may be complicated by both infections and non-infectious problems. Either a patient may have a co-infection caused by two or more different pathogens, or one disease may be complicated by other diseases because of the character of the disease. A special position in this has HIV infection, that influences lymphocytes and so it is complicated by some typical diseases, like TB, atypical mycobacteriosis, pneumocystosis, intestinal coccidia, some fungi (e. g. *Penicillium marneffei* infection) and many others. The diagnostics of these diseases might be complicated as the markers are already altered by the HIV infection itself.

(h) Treatment

At treatment, we should follow the existing guidelines. The guidelines should respect the local situation, as some bacteria, fungi or parasites might be susceptible to given antiinfectives in some parts of the world, but resistant in other parts. A very specific situation exists for malaria; treatment recommendations are completely different for Africa, South-East Asia or other regions.

2. Some typical diseases

AIDS

Symptoms of HIV infection can include rapid weight loss, recurring fever or profuse night sweats, extreme and unexplained tiredness, headache, and aching muscles. The fever in HIV infection may be caused both directly by the virus and by the diseases and infections that are connected with the disease. Other symptoms are prolonged swelling of the lymph glands in the armpits, groin, or neck, sometimes diarrhoea that lasts for more than a week, sores of the mouth, anus, or genitals, and also pneumonia. Most people don't know right away when they've been infected with HIV. But the first symptoms (acute retroviral syndrome or primary HIV infection) usually start to develop within 2 to 6 weeks after they've gotten the virus. Later a rash can develop. AIDS Symptoms (third stage of infection) usually come in patients that did not know about the infection sooner. In such cases usually, the CD4 T-cell number drops below 200 and the patient's immune system is badly damaged. Some typical diseases, such as Kaposi's sarcoma (a form of skin cancer) and pneumocystis pneumonia (a lung disease), are also considered **"AIDS-defining illnesses."**

Diagnostics contains the detection of **antibodies**, detection of **antigens** and detection of **viral RNA**. After the start of the treatment, the viral load is an important sign of the effectiveness of retroviral therapy. In some countries, also tests for resistance (based on genes) may be available. Apart from these virology tests, there exist also other important markers. It is recommended to perform CD4 count, HLA B*5701, complete blood count, lipid profile, other biochemical tests and many others.

A combination of **medications** (called HIV drugs, antiretroviral therapy, or ART, sometimes also highly-active antiretroviral therapy, **HAART**) can help fight HIV, keep a patient's immune system healthy, and keep you from spreading the virus. If the patients take these medications and have healthy habits, his/her HIV infection probably won't get worse.

As infectious **complications** are common, tests for other infections may be useful. Especially it is recommended to perform a test for latent tuberculosis (usually those for cell-mediated immunity as interferon-gamma release assay – **IGRA**, see more in the part concerning tuberculosis). Other tests may include STD screening, hepatitis A, B, and C screening and many other tests depending on the symptoms. Enlarged skin lymph nodes might show the risk of atypical (non-TB) mycobacterioses.

Malaria

Symptoms of malaria are generally non-specific and most commonly consist of fever, malaise, weakness, gastrointestinal complaints (nausea, vomiting, diarrhoea), neurologic complaints (dizziness, confusion, disorientation, coma), headache, back pain, myalgia, chills, and/or cough. The diagnosis of malaria should also be considered in any person with a fever of unknown origin regardless of travel history. Patients suspected of having malaria infection should be urgently evaluated. Treatment for malaria **should not** be initiated until the diagnosis has been confirmed by laboratory investigations. "Presumptive treatment" without the benefit of laboratory confirmation should be reserved for extreme circumstances (strong clinical suspicion, severe disease, impossibility of obtaining prompt laboratory confirmation, usually by microscopy).

Laboratory diagnosis of malaria can be made through **microscopic examination of thick and thin blood smears**. Thick blood smears are more sensitive in detecting malaria parasites because the blood is more concentrated allowing for a greater volume of blood to be examined; however, thick smears are more difficult to read. Thin smears aid in parasite species identification and quantification. Blood films need to be read immediately; off-hours, qualified personnel who can perform this function should be on-call. A negative blood smear makes the diagnosis of malaria unlikely. However, because non-immune individuals may be symptomatic at very low parasite densities that initially may be undetectable by blood smear, blood smears should be repeated every 12–24 hours for a total of 3 sets. If all 3 are negative, the diagnosis of malaria has been essentially ruled out. After malaria parasites are detected on a blood smear, the parasite density should then be estimated. The parasite density can be estimated by looking at a monolayer of red blood cells. Several antigen detection tests (rapid diagnostic tests or RDTs) using a "dipstick" or cassette format exist, but they cannot confirm the species or the parasitaemia. Parasite nucleic acid detection using polymerase chain reaction (PCR) is more sensitive and specific than microscopy but can be performed only in reference laboratories and so results are not often available quickly enough for routine diagnosis.

Treatment: Treatment for malaria should not be initiated until the diagnosis has been established by laboratory investigations. "Presumptive treatment" without the benefit of laboratory confirmation should

be reserved for extreme circumstances (strong clinical suspicion, severe disease, impossibility of obtaining prompt laboratory diagnosis). Once the diagnosis of malaria has been made, appropriate antimalarial treatment must be initiated immediately. Treatment should be guided by three main factors:

• The infecting *Plasmodium* species

• The clinical status of the patient

• The drug susceptibility of the infecting parasites as determined by the geographic area, where the infection was acquired and the previous use of antimalarial medicines

P. falciparum and *P. knowlesi* infections can cause rapidly progressive severe illness or death while the other species, *P. vivax, P. ovale*, or *P. malariae,* are less likely to cause severe manifestations. On the other hand, *P. vivax* and *P. ovale* infections also require treatment for the hypnozoite forms that remain dormant in the liver and can cause a relapsing infection. Finally, *P. falciparum* and *P. vivax* species have different drug resistance patterns in differing geographic regions.

For *P. falciparum* infections acquired in areas without chloroquine-resistant strains, which include Central America west of the Panama Canal, Haïti, the Dominican Republic, and most of the Middle East, patients can be treated with oral **chloroquine**. Alternatively, hydroxychloroquine may be used. In addition, any of the regimens listed below for the treatment of chloroquine-resistant malaria may be used for the treatment of chloroquine-sensitive malaria. Prompt initiation of an effective regimen is vitally important and so using any one of the effective regimens that are readily at hand would be the preferred strategy. For *P. falciparum* infections acquired in areas with chloroquine resistance, four treatment options are available. The first two treatment options are **atovaquone-proguanil** (Malarone) or **artemether-lumefantrine** (Coartem). These are fixed-dose combination medicines that can be used for non-pregnant adult and paediatric patients. Both of these options are very efficacious. Quinine sulphate plus doxycycline, tetracycline, or clindamycin is the next treatment option. The problems with sensitivity also lead to the search for new drugs, but also the comeback of some "old fashioned" ones, including **quinine.** The use of particular drugs always depends on the particular plasmodium species and its resistance.

Complications. The significant complications of malaria are cerebral malaria, severe malarial anaemia, and nephrotic syndrome. Treatment includes specific therapy for the particular symptoms and treatment of the basic disease.

Tuberculosis and mycobacterioses

Symptoms. A productive cough, often accompanied by systemic symptoms such as fever, night sweats or loss of weight, is the commonest presentation of pulmonary tuberculosis. Every patient with a **positive symptom screen** must be investigated appropriately. Not all those with TB will have a cough; therefore, a high index of suspicion is required, particularly in people who are HIV-positive and may only have one of the above symptoms. A history of contact with a person with pulmonary TB increases the

likelihood of a TB diagnosis and symptoms such as weight loss need to be investigated. Some patients may present with chest pain (due to pleurisy, muscle strain), breathlessness (due to extensive lung disease or concomitant pleural effusion), localised wheeze (due to local tuberculous bronchitis), or because of external pressure on the bronchus by an enlarged lymph node.

TB **diagnosis** depends on symptom screening of all patients (including HIV-positive patients) presenting to the health facility and contacts of people with laboratory-confirmed pulmonary TB disease. All those who have symptoms of TB disease must be investigated for TB. The main symptoms of pulmonary tuberculosis are persistent cough of 2 weeks or more or any duration if HIV positive; fever for more than 2 weeks; drenching night sweats and unexplained weight loss (more than 1.5 kg in a month).

Physical signs may not help confirm the diagnosis, but it is important to examine the patient carefully. Some of the common signs are fever – the body temperature may be high or irregular (greater than 38.5 °C); pulse rate – it may be raised because of fever; chest – there may be no abnormal signs, crackles in the lung apices more pronounced on deep; breathing; localised wheeze in local obstruction or pressure; dullness where there is effusion and in chronic disease there may be extensive fibrosis with the trachea pulled to one side.

All individuals suspected of having **pulmonary tuberculosis** (PTB) should have at least one sputum specimen examined for bacteriological confirmation of TB disease using rapid diagnostic tests.

Extra-pulmonary TB (EPTB) can present with non-specific symptoms such as unintentional weight loss (more than 1.5 kg in a month), night sweats and fever for more than 2 weeks. Other symptoms depend on the site or organ affected. The most common types of extra-pulmonary tuberculosis are TB lymphadenitis, tuberculous pleural effusion (usually single-sided), TB of the bones and joints, tuberculous pericardial effusion, TB meningitis (should be differentiated from other types of meningitis, e. g. cryptococcal meningitis), disseminated / miliary tuberculosis. tuberculous empyema and TB peritoneal effusion. HIV-positive patients particularly those with low CD4 counts may present with extrapulmonary disease. The presentation of extrapulmonary TB is generally no different between HIV-positive and HIV-negative patients, however, differences do occur.

Mycobacterioses (diseases caused by non-TB mycobacteria) might be **pulmonary** or **non-pulmonary** and also these are common in HIV-positive patients. *Mycobacterium avium* complex (MAC) refers to infections caused by one of two nontuberculous mycobacterial species, either *M. avium* or *M. intracellulare*. Infection with these organisms can occur in patients with or without HIV infection. The two principal forms of MAC infection in patients with HIV are disseminated disease and focal lymphadenitis. By contrast, isolated pulmonary infection is typically seen in immunocompetent patients, often in those with structural lung disease. Among persons with HIV, MAC infection is most commonly seen among those with a CD4 count <50 cells/microlitre. Dramatic declines in the rate of new MAC cases accompanied the use of prophylaxis against MAC infection early in the epidemic, and more recently, the widespread use of effective antiretroviral therapy.

Appropriate **investigations** for extra-pulmonary TB and extra-pulmonary mycobacterioses mostly include: ultrasound examination may be suggestive of abdominal TB (lymphadenopathy, ascites and/or splenic hypodensities) or pericardial TB (pericardial effusion especially if there is stranding); TB blood culture (that means, not just common blood culture performed for other bacteria); culture of tissue or fluid from fine needle aspirate or biopsy; histological examination of tissue; cytological examination. TB lymphadenopathy needs to be differentiated from **persistent generalized lymphadenopathy** (PGL). PGL develops in up to 80% of HIV-infected individuals during the early stages of infection. These lymph nodes are typically non-tender, <2 cm in size and symmetrical. PGL requires no treatment.

Diagnostic tests for TB and mycobacterioses require a suitable **specimen**. We have to collect one spot specimen (sputum, gastric washing/ lavage, lymph node fine needle aspirate, pleural biopsy, cerebrospinal fluid). Sputum collection must be under supervision.

The **direct laboratory examination** includes microscopy (Ziehl-Neelsen of fluorescent stain), culture on special media, automated culture in liquid (MGITT) and PCR. For latent forms of TB there exist special tests that are **indirect** in principle (they check the immunity response and not the microbe itself), but they do not measure antibodies, but rather cell-mediated immunity, which is leading in TB. These tests are known as **IGRA (Interferon Gamma Release Assay)**, but there exist many synonyms, often derived from particular commercial products (ELISPOT, Quantiferon etc.). Antibody tests also exist, but they leave many cases of TB undetected, which is why they are not routinely used. The reason, why IGRA tests function better, is the intracellular existence of the TB bacilli – for intracellular pathogens cell-mediated immunity is usually more important than the antibodies.

Treatment. The key to stopping the spread of TB in a community is to start treating patients who are coughing up live TB bacilli as soon as possible. Apart from the public health imperative, effective treatment reduces individual morbidity and mortality. For treatment to be effective, the correct drugs must be given for the correct period. PTB and EPTB are both treated in the same way. The aims of TB treatment are to:

1) cure the patient of TB

2) decrease transmission of TB to others

3) prevent the development of acquired drug resistance

4) prevent relapse

5) prevent death from TB or its complications

TB drugs have varying properties: they may be bactericidal, bacteriostatic (sterilising) or have the ability to prevent resistance; they differ in the ability to act against the various populations of bacilli found in a tuberculosis lesion (metabolically active / intermediately active / semi-dormant); they can act on intra/extracellularly located bacilli.

There exist standardised **treatment protocols** with fixed-dose combination medicines used for TB treatment. They combine the essential TB drugs: **rifampicin (R), isoniazid (H), pyrazinamide (Z), ethambutol (E) and streptomycin (S)**. In particular situations, they may also include other drugs.

Complications of TB depend on the type (PTB/EPTB). They can include the spreading of TB to other adjacent organs, superinfections (such as lung aspergilosis in PTB) and many others. Also here the treatment should include the treatment of the basic disease combined with other therapeutical approaches.

Intestinal infections

A common cause of health problems worldwide, but in tropical countries more commonly, are intestinal infections.

Symptoms. Usually, they are characterized by diarrhoea, vomiting and abdominal pain, but sometimes the patients may suffer obstipation or extraintestinal problems. The presence of helminths in the intestine is often characterized by itching due to elevated concentrations of blood histamine. Fever also might be one of the symptoms, although the main group of symptoms are connected with the gastrointestinal tract.

Some intestinal infections can be also associated with other infections, especially some parasitic intestinal infections are more common in HIV-positive persons than in other patients.

Among bacterial **causes,** there are almost various types of *Escherichia coli*, mostly enterotoxic types (enterotoxic E. coli, ETEC). Cholera may be still important in some countries, especially with collapsed infrastructure due to natural disasters, war or state collapse. Viral causative agents are worldwide common, especially noroviruses, sapoviruses, rotaviruses and many others. Parasitic diseases may be caused by *Entamoeba histolytica*, *Giardia intestinalis*, and sometimes also other unicellular parasites including *Cryptosporidium parvum*, especially in HIV-positive persons. The problems may be also caused by helminths like tapeworms, common roundworms (worldwide), threadworms/pinworms (worldwide), some flukes etc.

Diagnostics is based mostly on a combination of bacteriology and parasitology examination of stool. Viral agents are determined only rarely, usually, we consider the disease viral when other agents are excluded, or if there is an epidemiological reason (being together or eating the same food as some people already known for having such a disease).

Treatment is almost symptomatic, only in parasitic infections do we use some antiparasitic drugs and in severe bacterial infections we might use antibiotics. Very important is quick rehydration, especially in diarrhoea mediated by toxins (cholera, but also severe cases of ETEC).

Complications may include systemisation of originally intestinal infection (extraintestinal localisation of intestinal parasites, sepsis developed from bacterial enteritis, etc.). Generally, in the case of

systemisation, antimicrobial therapy is much more likely to be indicated than in the case of non-complicated enteritis.

Leishmaniosis

Leishmaniosis is a parasitic zoonotic disease caused by a protozoan of the genus *Leishmania*. It is an endemic disease in 98 countries including South America, Asia, Africa and the United States. Some species of *Leishmania* are present also in the Mediterranean area. particularly in Spain is *Leishmania infantum*. In Spain, the main reservoir is the dog, although the parasite has been detected in other animals.

Leishmaniosis is **transmitted** by the bite of an infected vector, although some cases of congenital, parenteral, sexual and interpersonal transmission have been described.

There exist three main **clinical forms** of leishmaniosis: **cutaneous, mucocutaneous** and **visceral**. Visceral leishmaniosis or kala-azar is endemic and it presents a high mortality rate when untreated. Clinical symptoms may be very rich and in visceral forms that may also include fever.

Diagnostics is partially clinical, but it also includes laboratory diagnostics of various materials like bone marrow, skin biopsy and others. Usually, a Giemsa stained preparation is required.

The **therapy** is complicated and it includes **paromomycin, amphotericin** and some other drugs.

Viral hepatitis A, B, C, D, E

Five main types of hepatitis infect people worldwide, but some of them are typical for some regions (e. g. hepatitis E for India). Viral hepatitis is almost characterized by diseased liver function, so **jaundice** may be visible in the patient. In not yet fully developed cases jaundice may be absent and non-specific symptoms including fever might be present. Liver function tests usually show a problem already in this phase. Treatment strategy depends on the type of hepatitis.

Other infections

There exist also many other infective diseases that may occur in foreigners or people coming from abroad. Important diseases are viral fevers like **dengue fever, yellow fever, Zika fever** and many others. Their diagnostics may be complicated. Nucleic acid amplification methods (NAAT like PCR) are possible, but not always available. Tests for antibodies have all disadvantages related globally to indirect tests (negativity in very fresh disease, positivity after the infection). We should also think about some viral respiratory diseases, as in some cases fever might be a leading symptom rather than respiratory problems. These infections may include **influenza, parainfluenzas, COVID-19, SARS, MERS** and many other diseases caused by coronaviruses, adenoviruses, picornaviruses and other viruses.

This list of common diseases that might cause infections with fever in foreigners and travellers is far from complete. Of course, a much larger survey can be given by textbooks of infectiology or tropical medicine.

Main sources and further reading

- Hiv.gov webpage, available on <hiv.gov>, visited 2020-07-09
- HIV & AIDS Health Center, available on <https://www.webmd.com/hiv-aids/default.htm>, visited 2020-07-09
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