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RECOMMENDATIONS FOR THE MANAGEMENT OF RICKETTSIOSES

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INTRODUCTION

Rickettsioses constitute a group of acute febrile infections, caused by different bacterial species of the order *Rickettsiales*. They may be of similar clinical course, however, their epidemiological and etiological features are rather distinct. Attempts to systematize rickettsioses resulted in differentiation of the following groups of infections:

1. Typhus fever group: epidemic, sporadic and murine typhus fever.
2. Spotted fever group: Rocky Mountain spotted fever, Mediterranean spotted fever, North-Asian tick-bite fever, rickettsialpox, Queensland tick typhus, scrub typhus.
3. Infections caused by the pathogens of the genus *Coxiella*, *Bartonella*, *Anaplasma.*

In our country, imported rickettsioses prevail. Having considered the endemicity of infections, exclusively human granulocytic anaplasmosis and bartonellosis are of significance in Poland (2). Remaining infections are usually acquired abroad. According to the data of the National Institute of Public Health-National Institute of Hygiene, sporadic introductions of rickettsioses of spotted fever group to Poland are possible. In 2006-2012, serological markers for this group of bacteria were identified in 5 patients. It is considered that birds returning to Poland from distant regions also have a role in the epidemiology of these infections (3). In recent years, a patient returning from the Republic of South Africa was diagnosed with the African tick-bite fever in the Department of Infectious Diseases in Lublin (4).

There is a numerous group of representatives of the order *Rickettsiales*, which are isolated from vectors, however, their pathogenic potential to humans remains unknown with an example being *R. amblyommi*. In recent years, several of the Rickettsia species, previously considered to be non-pathogenic, e.g. *R. slovaca*, *R. helvetica* or *R. raoulti* proved to be etiological agents of TIBOLA/DEBONEL (5,6).

Rickettsial pathogens are transmitted by vectors, including various species of arthropods (ticks, fleas, lice, mites). Information on the contact with vector may be an important element in the diagnostic process, however, lack of such data in interview does not exclude the diagnosis of rickettsioses.

DIAGNOSIS OF RICKETTSIOSES

Components of diagnosis:

1. Epidemiological interview, clinical presentation:

Interview is of significant role due to the geographical distribution of particular infections as well as vectors transmitting rickettsial pathogens. It should not be forgotten that there is a considerable group of infections prevalent in the countries of temperate climate. A number of such infections occur in areas which are not traditionally associated with the endemicity of infectious diseases, e.g. the United States (7,8). Clinical presentation is dependent on the Rickettsia species that caused the infection. It should be highlighted that some authors claim that rickettsioses may be the second, following malaria, cause of fever in returnees from overseas trips.

2. Laboratory testing:

- Serology – usually immunofluorescent test is applied (it should not be forgotten that antibodies appear within 7-10 days after the onset of general symptoms).
- PCR – positive result prior to the appearance of antibodies, type of specimen for testing depends on the infection (suspected), e.g. blood, skin biopsy or eschar (e.g. African tick-bite fever).
- Cell culture (specific media).
- PCR based on cutaneous swab culture (novel technique).

3. Detection of IgM:

In case of serological testing, which serves for the purpose of indirect diagnosis of infection, it should not be forgotten that cross-reactivity between Rickettsia species may appear, e.g. *R. rickettsii*, *R. typhi*, *R. slova-*

ca. There is also a possible occurrence of false positive results in the course of infectious mononucleosis and HIV infection. Occasionally, some data may be obtained following the performance of Western-blot, however, it is not applicable for many of the aforesaid bacteria (7).

Table 1 presents the recommendations for the diagnosis of several infections caused by representatives of the family *Rickettsiale*, including possible deviations from the norm in routine laboratory testing and recommended diagnostic specific tests with their interpretation (9-14).

Differential diagnosis:

Human granulocytic anaplasmosis:

1. Presence of morulae in peripheral blood or bone marrow smears stained with Wright or Giemsa methods in the acute stage of infection is demonstrated in more than a half of patients.
2. In serological diagnostics, the possibility of cross-reactivity should be considered, which typically may occur in patient diagnosed with other rickettsioses, Q fever, Epstein–Barr virus infection or with the presence of antileukocytic autoantibodies.
3. In several laboratories, immunoblotting, using recombinant immunodominant antigens of *A. phagocytophilum* (membrane proteins up to 42-49 kDa) is available. In differential diagnosis of infections caused by *A. phagocytophilum* and *E. chaffeensis,* the presence of p44 protein in the serum of patients is determined.
4. *A. phagocytophilum* can be cultured in a human promyelocytic cell line HL-60. Isolation of bacterium and rapid progression of cytopathic changes in cells constitute a final and indisputable confirmation of human granulocytic anaplasmosis (9,13,14).

Bartonellosis:

1. Provided blood smears are stained properly (Giemsa, Warthin-Starry, Steiner), identification of particular *Bartonella* species is possible, however, diagnostic specificity of such method is disputable.
2. Immunochemical testing of clinical specimens, e.g. based on cat scratch disease, allows for making a correct diagnosis in less than a half of cases.
3. Culture is not recommended in the diagnosis of bartonellosis, however, it may be sometimes of

Table 1. Laboratory diagnostics of rickettsioses

Disease	Deviations from the norm in laboratory testing	Laboratory criteria for confirmation
Rocky Mountain spotted fever	• WBC N • PLT ↓ • Sodium level ↓(slightly) • Transaminases ↑ (slightly)	Serological testing of paired serum samples in acute and convalescent stages reveals a 4-fold increase of antibody titres or Detection of *R. rickettsii* DNA
Human monocytic erlichiosis	• WBC ↓ in ≤53% • PLT ↓ in ≤94% • Transaminases ↑ (2–8-fold of ULN)	Serological testing of paired serum samples in acute and convalescent stages reveals a 4-fold increase of antibody titres or Detection of *E. chaffeensis* DNA or Detection of morulae in leukocytes and positive test result in serology
Human granulocytic anaplasmosis	• WBC ↓ in ≤53% • PLT ↓ in ≤94% • Transaminases ↑ (2–8-fold of ULN)	Serological testing of paired serum samples in acute and convalescent stages reveals a 4-fold increase of antibody titres or Detection of *A. phagocytophilum* DNA or Detection of morulae in leukocytes and positive test result in serology
Bartonellosis (in general for Bartonella spp.)		Serological testing of paired serum samples in acute and convalescent stages (after 1-14 days) reveals a 4-fold increase of antibody titres or Detection of IgM (questionable diagnostic value) or Detection of *Bartonella* spp. DNA (most often gltA gene) or Histopathological examination reveals the presence of granulomas with necrosis which may be indicative of cat scratch disease Identification of vascular proliferation is indicative of bacillary angiomatosis Remark – it is required to adopt staining to diagnostic specimen and suspected disease

N-normal; ↑-increased; ↓-decreased; ULN-upper limit of the norm.

assistance while suggesting bartonellosis with an example being diagnosis of fever of unknown origin.
4. Having interpreted serological testing, cross-reactivity should be taken into account with, e.g. *Coxiella burnetii* or *Chlamydia* (10-12).

Patients presenting with rash and fever, who are suspected of rickettsioses, should be subject to an adequate differential diagnosis (15). Non-specificity of symptoms results in a situation in which a number of infections should be considered. Provided infection with Rickettsia species cannot be excluded, therapy should be initiated following the collection of proper specimen for testing.

COMPLICATIONS

- Boutonneuse fever: Possible multiple organ damage, encephalopathy and coagulation defects leading to death.
- Epidemic typhus fever: Complications are rare but of high severity, e.g. gangrene, otitis media, sialoadenitis, myocarditis, pericarditis, pneumonia.
- Brill-Zinsser disease: Complications comparable to those observed in primary infection.
- Tsutsugamushi disease: Complications are rare but of high severity, e.g. hearing loss, pneumonia, RDS, myocarditis, DIC.
- Q fever: chronic Q fever, endocarditis, myocarditis, meningoencephalitis, glomerulonephritis.
- Granulocytic anaplasmosis: opportunistic infections, renal failure, hepatic necrosis, thrombocytopenia.
- Bartonellosis: numerous complications depending on the localization of infection, e.g. in the course of ocular bartonellosis: retinitis, corneitis, optic neuritis (9-12).

THERAPEUTIC MANAGEMENT OF RICKETTSIOSES

Antibiotic susceptibility testing is not commonly applied. Due to an intracellular nature of infection, standard methods of determining susceptibility to antibiotics cannot be adopted (9,14).

- Cell culture is a gold standard (plaque assay system), however, it cannot be used for all Rickettsia species.

Table 2. Therapuetic management of rickettsioses (based on 9, 16-23)

Disease	**Adults** **Scheme: R-recommended** **A-alternative**		**Pregnancy**
Human granulocytic anaplasmosis	R	Doxycycline 100mg 2x/24 h for 14 days	Rifampicin 600mg/24 h
	A	Rifampicin 600 mg/24 h for 7-10 days Ciprofloxacin (or other fluoroquinolones) for 7-10 days	Doxycycline*
Bartonellosis Cat scratch disease	R	Doxycycline 2x100 mg or erythromycin for 3-6 weeks If therapy is ineffective, the use of azithromycin should be considered (some authors claim that it is a drug of choice) in a dosage of 500 mg in the first day, and then 250mg 1x/24 h for 4 days	Amoxicillin or erythromycin
	A	Cotrimoxazole or fluoroquinolon	
Bartonellosis Bacillary angiomatosis	R	Doxycycline or erythromycin In severe cases, doxycycline + rifampicin up to 3 months	Erythromycin or rifampicin
Mediterranean spotted fever	R	Doxycycline 200mg 1x or 100mg 2x/24 h for 2-5 days	Josamycin 1g every 8 hours (in severe manifestation, it is accepted to use a single dose of doxycycline)
	A	Josamycin 1g every 8 hours for 5 days Ciprofloxacin (in Europe, there are reports on its ineffectiveness)	
Rocky Mountain spotted fever	R	Doxycycline 100mg 2x/24 h for 5-10 days	Doxycycline 100mg 2x/24 h for 5-10 days (in case of life-threatening manifestation for pregnant woman)
Other spotted fevers	R	Doxycycline 200mg 1x or 100mg 2x/24 h for 2-5 days	
Murine typhus fever	R	Doxycycline 100mg 2x/24 h continued for 3 days following the disappearance of symptoms	Doxycycline in the 3rd trimester*
	A	Fluoroquinolones Ciprofloxacin (in Europe, there are reports on its ineffectiveness) Chloramphenicol 60-75 mg/kg/24 h in 4 divided doses	
Epidemic typhus fever	R	Doxycycline 100mg 2x/24 h for 5 days or 2-4 days following the disappearance of fever	
	A	Chloramphenicol 60-75 mg/kg/24 h in 4 divided doses	Doxycycline 100-200mg in a single dose*

*Recommendations for the use of doxycycline in pregnancy were derived from the American settings, in Poland, doxycycline may be administered in children aged >12 years old, in the Unites States >8 years old.

- In recent times, quantitative polymerase chain reaction (PCR) is used to determine the susceptibility to antibiotics.

In general, treatment of different rickettsioses is similar, however, there are certain differences with regard to particular infections (9, 16-23).

1. Doxycycline is the drug of choice. Its use is contraindicated in pregnant women, children and persons allergic to tetracyclines.
2. Alternative antibiotics: their tolerance and effectiveness may be a cause of therapeutic failures. There are differences between recommendations binding in various countries resulting from acceptance or its lack of a medicine agency (e.g. FDA, EMEA).

Comments on therapies of rickettsioses:

1. Short-term use of doxycycline (200mg for a day) in spotted fever group seems to be equally effective as multiple-day therapy, and safe for children aged <8 years old.
2. Fluoroquinolones displayed considerably lower mode of action compared to doxycycline – longer persistence of symptoms, development of severe rickettsiosis manifestations – and were associated with longer duration of hospitalization.
3. Macrolides (clarithromycin 15mg/kg/24 h; josamycin 50mg/kg/24 h; azithromycin 10mg/kg/24 h) were used in the past to treat the Mediterranean spotted fever. They may constitute an alternative for doxycycline, however, comparative studies with doxycycline are lacking.
4. Legitimacy of the use of glucocorticoids has not been demonstrated, however, it is considered that they may prevent early death following the administration of antibiotics (especially chloramphenicol) which probably is associated with the activation of toxin-antitoxin system (vapC-vapB).
5. In human granulocytic anaplasmosis, as well as other infections, initiation of therapy is not recommended for seropositive patients who do not present with symptoms (9, 19).

Undoubtedly, as with all diagnostic recommendations and especially therapeutic recommendations, a proper management depends on a number of factors. Individualization of approach to each of the patients is an inseparable element of medicine. Recommendations presented above result from the experience of many authors, specified in research articles, as well as the recommendations of scientific societies and own experience.

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