8.6.40 Rickettsioses 1230

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section 8 Infectious diseases 1230 8.6.40 Rickettsioses Karolina Griffiths, Carole Eldin, Didier Raoult, and Philippe Parola ESSENTIALS Rickettsioses are zoonoses caused by obligate Gram-negative intra- cellular bacteria of the order Rickettsiales, comprising (1) rickettsioses due to bacteria of the genus Rickettsia, including spotted fever groups and typhus groups (Rickettsiaceae), (2) ehrlichioses and anaplasmoses due to bacteria of the Anaplasmataceae, and (3) scrub typhus due to Orientia tsutsugamushi (see Chapter 8.6.41). Epidemiology, clinical features, and prognosis of
particular rickettsioses Tick-borne spotted fever group—around 25 species or subspecies of spotted fever group rickettsiae can infect humans following trans- mission from their natural vertebrate hosts by ixodid (hard) ticks. Many species are restricted to certain geographical areas, although research continues to demonstrate the presence of these emerging pathogens in previously undocumented areas and tick species. Clinical presentation is typically with fever, headache, muscle pain, rash, local lymphadenopathy, and—for some diseases—a typical in- oculation eschar (the ‘tache noire’) at the tick bite site. These signs vary depending on the rickettsia involved and might allow distinction between different rickettsioses occurring at the same geographical location. Diseases range in severity from mild to severe. Murine (endemic) typhus is caused by Rickettsia typhi, whose nat- ural host is rodents, and is spread by the rat flea. Human infection usually results from contamination of disrupted skin or inhalation of flea faeces containing the organism. Disease is generally mild and self-limiting with nonspecific features. Epidemic typhus—caused by R. prowazekii, for whom humans are the major host, and transmitted by body lice, hence the disease is a par- ticular problem during times of war, conflict, famine, and natural catas- trophes. Following a nonspecific prodrome, presentation is with fever, headache, myalgia, and a macular, maculopapular, or petechial rash. Mortality ranges from 4% (recent series) to 60% (without antibiotics). Other rickettsioses—include (1) flea-borne spotted fever—cat flea typhus; (2) rickettsialpox—transmitted from mice by house mouse mites. Diagnosis and treatment of rickettsioses Diagnosis is by direct evidence of infection by culture or polymerase chain reaction, or by serological testing. Polymerase chain reaction of skin swabs can be particularly useful. Identification of the tick vector is important. Aside from supportive care, doxycycline remains the drug of choice for immediate empirical treatment of all rickettsioses on clinical suspicion, with some of these infections having high mortality if untreated. Identification of new Rickettsia species in ticks by molecular tools and their potential role in pathogenicity in hu- mans remains an increasing area of research. Human ehrlichioses and anaplasmosis These diseases are tick-borne zoonoses, whose causative agents are maintained through enzootic cycles between ticks and animals. Three main species cause human diseases: (1) Ehrlichia chaffeensis—causes human

monocytic ehrlichiosis; (2) Anaplasma phagocytophilum— causes human anaplasmosis; and (3) E. ewingii—causes granulocytic ehrlichiosis. These all present as undifferentiated seasonal febrile illnesses, ranging in severity from mild to severe, with multisystem organ failure. Diagnosis is by direct evidence of infection by culture or polymerase chain reaction, or (most commonly) by serological testing. Doxycycline is the antibiotic of choice. New subspecies causing human infection continue to be identified. Prevention Prevention of rickettsioses in general is by (1) avoiding arthropod bites—by applying topical N,N-diethyl-m-toluamide repellent to ex- posed skin, and treatment of clothing with permethrin; and (2) those staying in infested areas checking their bodies routinely for the presence of arthropods, and promptly removing ticks. In addition, (3) epidemic typhus—louse eradication is the most important pre- ventive measure. No vaccines are available. Introduction Rickettsioses are mild to life-threatening zoonoses caused by ob- ligate intracellular bacteria of the order Rickettsiales (family Rickettsiaceae). Arthropods, including ticks, fleas, and mites, are implicated as their vectors, reservoirs, or amplifiers. With an increasing number of new pathogens and recognition of new pathogenicity and affected geographical areas over the past few dec- ades, there is a better understanding of the scope and importance of these pathogens, particularly as a paradigm to understanding emerging and remerging infections. The taxonomy has under- gone numerous changes, with now three main groups classified as rickettsioses according to morphological, antigenic and metabolic characteristics: (1) Rickettsioses due to the bacteria of the genus Rickettsia, including spotted fever group (SFG), typhus groups (Rickettsiaceae); (2) Ehrlichioses and Anaplasmoses due to bacteria of the Anaplasmataceae; and (3) scrub typhus due to Orientia tsu tsugamushi (Chapter 8.6.41.) (See Fig. 8.6.40.1.) Phlyogenomic studies of complete genome sequences have pro- vided further insight into the genus Rickettsia, which can be clas- sified into four groups: (1) The spotted fever group (SFG), mainly associated with ticks, such as Rickettsia conorii, the causative agent of Mediterranean spotted fever and Rickettsia rickettsii, the agent of Rocky Mountain spotted fever, but also associated with fleas (Ricketttsia felis) and mites (R. akari). (2) Typhus groups are asso- ciated with human body lice, R. prowazekii, the agent of epidemic typhus and fleas, which transmit R. typhi, the cause of murine ty- phus. Groups; (3) Rickettsia belli; and (4) Rickettsia canadensis are currently of unknown pathogenicity. Rickettsioses (human infections attributable to Rickettsia spp.) Bacteriology Rickettsioses are short Gram-negative rods that retain basic fuchsin when stained by Gimenez’s method. Rickettsiae are 0.3–0.5 by

 0.8–2.0 µm in size. Their cytoplasm contains ribosomes and strands of DNA, limited by a typical Gram-negative trilamellar structure consisting of a bilayer inner membrane, a peptidoglycan layer, and a bilayer outer membrane. Within host cells they are surrounded by an electron-lucent slime layer. SFG rickettsiae have an optimal growth temperature of 32°C, their G + C content is 32–33, and they can polymerize actin and thus move into the nuclei of host cells causing spotted fevers in humans. One exception is Rickettsia felis that is grown at a lower temperature (28°C). Typhus-group rickett- siae have an optimal growth temperature of 35° C and a G + C con- tent of 29. They do not enter host cell nuclei but are confined to host cell cytoplasm, causing typhus in humans. Rickettsiae are rapidly inactivated at 56° C. They grow in eukaryotic cells where they live freely and divide by binary fission in the cytoplasm. They must be grown in tissue culture (L929 or Vero cells) or in yolk sacs of developing chicken embryos. Growth in cell monolayers is shown by plaque formation, representing disruption of massively in- fected cells. SFG rickettsiae form plaques of 2–3 mm diameter after 5 to 8 days, whereas typhus-group rickettsiae form plaques 1 mm in diam- eter after 8 to 10 days. Rickettsia spp demonstrate large

variations in antigenic heterogeneity, influenced by the diversity in their ecological distribution. This results in the induction of different specific immune responses. The major rickettsial antigens are lipopolysaccharides, lipo- proteins, outer membrane proteins of the surface cell antigen (SCA) family, and heat shock proteins. Other antigens include a 17-kDa lipo- protein, and autotransporter family SCA proteins include the 120- kDa S-layer protein (OmpB or Sca5), OmpA (SGF only), and Sca4. Fourteen genes that may encode SCA proteins have been identified in sequenced rickettsial genomes, of which sca1 is present in all species. Vectors Vectors of rickettsial agents include mainly ticks (order Ixodidea), lice (order Phtiraptera), and fleas (Siphonaptera). Mosquitoes have also been recently suggested as vectors for R. felis. Transmission of the bacteria can either occur vertically or via co –feeding (the pres- ence of several arthropods on the same host feeding alongside each other). Arthropods can act as a bacterial reservoir when efficient transstadial or transovarial transmission occurs. Ticks are the most important vectors and reservoirs of rickettsiae worldwide. Table 8.6.40.1 demonstrates the most important recog- nized tick vectors for each type of rickettsiae, with some rickettsiae specific to certain ticks and others carried by numerous arthropods. The geographical distribution of Rickettsiae and that of their specific vectors are closely related. R. akari is transmitted by the mouse mite Lyponyssoides san guineus. However, increasing numbers of rickettsiae have also been found in other mites, including R. felis and another genotype similar to R. australis. Taxonomy and genomics Traditional bacteriological identification methods cannot be applied to rickettsiae because they are strictly intracellular. New specific and sensitive molecular tools have revolutionized the identification of new rickettsia, demonstrating the diversity in previously uniden- tified geographical areas and vectors. Molecular techniques and phylogenomic analysis have enabled the reorganization and clari- fication of the genus Rickettsia. Genotyping methods continue to identify new species in this genus (Fig. 8.6.40.2). Several dozen strains remain to be characterized. In 2001, the first genome of a tick-transmitted rickettsia (R. conorii strain Seven) was fully sequenced, revealing several characteristics that are unique among bacterial genomes, including long, irregu- larly distributed, palindromic repeat fragments. Forty-five strains of rickettsiae have been fully sequenced, exhibiting large variations in gene content and size. Their genome size remains small, due to genome reduction through gene loss; reduced during specialization Rickettsioses (Order Rickettsiales) Ehrlichiosis and anaplasmosis Ehrlichia chaffeensis Anaplasma phagocytophilum Ehrlichia ewingii Genus Rickettsiae Typhus group Epidemic typhus (R. prowazekii) Murine typhus (R. typhi) Rickettsia bellii group Spotted Fever Group, including (amongst others): TICK BORNE (See Table 1) including: (Mediterranean Spotted Fever (R. conorii) Rocky Mountain Spotted Fever (R. rickettsii) R. felis infections
RICKETTSIALPOX MITES (R. akari) Rickettsia canadensis Scrub typhus (O. tsutsugamushi)
Fig. 8.6.40.1 Overview of the rickettsioses covered in this chapter.

 Table 8.6.40.1 Characteristics of tick-borne rickettsioses identified in human infections in 2015 Rickettsia sp. Recognized or potential tick vector(s) First identification in ticks Disease (first
clinical
description) First microbiological documentation
of human cases Selected clinical and epidemiological characteristics Confirmed pathogens
Rickettsia aeschlimannii Amblyomma variegatum, Rhipicephalus annulatus, R. evertsi evertsi, H. marginatum marginatum H. marginatum rufipes, H. truncatum, H. anatolicum excavatum, I. ricinus, R. sanguineus, R. turanicus, R. bursa, H. punctate, H. detritum, H. aeguptium,

H. dromedary, R. appendiculatus 1997 Spotted fever
(2002) 2002 First case described in a French patient returning from Morocco. Few human cases described in patients from Morocco, Algeria, and South Africa. Symptoms include eschar and maculopapular rash. Detected throughout countries in Europe, detected in ticks from migratory bird species. No autochthonous cases reported in Europe. No human cases identified in Asia, identified in ticks in Kazakhstan and Israel. Detected in 8 sub-Saharan countries. Rickettsia africae Amblyomma hebraeum, A. variegatum, A. compressum, A. lepidum, A. loculosum, Rhipicephalus annulatus, R. evertsi, R. decoloratus, R. sanguineus, R. geugyu, Hyalomma impeltatum,
H. aegyptium, Hy. dromedarii 1990 African tick-bite
fever (1934) 1992 Disease distribution includes sub-Saharan Africa, North and Central America, the Caribbean Pacific Islands. No human cases reported in Asia, or North Africa (identified in dromedary ticks in Algeria and Egypt). Outbreaks and clustered cases common (74%), Sudden onset of symptoms occur 5–7 days after the tick bite, with fever (88%), headache, myalgia, and fatigue. eschars, often multiple, are reported inconsistently (50–100%). maculopapular (49%) or vesicular (50%) rash, and lymphadenopathy (43%) are also reported. No fatal cases reported. Rickettsia australis Ixodes holocyclus, I. tasmani, I. cornuatus 1974 Queensland tick
typhus (1946) 1946 Disease occurs in predominantly rural settings. Cases occur from June to November. Vesicular rash (100%), eschar (65%), and lymphadenopathy (71%). Two fatal cases have been described. Rickettsia strain Atlantic rainforest (or strain Bahia) Amblyomma ovale,
A. aureolatum, A. dubitatum, R. sanguineu, ? Unnamed () 2010 A novel strain closely related to R. parkeri, R, africae, and R. sibirica. Disease clinically similar to R. parkeri. Two human cases identified in Brazil. Also detected in ticks in Columbia and Argentina. Rickettsia conorii caspia
R. sanguineus, R. pumilio, 1992 Astrakhan fever
(1970s) 1991 Endemic to Astrakhan region and Caspian Sea. Also detected in Kosovo and France, and a returning traveller from Chad. Disease occurs in predominantly rural settings. Associated with eschar (23%), maculopapular rash (94%), and conjunctivitis (34%). Rickettsia conorii conorii R. sanguineus, R. evertsi evertsi, R. simus, R. mushamae, Haemaphysalis puntaleachi, H leachi,
R. bursa 1932 Mediterranean
spotted fever
(1910) 1932 Endemic in southern Europe. Disease occurs in urban and rural settings. Cases reported across North Africa and nine sub-Saharan African countries. Incubation period of 6 days, sudden onset. Symptoms include fever, flu-like symptoms, shingles, and rash. Cases generally sporadic. Atypical and life- threatening presentations recently reported. Rickettsia conorii indica Rhipicephalus sanguineus 1950 Indian tick typhus 2001 Prevalent in India and Pakistan. Solitary case reports in Laos, Sri Lanka, and Sicliy, Italy. Compared to Mediterranean spotted fever, rash usually purpuric. Eschar rarely found. Mild to severe. Reported in Spain and Italy. Rickettsia conorii israelensis R. sanguineus 1974 Israeli spotted fever (1940) 1971 Reported in Israel, Italy, and Portugal, Tunisa. Compared to Mediterranean spotted fever, eschars are rare (7%) and more frequent gastrointestinal symptoms reported. Mild to severe illness. 29% mortality among Portugal cohort. Rickettsia heilongjiangensis D. silvarum, H. concinna, H. japonica douglasi, H. flava 1982 Far Eastern spotted fever (1992) 1992, 1996 Russia, China, South Korea, Japan. Rash, eschar, and lymphadenopathy. Peak in Russia in July in patients aged 50+. Genetically related strain identified in severe case in Thailand. No fatal cases reported. Rickettsia helvetica Ixodes ricinus, I. ovatus,
I. persulcatus, I. monospinus 1979 Unnamed (1999) 1999 Prevalent in Europe. Solitary cases identified in Laos and Thailand. Isolated in ticks in over 24 European countries, in Japan, Turkey, Algeria, and Morocoo. Although implicated in perimyocarditis and sarcoidosis, the validity of these

associations has been debated or not accepted by rickettsiologists. Rash and eschar seem to occur rarely.

8.6.40 Rickettsioses 1233 (continued) Rickettsia sp. Recognized or potential tick vector(s) First identification in ticks Disease (first
clinical
description) First microbiological documentation
of human cases Selected clinical and epidemiological characteristics Rickettsia honei Bothriocroton hydrosauri Ixodes sp. 1962 Flinders island spotted fever (1991) 1992 In Asia, Australia, and Pacific. Disease occurs in predominantly rural settings. Peak in December and January. Mild disease, symptoms include fever, rash (85%), eschar (25%), and lymphadenopathy (55%). Rickettsia honei strain marmionii Haemaphysalis novaeguineae Ixodes holocyclus 2003–2005 Australian spotted fever (2005) 2003–2005 Four states in Australia (South Australia, Victoria, Tasmania, Queensland). Between February and June. Six confirmed cases including one with eschar and two with a maculopapular rash. Similar clinical presentation to Flinders Island spotted fever. ‘Rickettsia kellyi’ Unknown Not done Unnamed (2006) 2006 A single case in a 1-year-old boy with fever and maculopapular rash. Rickettsia japonica I. ovatus, D. taiwanensis Haemaphysalis longicornis, H. flava, H. hystricis, H. cornigera, H. formosensis 1996 Oriental or Japanese spotted fever (1984) 1985 Typical spotted fever in southwestern Japan, recently identified in South Korea and Thailand and Shenyang, China. Disease occurs in predominantly rural settings. Agricultural activities, bamboo cutting. April to October. Fever, headache, eschar (91%) and rash (100%). May be severe. One fatal case reported. Rickettsia massiliae Rhipicephalus sanguineus, R. turanicus, R. muhsamae, R. lunulatus, R. sulcatus, R. bursa, R. pusillus, I. ricinus, H. paraleachi, R, senegalensis, R. guilhoni, R. 1992 Unnamed (2005) 2005 The strain was obtained from the blood of a patient from Sicily in 1985, stored, and definitively identified in 2005. A second case was identified in 2008 in southern France, with fever, chorioretinitis, and rash. A third case, a traveller in Spain returning from Buenoes Aires was identified, symptoms included fever, purpuric rash, eschar on the right leg. The 4th case was a 13-year-old boy in Italy with fever, scalp eschar, and alopecia. One other potential case with positive serology was detected in a man bitten in England. Also detected in ticks in across Europe and in Israel, Morocco, Algeria, Tunisia, Uganda, Ethiopia, Arizona, and California. Rickettsia monacensis Ixodes ricinus, I. persulcatus, I. sinensis 1998 Spotted fever (2006) 2006 Two cases in tick-bitten patients from Spain with fever and a maculopapular rash and one patient in Sardinia, Italy with an eschar. Detected in ticks across Europe, Morocco, Algeria, Tunisia, Korea, and China. Rickettsia parkeri Amblyomma maculatum A. americanum, A. triste, D. variabilis 1939 Unnamed (2004) 2004 Over 25 cases reported in the literature from North and Central America and South America (Argentina and traveller from Uruguay). Symptoms include fever, multiple eschars, and macuolopapular rash. ‘Rickettsia philipii’ (364D) 1966 2008 Several cases of a mild illness with eschar reported in California. Rickettsia raoultii Dermacentor reticulatus, D. silvarum, D. marginatus, R. pumilio, I. ricinus, D. nuttalli, D. niveus, H. ornithophila, H. shimoga, H. lagrangei, A. testudinarium, 1999 SENLAT/Tick-borne lymphadenopathy (2006) 2006 Human cases identified in France, Slovakia, Poland, and China. Detected in ticks acroos Europe, Algeria, Morocco, Far East Russia, Kazakhstan, China, Mongolia, and similar strains across Asia. Eschar on the scalp with cervical lymphadenopathy. Rickettsia rickettsii D. andersoni, D. variabilis R. sanguineus Amblyomma cajennense A. aureolatum D. nitens, A. americanum, A. imitator, Haemaphysalis leporispalustris, 1906 Rocky Mountain spotted fever (1899) 1906 Has the reputation of being the most severe tick-borne spotted fever rickettsiosis.

Case fatality rate of untreated infections can be >20%. However, case fatality has decreased dramatically in recent years in the USA, but fatal cases are still reported in South America. Peak occurrence during spring and summer. Eschars rarely reported. Broadly distributed in the western hemisphere and associated with several species of tick vectors. Fatal report of coinfection with Streptococcus pyogenes. Rickettsia sibirica mongolitimonae Hyalomma asiaticum H. truncatum, H. anatolicum excavatum, Rhipicephalus pusillus 1991 Lymphangitis associated rickettsiosis (1996) 1996 First isolated from ticks collected in Mongolia. Identified in Europe (France, Portugal, Greece, Spain) in the spring and summer, and Africa (Egypt, Algeria, South Africa). Detected in ticks in Senegal and Israel. No cases in Asia. 29 cases in the literature. Symptoms include fever (100%), headache (86%), myalgia (90%), single or multiple eschars (92%), macuolopapular rash (77%), and lymphangitis (43%). Usually mild, although severe cases with septic shock have been described.

section 8 Infectious diseases 1234 Table 8.6.40.1 (Continued) Rickettsia sp. Recognized or potential tick vector(s) First identification in ticks Disease (first clinical description) First microbiological documentation of human cases Selected clinical and epidemiological characteristics Rickettsia sibirica sibirica Dermacentor nuttalli, D. marginatus, D. silvarum, D. reticulates, D. sinicus, Haemaphysalis concinna, H. yeni, Ixodes persulcatus. Unknown Siberian tick typhus (1934) 1946 Probably most prevalent rickettsiosis in Asia. Identified in Siberia, Russia, China, Mongolia, Kazakhstan, and South Korea. Cases occur during spring and summer. Increasing reports of cases. Cases generally associated with rash (100%), eschar (77%), and lymphadenopathy. Usually mild. Severe case of subspecies sibirica BJ-90 with multiorgan dysfunction reported in China in 2013. Dermacentor sinicus 1974 North Asian tick typhus (1977) 1984 Rickettsia slovaca Dermacentor marginatus Dermacentor reticulatus 1968 SENLAT, Tick-borne lymphadenopathy (1997) Dermacentor- borne necrosis and lymphadenopathy (DEBONEL)(1997) 1997 2003 Present throughout mainland Europe. Cases present March to May, September—November (increased activity of Dermacentor ticks). Detected in ticks in North Africa, Russia, Georgia, and China. One possible human case in United Kingdom. More frequent in women and children. Syndrome characterized by scalp eschars (64%) and neck lymphadenopathy (69– 100%) (SENLAT) Fever and rash rare. Other symptoms include asthenia, headache, facial oedema. Alopecia around the eschar and chronic asthenia may occur. Rickettsia tamurae Amblyomma testudinarium 2006 Unnamed 2011 Two human cases reported in Japan and Laos. Reservoirs include pigs and wild boars. ‘Candidatus Rickettsia tarasevichiae’ Ixodes persulcatus 2003 Unnamed 2013 Five human cases reported in China, symptoms included fever, asthenia, anorexia, nausea, and headache. Eschar present in three patients. One fatal case. Previously identified in Russian ticks. Potential pathogens Rickettsia amblyommii Amblyomma americanum, A. cajennense, A. coelebs. Various other Amblyomma species 1974 Unnamed (1993) 1993 Possible cause of mild spotted fever rickettsiosis in the USA. Rickettsia also recently identified in ticks in Central and South America. Rickettsia asiatica Ixodes ovatus, I. pomerantzevi 2006 Unknown Identified in sika deer in Japan. Rickettsia bellii Various species of Amblyomma D. occidentalis, D. variabilis, D. parumapertus, D. albipictus, H. leporispalustris, Argas cooleyi, Ornithodoros concanensis, H. juxtakochi, I. loricatus 1966 – – Distinct group of rickettsial diseases. Largest known number of tick hosts. Detected in ticks in the North, Central, and South America. No known cases in humans. Rabbits and guinea pigs develop eschars after inoculation. Rickettsia canadensis Haemaphysalis leporispalustris 1967 – – Possible Rocky Mountain spotted fever-like disease described in California and Texas. Suspected cause of

acute cerebral vasculitis in Ohio. Febrile response in guinea pigs. Rickettsia hoogstraalii Carios capensis, Haemaphysalis punctata, H. sulcata, Argas persicus, Ornithodoros moubata 2006 - - Initially identified in 2006 in soft ticks in Japan. Isolated in ticks from sheep and goats in Croatia, Cyprus, Spain, Ethiopia, Turkey, the United States, and the west Indian Ocean.

8.6.40 Rickettsioses 1235 for intracellular conditions. The variation in size ranges from 1.11 to 1.2 Mb, with a mean gene count of 1236.54 +-281.22 and a mean GC content of 31.5 +- 1.52. This genome reduction, or degradation, is the driving force behind the adaptation of intracellular bacteria to life within a eukaryotic cell. Genome reduction by different methods, including reversible split genes and the creation of ‘pseudogenes’ and gene remnants, contributed to the specialization necessary to restrict potential hosts. A difference of 250 lost genes has been demonstrated between the group of rickettsioses associated with ticks (including R. conorii, Ri rickettsia, R africae and R massiliae) when separating from R. felis and R. akari. Comparisons between genomes have demonstrated that genome reduction is related to in- creased pathogenicity. Numerous studies have explored the genomic difference between pathogenic and less virulent strains, indicating that it is the likely loss of transcriptional regulating genes that cause pathogenicity, as opposed to the acquisition of other virulent genes. Further phylogenomic analysis has allowed further description of the differences and mix of rickettsial gene content between species. The core genome contains 566 genes. These primarily code for translation, ribosomal structure, the biosynthesis of cell wall/membrane and ribo- somes, replication, and energy production and conversion. However, conservation of noncoding sequences has been docu- mented, with a potential, but yet undefined role. Although it was previously thought that Rickettsiae lack plas- mids, they have been identified in at least 10 species. The presence of plasmids might indicate horizontal gene transfer between rickett- siae. Furthermore, recently 165 rickettsial genes in R. felis have been identified as potentially originating from other bacteria, including R. belli, R typhi, Legionella sp. and Francisella sp. Chimeric genes between R. felis and R. typhi have also been identified. We are pre- sented with an increasingly diversified genetic depiction of rickett- siae and this will continue to change with future research. Pathophysiology There is a large variation between the pathogenicity of different Rickettsia spp, with no current identification of the precise mo- lecular basis. When transmitted to a susceptible human host, patho- genic tick-borne SFG rickettsiae localize and multiply in endothelial R. rickettsii str. Sheila Smith R. rickettsii str. Iowa R. rickettsii str. H1p2 R. philipii str. 364D R. peacockii str. Rustic R. montanensis str. OSU 85-930 R. sibirica str. 246 R. sibirica subsp mongolitimonae R. africae ESF 5 R. parkert str. Portsmouth R. conorii str. Malish 7 R. slovaca str. 13-B R. slovaca str. D-CWPP R. honei R. heilongiiangensis 054 R. japonica YH R. massiliae MTU5 R. massiliae AZT80 R. aeschlimannii R. raoulrii R. helvetica C9P9 R. asiatica R. tamurae R. endosymbiont of Ixodes scapularis R. monacensis IrR/Munich R. akari str. Harford R. felis URRWXCal2 R. hoogstralii R. prowazekii str. Madrid E R. prowazekii str. BuV67 CWPP R. prowazekii str. Chernikova R. typhi str. TH1527 R. typhi str. Wilmington R. typhi str. B9991CWPP R. canadensis str. CA410 R. canadensis str. McKiel R. bellii OSU 85 389 R. bellii RML369 C R. atusralis str. Cutlack R. rhipicephalistr. 3 7 fernale6 CWPP Candidatus R. amblyommii str. GAT 30V Rocky mountain spotted fever Avirulent Unknown pathogenesis Unnamed rickettsiosis Unknown pathogenesis Unknown pathogenesis Siberian tick typhus Lymogabgutus associated rickettsiosis African tick bite fever R. parkeri ricketisiosis Mediterranean spotted fever Tick-borne lymphadenitis Flinders Island spotted fever Far-easern tick-borne rickettsiosis Oriental spotted fever Unknown pathogenesis Unnamed rickettsiosis Unknown pathogenesis Unknown pathogenesis Spotted fever rickettsiosis SENLAT

Unnamed rickettsiosis Unknown pathogenesis Spotted fever rickettsiosis Unknown pathogenesis Spotted fever rickettsiosis Rickettsialpox Queensland tick typhus Spotted fever rickettsiosis Unknown pathogenesis Epidemic typhus Murin typhus Unknown pathogenesis Unknown pathogenesis R. rickettsii R. massiliae R. helevetica R. akari R. prowazekii R. canadensis R. bellii TG SFG Fig. 8.6.40.2 Phylogenetic tree of Rickettsia species and pathogenic potential. Reprinted from Infection, Genetics and Evolution, Vol 25, Merhej V et al., Genotyping, evolution and epidemiological findings of Rickettsia species, Pages 122–37, Copyright © 2014, with permission from Elsevier.

section 8 Infectious diseases 1236 cells of small to medium-sized blood vessels, causing a vasculitis that is responsible for the clinical and laboratory abnormalities that occur in tick-borne rickettsioses. The severity of the Rickettsia is probably determined by the degree of growth on the endothelial cells, with the exception of R. akari (the Rickettsialpox agent) that mainly attacks macrophages. There are, therefore, numerous steps involved in the rickettsia-host cell interaction and it is the molecular characteristics and expression of particular rickettsial gene products that contribute to differences in pathogenicity among species. Since Rickettsiae are obligate intracellular bacteria, the first steps involve adherence and invasion of the host cells. Expression of OmpA, a SFG rickettsia ‘outer membrane protein’ or surface antigen protein, allows adhesion and entry into host endothelial cells. TG rickettsia do not possess this OmpA, although an ORF remnant remains in R. prowazekii. OmpB, a major surface antigen protein common to the genus Rickettsia, other outer membrane proteins, and new adhesins also contribute to adherence and invasion. After phago- cytosis and internalization, the phagocytic vacuole is rapidly lysed and rickettsiae escape phagocytic digestion to multiply freely in the host’s cytoplasm and nucleus (SFG species). The rickettsial infection not only causes host endothelial cell damage, but also initiates further endothelial activation as a form of procoagulant and proinflamattory cellular response, strongly cor- relating to the severity of the infection. R. rickettsia and R. conorii infection can cause surface platelet adhesion, increased expression of tissue factor, IL-1A, cell adhesion molecules and plasminogen activator inhibitor-1, and the release of von Willebrand factor. R. prowazekii infection can induce prostaglandin secretion. The inoculation eschar or ‘tache noire’, is the site of bacterial entry which has developed into a local inflammatory and necrotic skin le- sion. This eschar represents the first interaction between the human host and bacterium. There is an association between the eschar and the presence of many toxin-antitoxin systems in the Rickettsia genome. This might be explained by the toxic effect of these sys- tems increasing the local reaction and constraining the spread of the Rickettsia, corresponding to the inverse correlation between toxin-antitoxin systems and human host mortality. Rickettsioses as an emerging infection Unlike fleas, lice, and mites, which have a global distribution, ticks are highly dependent on their biotopes and have reduced mobility resulting in more regional distributions of rickettsial infections. The spread of arthropods is often linked to host animal migration, including cattle and migratory birds. There are numerous factors that contribute to the increasing iden- tification of rickettsioses in previously undocumented areas. This includes increasing international travel, with tick-borne spotted fever a more common cause than typhoid or dengue in travellers returning from sub-Saharan Africa. Other causes include changes to land rehabilitation practices, such as forestry. Of particular im- portance to the changing epidemiology of rickettsioses, is the role of global climate change causing longer seasonal warm temperat- ures. Warmer climates can influence the rickettsial transmission by arthropods, due to increased aggressiveness and number of attacks by the brown dog tick Rh. sanguineus seen with higher tem- peratures. This has been noted clinically, with higher numbers of

Mediterranean spotted fever cases and R. massilliae infections docu- mented during a warm period unusual for the time of year. Tick-borne SFG rickettsioses Epidemiology Ixodid (hard) ticks were first implicated as vectors of SFG rickettsioses in 1906, when the Rocky Mountain wood tick (Dermacentor ander soni) was shown to transmit R. rickettsii, the agent of Rocky Mountain spotted fever in the United States of America. In the 1930s, the role of the brown dog tick (Rhipicephalus sanguineus) in transmitting R. conorii, the causative agent of Mediterranean spotted fever, was described. However, between 1984 and 2015 at least 18 additional rickettsial species or subspecies causing tick-borne rickettsioses around the world were identified. Numerous agents are often ini- tially isolated from ticks, often years or decades before a definitive association with human disease is established. Keys to the epidemi- ology of tick-borne diseases are the ecological characteristics of their tick vectors. The life cycles of most tick-borne rickettsiae are poorly understood. In their natural vertebrate hosts, infection can result in a rickettsaemia that allows noninfected ticks to become infected and for the natural cycle to be perpetuated. Ticks can also acquire rickettsiae through transovarial passage. Because ixodid ticks feed only once at each life stage, the rickettsiae acquired can only be transmitted to another host when the tick has moulted to its next developmental stage (transstadial passage) and takes its next blood meal. When rickettsiae are efficiently transmitted both transstadially and transovarially, the tick serves as a reservoir and the distribution of the rickettsiosis and its tick host will be identical. However, transmission of R. rickettsii by Dermacentor andersoni diminishes the ticks' survival and reproductive capacity of their filial progenies. R. rickettsii has been shown to be lethal for most experimentally and transovarially infected Dermacentor andersoni. Similarly deleterious effects have been reported in Rhipicephalus san guineus group ticks experimentally infected by R. conorii conorii. This has been suggested as a potential reason to explain a low prevalence of Rh. sanguineus infected with R. conorii in nature (usually <1%). However, naturally infected colonies of ticks have been maintained in laboratory conditions over several generations. External factors such as temperature can have an essential role in the survival of Rh. sanguineus naturally infected with R. conorii compared with uninfected, in liaison with the long-recognized phenomenon known as reactivation—that is, the change in temperature and physiology of the tick host induces the rickettsia to emerge from dormancy and attain infectivity with bad effects on ticks. Clinical features Symptoms of tick-borne SFG rickettsioses begin 4 to 10 days after the bite and typically include fever, headache, muscle pain, rash, local lymphadenopathy, and, for some diseases, a typical inoculation eschar (the 'tache noire') at the site of the tick bite (Fig. 8.6.40.3). These signs vary depending on the rickettsia involved and might allow distinction between different rickettsioses occurring at the same geographical location (Table 8.6.40.1). For example, there is no eschar in Rocky Mountain spotted fever, whereas they do occur in R. parkeri infections. European Dermacentor ticks that bite hu- mans are most active during early spring, autumn, and occasionally winter, and are well known to bite on the scalp. Since R. slovaca is transmitted by Dermacentor ticks, the inoculation eschar of R. slo vaca infection is characteristically located on the scalp during these seasons (Fig. 8.6.40.4).

 SFG rickettsioses range in severity from mild to severe and fatal disease. Common nonspecific laboratory abnormalities in rickettsioses include mild leucopenia, anaemia, and thrombocyto- penia. Hyponatraemia, hypoalbuminaemia, and hepatic and renal abnormalities can also occur. Elevated C-reactive protein and lactate dehydrogenase are also common. Agents and diseases around the world Since 2008, five further species or subspecies of SFG rickettsiae have been confirmed to infect humans, bringing the total to 25, with a further five potential

pathogens. Table 8.6.40.1 demon- strates the characteristics of tick-borne rickettsiae identified in human infections by 2015. Newly identified rickettsia in humans since 2008 include Rickettsia sp. Strain Atlantic rainforest or strain Bahia, Candidatus Rickettsia tamaresvichiae, Rickettsia tamurae, and Rickettsia 364D. Rickettsia helvetica has been confirmed as a pathogen. Newly identified potential pathogens include Rickettsia asiatica and Rickettsia hoogstraalii. Geographical distributions have been updated in Figs. 8.6.40.5–8.6.40.12. There are more rickettsiae 'of unknown pathogenicity' or 'sus- pected to be pathogens' to be identified as emerging pathogens in the near future. Mediterranean spotted fever This is one of the oldest known vector-borne diseases. Rickettsia conorii conorii is the agent of Mediterannean spotted fever, which is endemic to southern Europe. Foci of cases are sometimes seen in Northern and Central Europe. Increasing numbers of cases are reported in Algeria, Tunisia, and Morocco. Rickettsia conorii conorii has been identified in nine sub-Saharan African countries. The main vector is Rhicephalus sanguineus, the brown dog tick. Studies on nat- urally infected Rhicephalus sanguineus have demonstrated very high transovarial transmission rates (100%) over several generations. The animal reservoir has yet to be conclusively demonstrated, with high seroprevalence rates noted in dogs and hedgehogs. The usually low affinity of Rhipicephalus sanguineus for people increases in warmer temperatures and, in Europe, most cases occur in the summer. Classical risk factors include advanced age, immunodepression, chronic alcoholism, glucose-6-phosphate dehydrogenase deficiency, previous inappropriate antibiotic use, and delayed treatment. The most common presentation includes fever (94–100%), flu- like symptoms (78%), asthenia (64%), single eschar (53–57%), and maculopapular or petechial rash (87–96%); the rash can spread to the palms and soles. A large case series in Portugal reported the most common symptoms as fever, myalgia, arthralgia, and headache. Clusters of cases and multiple eschars have been reported. These are novel findings, since the probability of receiving multiple concomi- tant tick bites is thought to be small. Furthermore, life-threatening complications and atypical presentations have been reported. These include cardiac complications such as myocarditis and atrial fibril- lation. Rare complications include ocular and neurological symp- toms, pancreatic involvement, splenic rupture, acute renal failure, and haemophagocytic syndrome. The case fatality rate has been reported as 2.5%. Similar mortality rates of 3.6% were seen in case series in Algeria and Portugal, al- though previous mortality rates have been reported of up to 13%. Predictors of mortality included hyperbilirubinaemia, acute renal failure, and the absence of rash. Rocky Mountain spotted fever The agent of Rocky Mountain spotted fever is Rickettsia ricketsii. It is the most commonly reported SFG rickettsioses reported in the United States of America, but confirmed cases have also been re- ported across North and South America, including Canada, Mexico, Panama, Costa Rica, Argentina, Brazil (Brazilian spotted fever) and Columbia. The incidence of Rocky Mountain spotted fever in the United States was reported at seven cases per million in 2007, rising sharply to 14.3 cases per million to 2012, although this is likely ex- plained by cross-reactivity of serological tests, highlighting the im- portance of polymerase chain reaction (PCR) to clearly identify the rickettsial species and improve disease surveillance. Symptoms include sudden onset fever, headache, nausea and vomiting, anorexia, and generalized myalgia. A maculopapular rash appears on the second to fourth day of illness, becoming petechial (a) (b) (d) (c) Fig. 8.6.40.3 Inoculation eschar, the hallmark of SFG rickettsiosis which may be absent or uncommon in some specific diseases, such as Rocky Mountain spotted fever, or associated with a lymphangitis, as in the case of R. sibirica mongolitimonae (a) and R. africae infection (b), or a rash, as in R. africae (c) and R. heilongjiangensis infection (d). (a) From Fournier PE, et al. (2000). Rickettsia mongolotimonae: a rare pathogen in France. Emerg Infect Dis, 6, 290–2, with permission; (b) copyright DA Warrell; (c) copyright Dr Ed Dunbar,

Manchester; (d) from Mediannikov O, et al. (2004). Acute tick-borne rickettsiosis, caused by Rickettsia heilongjiangensis variant in the Russian Far East. Emerg Infect Dis, 10, 810–17, with permission. (a) (b) Fig. 8.6.40.4 Patients with R. slovaca infection. Inoculation lesion on the scalp (a), residual alopecia (b). From Gouriet F, Rolain JM, Raoult D (2006). Rickettsia slovaca infection, France. Emerg Infect Dis, 12, 521–3, with permission.

section 8 Infectious diseases 1238 or purpuric in 50–60% of patients. The illness can rapidly progress, causing a severe vasculitis. The case fatality rate 2008–2012 in the United States was low (0.4%, rising to 10% in Arizona, particularly among affected tribal communities), in comparison to previous re- ports of untreated case fatality rates around 20–25%. A more severe clinical picture is seen in South America, with severe and fatal cases of R. rickettsii infection reported. Higher case fatality rates have been reported in populations living in endemic regions in Brazil and paediatric populations in Mexico. Numerous host factors can result in increased severity, for example, increasing age, male gender, and presence of G6PD deficiency. Severe complications include renal failure, pulmonary oedema, cerebral oedema, and disseminated intravascular coagulopathy. African tick bite fever The pathogen Rickettsiae africae has been identified across most of the African continent and causes African tick bite fever, where it is most commonly transmitted through Amblyomma ticks, mainly A. hebraeum and A. variegatum. Human cases have also been identified in the Caribbean and West Indies. These ticks demonstrate aggressive behaviour and in areas of high endem- icity have been found to have high infection rates, reaching 100%. Naturally infected A. variegatum can have a 100% transovarial transmission rate. The disease occurs in predominantly rural settings and is com- monly associated with international travellers returning from safari, hunting, camping, or adventure races. It has been identified as the second most common illness, after malaria, in travellers from sub- Saharan Africa. African tick-bite fever is characterized by the occur- rence of multiple inoculation eschars in clusters of cases, explained by simultaneous mass attacks by infected Amblyomma hebraeum ticks at a particular geographical location, for example, groups of tourists on safaris. Clinical symptoms include sudden onset of fever, fatigue, myalagia, and a headache 5–7 days following a tick bite. Inoculation eschars are reported in 50–100% of cases. Other symptoms include generalized maculopapular or papulovesicular rash and regional lymphadenopathy. More serious complications can occur, especially in older people. Complications include myocarditis and neuropathy, but no fatal cases have been reported. Infection caused by R. felis Epidemiology R. felis was probably first detected in cat fleas (Ctenocephalides felis) in 1918 and rediscovered in 1990. R. felis was initially characterized by molecular biology techniques and named the ELB agent for the EL Laboratory (Soquel, California, United States of America). In 1994, ELB agent DNA fragments were detected in blood samples from a Texan patient that had been kept since 1991. In 1994 and 1995, iso- lation of the ELB agent was reported and the name R. felis was pro- posed, but it was not cultivated definitively at low temperature and fully characterized until 2001 in Marseille, France. Infections caused by R. felis have been initially called flea-borne spotted fever or cat flea typhus. R. rickettsii R. parkeri R. massiliae “Rickettsia philipii” (364D) “Candidatus R. amblyommii” “Candidatus R. andeanae” R. bellii R. canadensis “Candidatus R. cooleyi” R. montanensis R. peacockii R. rhipicephali Fig. 8.6.40.5 Tick-borne rickettsiae in North America (except Mexico). Pathogenic rickettsiae are indicated by coloured symbols and rickettsiae of possible/unknown pathogenicity by white symbols. Reprinted from Parola P, Paddock CD, Socolovschi C, Labruna MB, Mediannikov O, Kernif T, et al. (2013). Update on tick-borne rickettsioses around the world: a geographic approach. Clin Microbiol Rev, 26(4), 657–702. R. rickettsii R. africae R. bellii “Candidatus R. amblyommii”

Fig. 8.6.40.6 Tick-borne rickettsiae in Mexico and Central America (except Mexico). Pathogenic rickettsiae are indicated by coloured symbols and rickettsiae of possible/unknown pathogenicity by white symbols. Reprinted from Parola P, Paddock CD, Socolovschi C, Labruna MB, Mediannikov O, Kernif T, et al. (2013). Update on tick-borne rickettsioses around the world: a geographic approach. Clin Microbiol Rev, 26(4), 657–702.

8.6.40 Rickettsioses 1239 R. africae R. conorii conorii R. conorii israelensis R. conorii caspia R. conorii indica R. sibirica mongolitimonae R. aeschlimannii R. slovaca R. raoultii R. massiliae R. monacensis R. hoogstraalii R. helvetica R. rhipicephali Rickettsia sp. DmS1 «Candidatus R. barbariae» Rickettsia sp. AvBat «Candidatus R. kuligani» «Candidatus R. siciliensis» «Candidatus R. rioja» «Candidatus R. vini» Rickettsia sp. strain Davousti «Candidatus R. kotlanii» Fig. 8.6.40.8 Tick-borne rickettsiae in Europe. Pathogenic rickettsiae are indicated by coloured symbols and rickettsiae of possible/unknown pathogenicity by white symbols. Reprinted from Parola P, Paddock CD, Socolovschi C, Labruna MB, Mediannikov O, Kernif T, et al. (2013). Update on tick-borne rickettsioses around the world: a geographic approach. Clin Microbiol Rev, 26(4), 657–702. R. rhipicephali R. bellii R. monteiroi “Candidatus R. amblyommii” “Candidatus R. andeanae” R. rickettsii R. parkeri R. massiliae Rickettsia strain Atlantic rainforest (or strain Bahia) Fig. 8.6.40.7 Tick-borne rickettsiae in South America. Pathogenic rickettsiae are indicated by coloured symbols and rickettsiae of possible/unknown pathogenicity by white symbols. Modified from Parola P, Paddock CD, Socolovschi C, Labruna MB, Mediannikov O, Kernif T, et al. (2013). Update on tick-borne rickettsioses around the world: a geographic approach. Clin Microbiol Rev, 26(4), 657–702.

section 8 Infectious diseases 1240 Human cases have been identified worldwide, in Europe, Northern Africa, Asia, and Central and South America. More re- cently, cases in Australia have also been reported. Numerous fleas have been associated with R. felis, including C. felis, C. canis, Pulex irritans, Archeopsylla erinacei, and Anomiopsyllus nudata. The sole confirmed biological vector for R. felis is the cat flea (Ctenocephalides felis), however within the past few years new potential vectors have been identified. In 2012, molecular tools enabled its identification in mosquitoes, including Aedes albopictus in Libreville, Gabon, and Anopheles gambiae from the Côte d’Ivoire. Furthermore, the iden- tification of R. felis by molecular techniques in febrile patients in regions endemic for malaria suggests that mosquitoes may be com- petent vectors for this infection. Studies have demonstrated this bac- terium being found in up to 15% of patients with ‘fever of unknown origin’ in sub-Saharan Africa. These new findings and the sharing of a common vector for Plasmodium highlights the importance of this emerging infection, with suggestions that R. felis infections should be considered in all malaria endemic regions. The potential of An. gambiae as vectors of R. felis was further demonstrated, with a recent study demonstrating rickettsemias in mice bitten by R. felis infected An. gambiae. Further study is needed on the life cycle of R. felis, its potential reservoir hosts, and the role of humans as these reservoirs. R. conorii conorii R. conorii israelensis R. aeschlimannii R. massiliae R. monacensis R. helvetica R. slovaca R. raoultii R. sibirica mongolitimonae R. africae Rickettsia sp. R. hoogstraalii Fig. 8.6.40.9 Tick-borne rickettsiae in North Africa. Pathogenic rickettsiae are indicated by coloured symbols and rickettsiae of possible/unknown pathogenicity by white symbols. Modified from Parola P, Paddock CD, Socolovschi C, Labruna MB, Mediannikov O, Kernif T, et al. (2013). Update on tick-borne rickettsioses around the world: a geographic approach. Clin Microbiol Rev, 26(4), 657–702. R. africae R. conorii conorii R. conorii caspia R. massiliae R. sibirica mongolitimonae R. aeschlimannii R. rhipicephali Rickettsia hoogstraalii Rickettsia sp. Strain Davousti «Candidatus R. liberiensis»

Rickettsia sp. Strain Uilenbergi Fig. 8.6.40.10 Tick-borne rickettsiae in Africa. Pathogenic rickettsiae are
indicated by coloured symbols and rickettsiae of possible/unknown pathogenicity by white symbols. Reprinted from Parola P, Paddock CD, Socolovschi C, Labruna MB, Mediannikov O, Kernif T, et al. (2013). Update on tick-borne rickettsioses around the world: a geographic approach.
Clin Microbiol Rev, 26(4), 657–702.

8.6.40 Rickettsioses 1241 Clinical features The principal symptoms reported in the literature are nonspecific, commonly headache, fever, and a maculopapular rash. Single eschars can also be reported, making it difficult to distinguish from tick-borne spotted fevers. Other reports include digestive symptoms and pneumonia. Neurological involvement has also been reported, including acute polyneuropathy and cases in Sweden include subacute meningitis, Bell's palsy, and deafness. Rickettsialpox Epidemiology Rickettsialpox is a cosmopolitan mite-borne spotted fever rickettsiosis caused by R. akari. Originally described in New York R. sibirica sibirica R. heilongjiangensis R. japonica R. sibirica mongolitimonae R. conorii indica R. conorii conorii R. conorii israelensis R. aeschlimannii R. raoultii R. slovaca R. helvetica R. massiliae R. monacensis R. honei R. africae «Candidatus R. kellyi » R. tamurae « Candidatus R. tarasevichiae » R. asiatica Rickettsiasp. Rickettsia sp. IG-1 R. hoogstraalii «Candidatus R. principis » R. bellii Rickettsia sp. Rickettsia sp. TwKM02 Fig. 8.6.40.11 Tick-borne rickettsiae in Asia. Pathogenic rickettsiae are indicated by coloured symbols and rickettsiae of possible/unknown pathogenicity by white symbols. Modified from Parola P, Paddock CD, Socolovschi C, Labruna MB, Mediannikov O, Kernif T, et al. (2013). Update on tick-borne rickettsioses around the world: a geographic approach. Clin Microbiol Rev, 26(4), 657–702. Rickettsia gravesii Rickettsia honei strain "marmionii" Rickettsia honei Rickettsia australis Rickettsia argasii Rickettsia africae Fig. 8.6.40.12 Tick-borne rickettsiae in Australasia. Pathogenic rickettsiae are indicated by coloured symbols and rickettsiae of possible/unknown pathogenicity by white symbols. Reprinted from Parola P, Paddock CD, Socolovschi C, Labruna MB, Mediannikov O, Kernif T, et al. (2013). Update on tick-borne rickettsioses around the world: a geographic approach. Clin Microbiol Rev, 26(4), 657–702.

section 8 Infectious diseases 1242 in 1946, it is still reported mainly in the United States of America. Only three confirmed cases are reported from Europe: Ukraine, Croatia, and the Netherlands. Low R. akari antibody titres in sero- logical surveys and case reports have been documented in Albania, France, Germany, and Italy, but no confirmed cases. Recently, rickettsialpox emerged in Turkey. The disease is probably ubiquitous but underdiagnosed, particularly in the tropics. House mouse mites (Liponyssoides sanguineus) are the primary reservoir host of R. akari, haematophagous arthropods that main- tain R. akari in house mice (Mus musculus). It transmits the disease when nymphs or adults bite people exposed by contact with house mice. This mite has been harvested from various other rodents in the United States of America, Eurasia, Africa, and Korea. Clinical features The first identified case in New York was an 11-year-old boy who presented with a high fever, a papulovesicular lesion on his back, and axillary lymphadenopathy and, over the next few days, developed a diffuse rash and fever (40.5°C) despite penicillin therapy. He made a complete recovery. During the next few months more than 100 more cases were recognized and the causative agent, named R. akari from the Greek word for mite, was described. Rickettsialpox is often described as chickenpox-like because the rash is often vesicular. In 83–100% of cases, a primary eschar ap- pears at the site of a mite bite, starting as a painless vesicle that rup- tures and a dark-brown or black crust develops over the lesion. The exanthem

consists of 2–10-mm-diameter discrete erythematous maculopapules distributed over the extremities, abdomen, back, chest, and face, but only rarely on palms and soles. After 2–3 days, some lesions become indurated and small vesicles develop. Around a quarter of patients have vesicular buccal mucous membrane le- sions. Symptoms 2–7 days after the appearance of the primary lesion include fever, sweating, lassitude, myalgia, and headache, which per- sist for 7–10 days in the absence of antibiotic treatment. Although generally described as benign and self-limiting, neurological symp- toms such as photophobia, vertigo, pain on movement of the eyes, and nuchal rigidity may be severe enough to warrant lumbar punc- ture. R. akari has been isolated from eschar biopsy specimens from patients with rickettsialpox. Typhus group Murine typhus Epidemiology Murine or endemic typhus was probably first reported by Bravo in Mexico in 1570, making it one of the oldest recognized arthropod- borne zoonoses. The first case was described clinically in grain silo workers in Australia and the disease distinguished from epidemic typhus in the 1920s. The causative organism was named R. mooseri and thereafter R. typhi. Its main vector is the rat flea (Xenopsylla che opis) while rodents, mainly Rattus norvegicus and Rattus rattus, are its reservoirs. Other fleas or arthropods can also transmit R. typhi, including cat fleas (C. felis), mouse fleas (L. segnis), lice, mites, and ticks, and other rodents and wild and domestic mammals may be hosts. The classic cycle of infection is flea-borne between rats. R. typhi is only rarely transmitted transovarially in fleas. Rats are not fatally infected and rickettsaemia persists from day 7 to day 12 after inoculation. Fleas are infected for life, but their lifespan is not shortened. Rickettsiae are excreted in their faeces, where they re- main viable for several years. Most people are thought to become infected when flea faeces containing R. typhi contaminate disrupted skin or are inhaled into the respiratory tract. Rarely, infections can result from flea bites. Murine typhus is distributed worldwide but is often unrecognized, especially in tropical countries. Cases are regularly documented in the United States of America (recently in 2013 in Texas), Mexico, and Europe, and it recently re-emerged in Japan. Ideas of prevalence are based principally on serosurveys and on cases in travellers from China, Indonesia, India, Morocco, Canary Islands, Africa, Malaysia, Thailand, and Vietnam. Serosurveys suggest that the disease is more prevalent in coastal areas of tropical countries, where rats are par- ticularly common. Epidemiological shifts have been described in the United States, such as in Southern California with a shift from urban Los Angeles to suburban cases due to opossums carrying R. typhi in- fected cat fleas. Murine typhus has also been reported from Tunisia, Brazil, and on the Thailand–Myanmar border. Recent studies have identified populations at risk in urban areas including the home- less, such as in Marseille, France, and immigrant workers, such as in Singapore. Murine typhus should be considered as an important differential diagnosis for fever of unknown origin. Furthermore, murine typhus should be considered in returning travellers with fever of unknown origin, especially those with unspecific symptoms and those returning from tropical or subtropical countries in Africa or Southeast Asia. Clinical features Murine typhus is a mild disease with nonspecific features. The incu- bation period is 7–14 days. Adults typically present with the classical triad of fever, headache, and rash, but this has been reported in less than 15% of cases in children. Fever and headache are more common than the rash, which can be of variable frequency (20–80%) and often transient or difficult to observe. Among 83 patients in Crete, 49 (59%) presented with rash and 17 additional patients (20%) de- veloped rash subsequently. Fever (100%), headache (88%), and chills (87%) were also common. Nausea, abdominal pain, diarrhoea, jaundice, cough, confusion, and seizures have been reported and can lead to misdiagnosis. Less than 50% of patients report exposure to fleas or rats. In untreated patients, symptoms last for 7–14 days, after which there is usually a rapid return to health. Neurological complications are rare, but have been reported, including aseptic meningitis and abducens nerve palsy, and are usually

reversible with correct antibiotic treatment. Epidemic typhus Epidemiology Epidemic typhus is caused by R. prowazekii, a typhus-group rick- ettsia. It is suspected to have been responsible for the ‘Great Plague’ of Athens in the 5th century bc. In 1909, Charles Nicolle discovered the role of lice in the transmission of typhus and later performed the first successful cultures in animals. He was rewarded with a Nobel Prize. The vectors of epidemic typhus, body lice (Pediculus humanus humanus or P. humanus corporis), are a problem particularly during times of war, conflict, famine, and natural catastrophes. They live in clothes and thrive in cold weather when clothes might be washed

8.6.40 Rickettsioses 1243 infrequently and general hygiene declines. After the Second World War, foci persisted in the cooler mountainous countries in Africa, but epidemic typhus was considered a disease of the past. However, in recent years, intermittent outbreaks have occurred in Africa (Ethiopia, Nigeria, Burundi), Mexico, Central America, South America, Eastern Europe, Afghanistan, northern India, and China. The most recent outbreak, the largest since the Second World War, occurred during the civil war in Burundi in the 1990s. Travellers are rarely infected, but those who visit or work with homeless popula- tions or refugee camps might be infected. R. prowazekii is transmitted to people when infected louse feeding sites are contaminated by their faeces, or when the conjunctivae and other mucous membranes are exposed to crushed bodies or faeces of infected lice. Transmission might also result from the inhalation of infected faeces, which is thought to be the main route of infection in health workers. People who survive epidemic typhus remain infected with R. prowazekii for life; when stressed, they might experience a recrudescence (Brill–Zinsser disease), and can be the source of a new epidemic if they become infested with body lice. Sporadic cases continue to be re- ported in the United States. Humans were long considered the sole reservoir of R. prowazekii but its discovery in flying squirrels and their ectoparasites in North America indicates an alternative res- ervoir. Sylvatic (flying squirrel) typhus has not yet been associated with human fatalities, but North American flying squirrel strains of R. prowazekii appear similar to those isolated from patients during louse-borne outbreaks. A nonhuman typhus reservoir has also been reported in Ethiopia, where 10 isolates of R. prowazekii were obtained from hyalomma ticks recovered from livestock. In addition, evidence suggests an association of typhus-group rick- ettsiae with ticks. There have been concerns about the use of R. prowazekii as a potential Category B bioterrorism agent. First developed by the Soviets in the 1930s, it has numerous qualities optimal for use as an aerosol weapon, including high infectivity and stability, high virulence, and the potential to engineer complete antimicro- bial resistance, while initially presenting only nonspecific symp- toms. Physicians should be aware of the virulent Rickettsiae as potential infections and inefficacy of usual empirical antibiotic treatment. Clinical features After an incubation period of 10–14 days, patients develop malaise and vague symptoms before the sudden development of fever (all cases), headache (all cases), and myalgia (70–100%). In Burundi, a crouching attitude was observed, attributable to myalgia. Other common features are nausea or vomiting, coughing, and abnormal- ities of central nervous system function ranging from confusion to stupor and coma. Diarrhoea, pulmonary involvement, myocarditis, splenomegaly, and conjunctivitis can also occur. Most patients de- velop a macular, maculopapular, or petechial rash that classically begins on the trunk and spreads to the limbs (Fig. 8.6.40.13). It is difficult to detect in pigmented skins. Gangrene of the distal extrem- ities can occur in severe cases as mentioned in Thucydides’ descrip- tion of the Great Plague of Athens. Case fatality ranges between 4% in the antibiotic era up to 60% before antibiotics were available, with clinical severity dependant on age over 60 years and the patients’ nutritional state. Brill–Zinsser disease can appear many years after

the acute disease. It is less severe, and the rash is less frequent. Investigation and specific diagnosis Fig. 8.6.40.14 demonstrates the investigations that should be per- formed in the work up of a patient with clinical suspicion of rickett- sial infection. Serology Serological tests are the most frequently used and widely available methods for diagnosis. The Weil–Felix test, the oldest test, is based on the detection of antibodies to various proteus antigens that cross- react with rickettsiae. Although it lacks specificity and sensitivity, it continues to be used in many developing countries. However, im- munofluorescence assay (IFA) is currently considered the reference method. Acute-phase and convalescent-phase serum specimens must be collected, several weeks apart. One limitation of serology is cross-reactivity between antigens of pathogens within the same genus, and other genera. Furthermore, seroconversion is usually only detected at day 7–15 post onset, extending to 25–28 days for in- fection with R. africae. Most commercially available IFAs offer a very limited selection of antigens. IFA can be adequate to diagnose the class of infection (e.g. SFG rickettsiosis), but is unlikely to provide a specific aetiological agent unless more sophisticated assays are per- formed. Serology should be considered an initial, but not the sole, method for recognizing and diagnosing ‘emerging rickettsioses’. In the Unité des Rickettsies, Marseille, when cross-reactions are noted between several rickettsial antigens, a rickettsia is considered to be causal when titres of IgG or IgM antibody against this antigen are (a) (c) (b) Fig. 8.6.40.13 (a) Rash in a patient with epidemic typhus due to R. prowazekii imported from Algeria to France. (b) Rash of epidemic typhus in an Ethiopian patient. (c) Peripheral gangrene in an Ethiopian patient with epidemic typhus. (a) From Niang M, Brouqui P, Raoult D (1999). Epidemic typhus imported from Algeria. Emerg Infect Dis, 5, 716–18, with permission; (b) courtesy of the late
Dr P. L. Perine; (c) copyright D. A. Warrell.

 at least two serial dilutions higher than those against other rickett- sial antigens. When differences in titres between several antigens are lower than two dilutions, western blot assays and, if necessary, cross-absorption studies are used. Other diagnostic tests have been developed, such as using monoclonal antibodies. Culture Rickettsial isolation in culture is the definitive diagnostic method, but can be performed only in P3 facilities that can maintain living host cells or cell cultures. The centrifugation shell-vial technique using HEL fibroblasts has proved effective. Rickettsiae can be isolated from buffy coat preparations of heparinized or ethylenediaminetetraacetic acid (EDTA)-anticoagulated whole blood, skin biopsies, and from arthropods. Culture results can be positive at 48–72 hours post inoculation. However, the sensitivity of culture dramatically diminishes in pa- tients receiving antibiotic treatment; therefore, samples should be taken before treatment and inoculated as soon as possible. Histochemical and immunohistochemical procedures Rickettsiae can been detected in tissue specimens by various histochemical methods, including Giemsa or Gimenez staining. Immunohistochemical methods are superior for SFG rickettsiae in formalin-fixed paraffin-embedded skin biopsies, particularly es- chars (Fig. 8.6.40.15). Most available assays are SFG specific but not species specific. Molecular tools PCR and sequencing methods are sensitive and rapid tools for detecting and identifying rickettsiae in blood, skin biopsies, and from vectors. Primers amplifying sequences of several genes have been used. Real-time quantitative PCR assays have been developed, as in the case of epidemic typhus. This could aid surveillance in public health programmes, especially for countries where human cases are underdiagnosed. Skin/eschar swabs Performing PCR on an eschar swab is a new noninvasive ap- proach that has demonstrated significant results and played a role in improving the diagnosis of these emerging infections (Fig. 8.6.40.16). This approach allows more widespread documen- tation, as swabs can more easily be taken than skin biopsies, espe- cially in low-resource

settings, and sent to reference laboratories for quantitative PCR testing. This simple technique involves re- moving the crust of an eschar and rotating a sterile swab vigorously at the base of the eschar. Wetting a compress with humidified sterile water and placing on the eschar beforehand, increases the material collected. Murine typhus has also been identified by PCR on the biopsy of a petechial skin lesion. Vector identification Identifying the vector as part of the standard investigation process can help clarify the diagnosis. When possible, the tick, louse, or flea should be collected and analysed, both morphological identification under the microscope and using MALDI-TOF. Arthropods are used as epidemiological tools to detect the presence of a pathogen in a specific geographical area. Knowledge of the correct species of the vector can help guide possible causes of infection in symptomatic patients. A recent study has proposed the dual identification, of both the tick species and pathogen infection status on collected ticks from patients using tick hemolymph protein mixture. This highly accurate, quick, and economical method is useful at the clinical level, with PCR Fig. 8.6.40.14 Investigations for clinical suspicion of rickettsioses: serology screening is often performed in local centralized laboratories. Specific PCRs are usually performed in National Reference Laboratories. Ticks should be sent in dry sterile pots to the National Reference Laboratory. All specimens should be accompanied with a request form with specific clinical details to aid diagnostic testing. Fig. 8.6.40.15 Inoculation eschar from a patient with African tick- bite fever showing numerous dermal inflammatory infiltrates mainly composed of polymorphonuclear leucocytes. Immunoperoxidase staining with an anti-CD15 antibody; original magnification ×100. From Lepidi H, Fournier PE, Raoult D (2006). Histologic features and immunodetection of African tick-bite fever eschar. Emerg Infect Dis, 12, 1332–7, with permission.

8.6.40 Rickettsioses 1245 no entomological knowledge necessary for identification and might also be useful to help monitor tick-borne diseases. Treatment and prognosis Early empirical antibiotic is the rule for any clinically suspected rickettsiosis, before confirmation of the diagnosis. SFG rickettsioses Doxycycline (200 mg/day) is the treatment of choice for all SFG rickettsioses (Table 8.6.40.2), including Rocky Mountain spotted fever or other severe rickettsial disease in young chil- dren. Duration of antibiotic therapy for SFG rickettsioses is gov- erned more by clinical response than a statutory number of days. However, for most of these infections, therapy should continue for at least 3 days after the patient’s fever has subsided. A single dose of 200 mg doxycycline has proved adequate for Mediterranean spotted fever, but patients with severe SFG rickettsioses should be given doxycycline intravenously for up to 24 h after they become afebrile; however, this is not available in all countries. Macrolides can also be used as an alternative in the case of pregnant women, where doxycycline is contraindicated. Josamycin (1 g tds) may also be used in certain situations with SFG rickettsioses without severe disease, including pregnant women with Mediterranean spotted fever; however, strict follow-up is essential. Other macrolides that can be used include clarithromycin (15 mg/kg/day) and azithromycin (10 mg/kg/day); however, erythromycin was found to be inferior to doxycycline and is not advised. Chloramphenicol is an alternative, but its use is limited by perceived side effects and it should only be considered as empirical treatment of severe cases if it is the only available drug, as in developing countries. Fluroquinolones are no longer recommended, as they are asso- ciated with worse outcomes in cell culture models and human R. conorii infections. Many classes of broad spectrum antibiotics including penicillins, cephalosporins, and aminoglycosides are ineffective against rickettsial diseases. Murine typhus Doxycycline is the drug of choice for nonpregnant adults and chil- dren. The optimal duration of therapy has not been assessed in clin- ical studies but 7 to 15 days, or for at least 48 h after the patient has become afebrile, has been recommended. A single dose of 200

mg doxycycline also proved adequate. Response to doxycycline is rapid with defervescence in 2 to 3 days. Chloramphenicol is an alternative, Table 8.6.40.2 Treatment options for SFG rickettsioses Preferred treatment for adults/children Alternatives Tick-borne rickettsioses Spotted fever group with inoculation eschar Mediterranean spotted fever
(Rickettsia conorii conorii) Doxycycline 200 mg two oral doses in a single day (preferred) or 200 mg single dose or 100 mg twice daily for 2–5 days For children <45 kg: Doxycycline 2.2 mg/kg every 12 h Josamycin 1 g every 8 h for 5 daysa (preferred for pregnant women, single dose of Doxycycline if severe forms) Clarithromycin 15 mg/kg/day Rocky Mountain spotted fever (Rickettsia rickettsii) Doxycycline 100 mg every 12 h for at least 3 days after the fever subsides, standard duration of treatment 7–14 days For children <45 kg: Doxycycline 2.2 mg/kg every 12 h Chloramphenicol 60–75 mg/kg/day in four divided doses (12.5–25 mg/kg every 6 h for 5–10 days in children), may be considered if mild illness in pregnant women (otherwise doxycycline first line) All other SFG rickettsioses (conorii subspecies, sibirica sibirica, sibirica monolitimonae, australis africae,
and slovaca) Doxycycline 200 mg single dose or 100 mg twice daily for 2–5 days Severe forms of spotted fever group Doxycycline IV (not available in all countries) Typhus group Murine typhus (Rickettsiea typhi) Doxycycline 100 mg twice daily for 3 days after resolution of symptoms Louse-borne Epidemic typhus
(Rickettsia prowazekii) Doxcycline 200 mg for 5 days or 2–4 days after defervescence Chloramphenicol a Erythromycin has been found to be inferior to doxycycline (Munoz Espin Arch Dis Child 1986), however other macrolides have also been used to treat 12–27% of MSF patients, such as clarithromycin (15 mg/kg/day) and azithromycin (10 mg/kg/day). Fig. 8.6.40.16 Swabbing a skin eschar in the diagnosis of Rickettsia sibirica mongolitimonae infection by PCR. Reprinted from Parola P, Paddock CD, Socolovschi C, Labruna MB, Mediannikov O,
Kernif T, et al. (2013). Update on tick-borne rickettsioses around the world: a geographic approach. Clin Microbiol Rev, 26(4), 657–702.

section 8 Infectious diseases 1246 with the reservations discussed earlier, but relapses have been re- ported. Fluoroquinolones proved effective in vitro against R. typhi, but the few clinical studies produced contradictory results. Other antibiotics effective against R. typhi in vitro, including rifampicin, thiamphenicol, macrolides, erythromycin, clarithromycin, josamycin, and telithromycin, have no clinical application, and amoxicillin, gen- tamicin, and trimethoprim/sulphamethoxazole are ineffective. Epidemic typhus Tetracycline and chloramphenicol are effective. Chloramphenicol is still widely used as empirical treatment of fever in tropical developing countries since its broad spectrum includes other ser- ious infections, such as meningococcaemia and typhoid fever, that can initially mimic epidemic typhus. Most patients improve mark- edly within 48 hours of starting treatment with either of these anti- biotics. However, many physicians prefer to use tetracycline for all typhus diseases, as it is cheaper and safer. A single dose of 200 mg doxycycline, the reference treatment, is extremely efficient. Few or no relapses are observed with this treatment, which should be pre- scribed for any suspected case, including children, as no risk of tooth staining has been demonstrated with this regimen. Ciprofloxacin should be avoided. Management should also include de-lousing to prevent further human transmission. Human ehrlichioses and anaplasmosis According to the current classification, the family Anaplasmataceae comprises the genera Anaplasma, Ehrlichia, Aegyptianella, Neorickettsia, and Wolbachia, as well as two candidate genera, ‘Candidatus Neoehrlichia’ and ‘Candidatus Xenohaliotis’ These diseases, long thought to be of purely veterinary import- ance, are caused by bacteria of the family Anaplasmataceae. Ten

species are now implicated in human diseases (Table 8.6.40.3) with the three main infections: Ehrlichia chaffeensis causing human monocytic ehrlichiosis, Anaplasma phagocytophilum causing human anaplasmosis, and E. ewingii causing granulocytic ehrlichiosis. These diseases are tick-borne zoonoses whose causa- tive agents are maintained through enzootic cycles between ticks and animals. Table 8.6.40.3 Human ehrlichioses and anaplasmosis in human infections in 2015 Genus Pathogen Disease Target cell Geographical region Vector Clinical symptoms/ investigations Ehrlichia Ehrlichia chaffeensis Human Monocytotropic ehrlichiosis (HME) Monocyte South-eastern/central, mid- Atlantic USA Amblyomma americanum Fever, malaise, fatigue, headache, nausea, and vomiting. Thrombo-cytopenia, lymphopenia E. ewingii Granulocytic ehrlichiosis Neutrophil South-eastern/central USA Amblyomma americanum E. canis HME Monocyte Reports from Venezuala Unconfirmed E. ruminantium Unconfirmed Monocyte Possible cases in South Africa Unconfirmed E. muris-like agent HME-like Monocyte Upper Midwestern states USA, patients exposed to ticks in Minnesota or Winsconsin, (2009) Ixodes scapularis Panola Mountain Ehrlichia Unconfirmed Atlanta, Georgia USA Amblyomma americanum No fever, myalgia Anaplasma Anaplasma phagocytophilum Human granulocytic anaplasmosis Neutrophils NE and Midwest USA, Europe Asia Ixodes persulcatus, Malaise, fever, myalgia, and headache. Thrombocytopenia, leucopenia elevated hepatic transaminase levels Anaplasma ovis Unnamed One case in Cyprus Fever, lymphadenopathy, and hepatosplenomegaly ‘Anaplasma capra’ Unnamed 28 patients in China, concurrently in local goats Ixodes persulcatus Fever, malaise, headache. Rash more common. Eschar in 3 patients Anaplasma platys Unnamed Platelets Possible case of a veterinarian after exposure in Grenada and South Africa Rhipicephalus sanguineus Migraines and seizures Neorickettsia Candidatus Neorickettsia sennetsu Infectious mononucleosis like syndrome Monocyte/ macrophage Europe and China Ixodes ovatus, I. ricinus, I. persulcatus, I. frontalis Fever, headache, and malaise

8.6.40 Rickettsioses 1247 Bacteriology, taxonomy, and genomics The family Anaplasmataceae consists of intracellular alphaproteobacteria including human and mammal pathogens, whose host cells are of bone marrow or haematopoietic origin including erythrocytes, monocytes, or macrophages, neutrophils, and platelets (Fig. 8.6.40.17). Members of this family share a high degree of nucleotide sequence similarity in several chromosomal genes, such as rrs, groESL operon, gltA, RpoB, and Ank. The organ- isms grow within cytoplasmic vacuoles containing one to many in- dividual organisms, which resemble mulberries when observed by light microscopy, and have been called ‘morulae’ (Fig. 8.6.40.18). Anaplasma marginale, a cattle pathogen, was the first discovered, by Theiler in 1910. Since then, others have been described in ani- mals and humans. In 2001, improvements in molecular phylogen- etic methods modified the taxonomy of the Anaplasmataceae, based on comparison of sequences obtained from rrs (16s rRNA encoding gene) and the groESL operon. Analyses of other gene sequences and the complete genome sequencing of several species of the family (A. phagocytophilum, E. chaffeensis, E. ruminantium, N. sen netsu, and W. pipientis) have confirmed the new organization of the family Anaplasmataceae. Ehrlichia and anaplasma display a unique large expansion of immunodominant outer membrane proteins, facilitating antigenic variation. Unlike Rickettsiaceae, pathogenic Anaplasmataceae are capable of making all major vitamins, cofac- tors, and nucleotides, which could be beneficial to the invertebrate vector or the vertebrate host. Ehrlichia and anaplasma lack genes for biosynthesis of the lipopolysaccharide and peptidoglycan activating host leucocytes. Human monocytic ehrlichiosis Epidemiology The first human case of monocytic ehrlichiosis was identified in 1986, when intracytoplasmic inclusions were seen in monocytes in the peripheral blood smear of a severely ill

man bitten by ticks in Arkansas, United States. This case was first assumed to be due to E. canis, the agent of monocytic canine ehrlichiosis, but E. chaffeensis was later isolated. E. chaffeensis is maintained in nature as a complex zoonosis, involving many vertebrate reservoirs for the bacterium and blood- meal sources for the tick vectors. The Lone Star tick (Amblyomma americanum) is its primary vector. All stages of this tick bite people. It is distributed in south, central, south-eastern, and mid-Atlantic areas of the United States of America, in meadows, woodlands, and hardwood forests. Primary hosts include many wild and domestic mammals, although deer are considered to be the definitive host. E. chaffeensis has been detected by PCR in other American ticks, but their role as vectors has not been demonstrated. There is no evidence of transovarial transmission, so ticks are not considered to be res- ervoirs. So far, the white-tailed deer (Odocoileus virginianus) is the principal reservoir of E. chaffeensis, but domestic dogs (with mild Anaplasma capra KM206273 Anaplasma centrale Aomori AF283007 Anaplasma sp E1 JN558820 Anaplasma sp Rongchang EU709493 Anaplasma centrale SS40C-L AB211164 Anaplasma sp Kamoshika17 AB509223 Anaplasma marginale M60313 Anaplasma centrale AF318944 Anaplasma ovis AY262124 Anaplasma bovis U03775 Anaplasma platys M82801 Anaplasma phagocytophilum AY527213 Anaplasma phagocytophilum JFBJ01000002 Anaplasma phagocytophilum U02521 Ehrlichia chaffeensis M73222 Candidatus Neoehrlichia mikurensis AB084582 Candidatus Xenohaliotis californiensis AF133090 Wolbachia pipientis X61768 Neorickettsia sennetsu M73219 Rickettsia rickettsii L36217 Orientia tsutsugamushi D38623 Escherichia coli X80725 0.05 100 54 58 89 40 92 97 91 98 76 100 72 95 99 100 52 43
Fig. 8.6.40.17 Current phylogeny and taxonomic classification of genera in the family Anaplasmataceae. Reprinted from The Lancet Infectious Diseases, Vol 15(6), Li H et al., Human infection with a novel tick-borne Anaplasma species in China: a surveillance study, Pages 663–670, Copyright © 2015, with permission from Elsevier.

section 8 Infectious diseases 1248 to inapparent disease), red foxes, and domestic goats are potential reservoirs. Between 1999 and 2004, more than 1300 cases were reported to the Centers for Disease Control and Prevention (CDC). Cases con- tinued to increase, with 4613 cases reported by the national surveil- lance system between 2008 and 2012. Changes in the host–vector ecology have influenced the emergence of monocytic ehrlichiosis, including increasing population densities and geographical distri- bution of Amblyomma americanum, increases in vertebrate host populations (wild turkeys, white-tailed deer) for this tick, the in- creases in reservoir host population for E. chaffeensis (e.g. white- tailed deer), the increasing proportion of people older than 60 years of age, as well as available diagnostic procedures and improved sur- veillance and reporting. Most cases of monocytic ehrlichiosis occur in the south, central, and south-eastern regions of the United States of America, where Amblyomma americanum reaches its highest prevalence. Monocytic ehrlichiosis is a seasonal disease whose incidence correlates with the activity of both nymphs and adult ticks. Most cases occur from May to July. Incidence based on active surveillance is 10 times higher than the highest rates reported using passive surveillance. Monocytic ehrlichiosis seems to be prevalent in Brazil and has been reported from other parts of the world including Latin America, Europe, Africa, and Asia. These diagnoses were based on serological studies, so infection by closely related organism cannot be completely ruled out. Gene fragments closely related to those of E. chaffeensis have been detected by PCR in ticks and rodents trapped in continental Asia but, so far, the disease has been clearly identified only in the United States of America. Clinical diagnosis Tick bite or tick exposure is reported in 70–90% of patients with monocytic ehrlichiosis. It is more common in males and can affect individuals of all ages,

including children and elderly people. The incubation period is 1–2 weeks (median 9 days). It presents as an undifferentiated febrile illness ranging in severity from a mild dis- ease to multisystem organ failure. More than one-half of patients must be hospitalized and case fatality was reported at 1% (rising to 3% for adults >70 years and 4% for children <5 years). Spatio-temporal analysis identified poverty status, relative humidity, the di- urnal temperature range as risk factors for monocytic ehrlichiosis, demonstrating the potential implications climate change might have on this tick-borne disease. Asymptomatic infection might also occur and, since Amblyomma americanum is the vector of other tick-borne agents, coinfection is possible. Clinical features include fever (98%), headache (77%), myalgias (65%), vomiting (36%), rash (35%), cough (25%), and neurological findings with impaired consciousness (20%). The maculopapular, or diffusely erythematous rash involves trunk, extremities, and, less commonly, the face and can be petechial in later stages. Malaise (30– 80%), lymphadenopathy, gastrointestinal symptoms, pharyngitis, and, less frequently, conjunctivitis, dysuria, and peripheral oedema can also occur. Leucopenia, thrombocytopenia, and elevated hep- atic transaminase levels are the most common laboratory findings. Severe complications can include central nervous system and renal involvement, adult respiratory distress syndrome, and disseminated intravascular coagulation.
E. ewingii granulocytic ehrlichiosis E. ewingii has been known since 1992 as the agent of canine gran- ulocytic ehrlichiosis, first described in a dog in Arkansas in 1971. The disease was described subsequently in several other states in the south-eastern and south-central United States of America, where the recognized vector is the Lone Star tick, Amblyomma america num. E. ewingii can also infect white-tailed and South Carolina deer. Human infections with E. ewingii were first reported in 1999, when blood samples collected from 413 patients with possible ehrlichiosis in Missouri between 1994 and 1998 were analysed retrospectively. The CDC in the USA report only 55 confirmed cases of E. ewingii infection between 2008 and 2012, despite the proportions of E. ewingii and E. chaffeensis infections reported in animals being similar. It has been suggested that a milder human infection might be caused by E. ewingii, therefore resulting in fewer presentations to medical centres. No fatal infections with E. ewingii have been re- ported. As no antigens for E. ewingii were available between 2008 and 2012, all diagnoses have been confirmed by PCR. Sixty-nine per cent (69%) of cases were reported in the states of Delaware and Missouri. An underlying immunosuppressive condition was noted in 26% with a hospitalization rate of 77%. Clinical signs include fever, headache, and thrombocytopenia, with or without leucopenia; a rash is rare. Transmission of E. ewingii infection via a platelet transfusion in an immunocompromised pa- tient has also been reported. (a) (d) (b) (c) Fig. 8.6.40.18 Anaplasma phagocytophilum (a) in human peripheral blood band neutrophil (Wright’s stain, original magnification ×1000), (b) in THP-1 myelomonocytic cell culture (LeukoStat stain, original magnification ×400), (c) in neutrophils infiltrating human spleen (immunohistochemistry with haematoxylin counterstain, original magnification ×100), and (d) ultrastructure by transmission electron microscopy in HL-60 cell culture (original magnification ×21 960). Courtesy of V Popov. From Dumler JS, et al. (2005). Human granulocytic anaplasmosis and Anaplasma phagocytophilum. Emerg Infect Dis, 1, 1828–34, with permission.

 Human granulocytic anaplasmosis History Human granulocytic anaplasmosis was first identified in 1990 in a patient in Wisconsin, United States, who died with a severe febrile illness two weeks after a tick bite. Clusters of small bacteria, as- sumed to be phagocytosed Gram-positive cocci, were seen inside neutrophils in the peripheral blood, but a careful review suggested the possibility of human ehrlichiosis. Over the ensuing two years, 13

cases with similar intraneutrophilic inclusions were identified. In 1994, through application of broad-range molecular amplification and DNA sequencing, the causative agent was recognized as distinct from E. chaffeensis. First known as the ‘HGE agent’, the disease was renamed human granulocytic anaplasmosis (HGA). Vectors Ixodes ticks are the recognized vectors. A. phagocytophilum is main- tained in a transmission cycle with Ixodes persulcatus complex ticks, including I. scapularis in the eastern United States of America, I. pacificus in the western United States of America, and I. ricinus in Europe. A role for I. persulcatus in Eastern Europe and Asia is also suggested. Tick infection is established after an infectious blood meal. The bacterium is transmitted in ticks transstadially but not transovarially, and so ticks are not reservoirs. The major mamma- lian reservoir for A. phagocytophilum in the eastern United States of America is the white-footed mouse Peromyscus leucopus. Other small mammals and the white-tailed deer, Odocoileus virginianus, can also be infected. Other reservoirs might include ruminants and other mammals. In Europe, horses, cattle, sheep, goats, dog, cats, and small mammals, particularly rodents, might be reservoirs. Epidemiology In the United States, the dynamics of HGA follows that of its vectors. Surveillance demonstrates increasing ranges for white-tailed deer and I. scapularis, particularly to the south-east. Case reports of HGA increased during 2008–2012, with 2867 confirmed cases (mainly by PCR) and 4982 probable cases compared to previous summaries (Fig. 8.6.40.18). This increase might be explained by a change in re- porting practices and increased clinician awareness. The national reported incidence rate was 6.3 cases per million persons-years, the main affected states being Minnesota, Wisconsin, and Rhode Island. Since 1997, the agent and disease have been recognized across 15 countries in Europe, where more than 60 cases have been docu-mented. Sporadic human cases have also been confirmed in China and the presence of A. phagocytophilum antibodies in humans pre- senting with rickettsia like infections in Japan. Seroepidemiological studies confirm that human A. phagocytophilum infection is highly prevalent in both the United States of America and in Europe. Clinical diagnosis HGA presents most commonly as an undifferentiated febrile illness occurring in spring or summer, with the highest number of cases seen May to August. The incidence rate increases with age, particu- larly aged 60 years and over. The most frequent symptoms are malaise (94%), fever (92%), myalgia (77%), and headache (75%). A minority of patients have arthralgia, gastrointestinal symptoms (nausea, vomiting, diar- rhoea), respiratory symptoms (cough, pulmonary infiltrates, acute respiratory distress syndrome), and liver or central nervous system disturbances. Rash was observed in 6%, but no specific rash has been described in HGA. Coinfections with other Ixodes-borne agents such as Lyme borreliosis and babesiosis have been reported. Frequent laboratory abnormalities identified in up to 329 patients included thrombocytopenia (71%), leucopenia (49%), anaemia (37%), and elevated hepatic transaminase levels (71%). The case fa- tality rate in the United States between 2008 and 2012 was 0.3%, with no deaths in patients under the age of 50. Emerging Ehrlichioses/Anaplasmoses In 2010, a Cypriot patient presented with fever, lymphadenop- athy, and hepatosplenomegaly following a tick bite. The identi- fied pathogen was Anaplasma ovis, known to infect goats and sheep worldwide, yet no other human cases have been reported. Recently, a new tick-borne pathogen of human anaplasmosis has been identified in northern China, with the suggested nomenclature ‘Anaplasma capra’. This pathogen was initially discovered in goats and the authors, after active surveillance, identified 28 infected pa- tients living in areas where this pathogen had previously been iden- tified. Similar clinical features were identified, with an acute onset of fever, headache, and malaise. However, rash seemed more common than with HGA, and other differences included rarer occurrences of leucopenia, thrombocytopenia, and abnormal hepatic trans- aminases. Interestingly, an eschar was reported in three patients with no

molecular biological or serological evidence of involvement of a Rickettsia species. Furthermore, the visualization of morulae in peripheral blood samples was less common and there was low-to-undetectable seroreactivity to the A. phagocytophilum antigen. As it is thought that HGA infections are generally underreported, it is plausible to think other undiscovered pathogens in the Anaplasma genus might be causing human disease. Physicians, particularly in the United States and China, need to be aware of these emerging pathogens. Furthermore, we are likely to see the emergence of these pathogens in humans in other parts of the globe where Ixodes ticks are present; for example, A. phagocytophilum has been reported in ticks in Brazil, Russia, Japan, and Korea. Diagnosis Laboratory confirmation of human ehrlichioses and anaplasmosis is based on several tests that are not yet widely available for routine use. PCR on whole blood samples is highly sensitive in severe cases, but the sensitivity may be low (70%). A. phagocytophilum can be cultured in special conditions. Indirect immunofluorescence serology is the most widely available technique and is the recommended technique using paired acute and convalescent sera. However, limitations in- clude delay in seroconversion and possible false-positive detection due to cross-reacting bacteria. Laboratory criteria for diagnosis have been defined (see Boxes 8.6.40.1 and 8.6.40.2). Treatment Tetracyclines are the reference drugs in treating human ehrlichioses and anaplasmosis for patients of all ages. Doxycyline is the anti- biotic of choice, the recommend dosage is 100 mg for adults and 2.2 mg/kg for children 8 years or older every 12 hours. It is recom-mended that the treatment be continued for 7–10 days, or for at least 3–5 days after defervescence. Most patients become afebrile within 1–3 days following treatment, and alternate diagnoses

section 8 Infectious diseases 1250 should be considered if such a response is not achieved. E. chaf feensis is susceptible in vitro to rifampicin (without in vivo evi- dence) but resistant to aminoglycosides, macrolides, and ketolides, co-trimoxazole, penicillin, cephalosporin, chloramphenicol, and quinolones. Rifampicin (300 mg bd for adults, 10 mg/kg, max 300 mg/dose for children) is only recommended in case of allergy, preg- nancy, or under 8 years of age. Prevention Currently, no vaccines are available for rickettsial infection. Prevention is based first on avoiding arthropod bites. The best method for avoiding tick, flea, and chigger bites is topical N,N-diethyl-m-toluamide repellent applied to exposed skin, and treat- ment of clothing (including army uniforms) with permethrin, which kills arthropods on contact. Those staying in infested area should routinely check their bodies for the presence of arthropods. Prompt tick removal using blunt rounded forceps is essential for the prevention of tick-borne illnesses. In the case of epidemic typhus, louse eradication (e.g. in refugee camps) is the most important pre- ventive measure and is essential in the control of outbreaks. Since body lice live only in clothing, the simplest method of delousing is to remove and then destroy or wash and boil all clothing. Dusting of all clothing with insecticides kills body lice and reduces the risk of reinfestation. Weekly doxycycline, 200 mg, prevents scrub typhus and a single 200 mg oral dose of doxycycline seemed effective in the epidemic typhus outbreak in Burundi, but the efficacy against rickettsial infections of doxycycline (100 mg daily), used for malaria chemoprophylaxis, is untested. Likely future developments Although they are among the oldest known vector-borne diseases, many new rickettsioses have emerged in recent years. What are the factors influencing their emergence and recognition? People are undertaking more outdoor activities and international ‘adven- ture’ tourism is developing in rural and remote areas, resulting in increased contact with arthropods and arthropod-borne rickettsial pathogens. The role of the primary physician, including careful his- tory taking and physical and laboratory examinations, has been em- phasized; essential for the description of

emerging SFG rickettsioses, such as Flinders Island spotted fever, Japanese spotted fever, and Astrakhan fever. Increasing clinical awareness and reporting of cases plays a crucial part in developing our understanding of the disease epidemiology. Considering not only the clinical symptoms but also the season, environmental risk factors, and geographical exposition in travellers will help skilful clinicians identify these in- fections. Knowledge on the appropriate diagnostic tests to perform is essential. Molecular techniques and noninvasive swabbing of es- chars have facilitated epidemiological studies of emerging human rickettsioses all over the world and, with the help of improved cul- ture systems, have incriminated new species as causes of human dis- eases. Further developments for the use of appropriate diagnostics are necessary, including the more widespread use of real-time PCR assays and developments in convalescent serology. Box 8.6.40.1 Case definitions of Ehrlichioses Clinical evidence: Any reported fever and one or more of the following: headache, myalgia, anaemia, leucopenia, thromobocytopenia, or any hepatic transaminase elevation. 1) Human ehrlichiosis caused by Ehrlichia chaffeensis. Laboratory confirmed: • Serological evidence of a fourfold change in immunoglobulin G (IgG)-specific antibody titre to E. chaffeensis antigen by indirect immunofluorescence assay (IFA) between paired serum samples (one taken in first week of illness and a second 2–4 weeks later), OR • Detection of E. chaffeensis DNA in a clinical specimen via amplifi- cation of a specific target by polymerase chain reaction (PCR) assay OR • Demonstration of ehrlichial antigen in a biopsy/autopsy sample by immunohistochemical methods OR • Isolation of E. chaffeensis from a clinical specimen in cell culture Laboratory supportive: • Serological evidence of elevated IgG or IgM antibody reactive with E. chaffeensis antigen by IFA, enzyme-linked immunosorbent assay (ELISA), dot-ELISA, or assays in other formats OR • Identification of morulae in the cytoplasm of monocytes or macro- phages by microscopic examination 2) Human ehrlichiosis caused by E. ewingii: E. ewingii DNA detected in a clinical specimen via amplification of a specific target by poly- merase chain reaction (PCR) assay. 3) Human anaplasmosis caused by Anaplasma phagocytophilum (see separate case definition). 4) Human ehrlichiosis/anaplasmosis—undetermined. http://c.ymcdn.com/sites/www.cste.org/resource/resmgr/ps/07-id-03.pdf From: http://wwwn.cdc.gov/nndss/conditions/ehrlichiosis-and-anaplasmosis/ case-definition/2008/ Box 8.6.40.2 Case definition of human anaplasmosis by Anaplasma phagocytophilum—laboratory criteria for diagnosis Supportive: Serological evidence of elevated IgG or IgM antibody reactive with A. phagocytophilum antigen by IFA, enzyme-linked immunosorbent assay (ELISA), dot-ELISA, or assays in other formats (CDC uses an IFA IgG cutoff of ≥1:64 and does not use IgM test results independently as diag- nostic support criteria), OR Identification of morulae in the cytoplasm of neutrophils or eosinophils by microscopic examination Confirmed: • Serological evidence of a fourfold change in IgG-specific antibody titre to A. phagocytophilum antigen by indirect immunofluorescence assay (IFA) in paired serum samples (one taken in first week of illness and a second 2–4 weeks later) OR • Detection of A. phagocytophilum DNA in a clinical specimen via amp- lification of a specific target by polymerase chain reaction (PCR) assay OR • Demonstration of anaplasmal antigen in a biopsy/autopsy sample by immunohistochemical methods OR • Isolation of A. phagocytophilum from a clinical specimen in cell culture From: http://wwwn.cdc.gov/nndss/conditions/ehrlichiosis-and-anaplasmosis/ case-definition/2008/

8.6.40 Rickettsioses 1251 Increasing cases of monocytic ehrlichiosis are being reported out- side the United States of America and numerous rickettsia, ehrlichia, or anaplasma species have been identified in arthropods, particularly ticks, throughout the world, although their pathogenicity for people has yet to be demonstrated. More studies throughout the world may lead to the continuing description of emerging rickettsioses, con- comitantly developing our knowledge on a variety of

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