8.8.2 Malaria 1395

8.8.2 Malaria 1395

8.8.2 Malaria 1395 Shirley DA, Moonah S (2016). Fulminant amoebic colitis after cortico- steroid therapy: a review. PLos Negl Trop Dis, 10, e0004879. Entamoeba gingivalis and Dientamoeba fragilis Bonner M, et al. (2014). Detection of the amoeba Entamoeba gingiva lis in periodontal pockets. Parasite, 21, 30. Foda AA, et al. (2012). Prevalence of genital tract infection with Entamoeba gingivalis among copper plate T380A intrauterine device users in Egypt. Contraception, 85, 108–12. Roser D, et al. (2014). Metronidazole therapy for treating dientamoebiasis in children is not associated with better clinical outcomes: a random- ized, double-blinded and placebo-controlled clinical trial. Clin Infect Dis. 58, 1692–9. Stark D, et al. (2014). Description of Dientamoeba fragilis cyst and precyst forms in human samples. J Clin Microbiol, 52, 2680–3. Free-living amoebae Bravo SG, Alvarez PJ, Gotuzzo E (2011). Balamuthia mandrillaris infection of the skin and central nervous system: an emerging disease of concern to many specialities in medicine. Curr Opin Infect Dis, 24, 112–7. Carter RF (1972). Primary amoebic meningo-encephalitis. Trans R Soc Trop Med Hyg, 66, 193–208. Fung KT-T, et al. (2008). Cure of Acanthamoeba cerebral abscess in a liver transplant patient. Liver Transplant, 14, 308–12. Garg P, Kaira P, Joseph J (2017). Non-contact lens related Acanthamoeba keratitis. Indian J Ophthalmol, 65, 1079–86. LaFleur M, et al. (2013). Balamuthia mandrillaris meningoencephalitis associated with solid organ transplantation—a review. J Radiol Case Rep, 7, 9–18. Lorenzo-Morales J, Khan NA, Walochnik J (2015). An update on Acanthamoeba keratitis: diagnosis, pathogenesis and treatment. Parasite, 22, 10. Ong TYY, Khan NA, Siddiqui R (2017). Brain-eating amoebae: predilec- tion sites in the brain and disease outcome. J Clin Microbiol, 55, 1989–97. Panja SC, Dinoop K, Venugopal H. (2015). Management granuloma- tous amebic encephalitis: laboratory diagnosis and treatment. Trop Parasitol, 5, 23–8. Qvarnstrom Y, et el. (2009). Molecular confirmation of Sappinia pedata as a causative agent of amoebic encephalitis. J Infect Dis, 199, 1139–42. Roy SL, et al. (2014). Risk of transmission of Naegleria fowleri from solid organ transplantation. Am J Transplant, 14, 163–71. Siddiqui R, Khan NA. (2014). Primary amoebic meningoencephal- itis caused by Naegleria fowleri: an old enemy presenting new chal- lenges. PLoS Neg Trop Dis, 8, e3017. Sood A, et al. (2013). Prompt diagnosis and extraordinary survival from Naegleria fowleri meningitis: a rare case report. Ind J Med Microbiol, 32, 193–6. Visvesvara GS (2013). Infections with free-living amoebae. Handb Clin Neurol, 113, 153–68. 8.8.2 Malaria Nicholas J. White and Arjen M. Dondorp ESSENTIALS In 2015, 3.4 billion people were at risk for malaria, of which 1.1 bil- lion were at high risk. According to World Health Organization’s World Malaria Report for 2016, there were an estimated 212 million cases of malaria worldwide in 2015 with 429 000 deaths. Africa accounted for 90% of the cases and 92% of deaths; 70% of the deaths were in children aged less than 5 years. Malaria remains endemic in 91 countries. Human malaria parasites, mosquitoes, and transmission

of malaria Malaria parasites and their impact on the human genome—six species of Plasmodium commonly cause malaria in humans: P. falciparum, P. vivax, P. ovale (two species), P. malariae, and P. knowlesi. P. falciparum, the most pathogenic species accounts for 99% of malaria deaths and has exercised immense selection pressure on the human genome. Biology of the parasite and mosquito vector—sporozoites are ijected into humans during the female Anopheles mosquito's blood meal. They invade hepatocytes. Hepatic schizogony releases merozoites into the blood stream where they invade red blood corpuscles and undergo further asexual multiplications before gametocytes form. If these are ingested by mosquitoes, male and female gametes fuse, resulting in ookinetes that penetrate the mosquito's midgut and de- velop into oocysts. Daughter sporozoites are released. They invade the mosquito's salivary glands, ready to infect a new human host. Persistent latent forms (hypnozoites) of P. vivax and P. ovale remain in the liver to give rise to later relapses of parasitaemia and symptoms. Other mechanisms of transmission—malaria can also be trans- mitted by transfusion of blood products, marrow transplants, and contaminated needles. Innate resistance and immunity In most stably endemic areas, acquisition of immunity, although never complete, ensures that death due to malaria is rare after the age of 5 years and hardly ever occurs in normally immune compe- tent adults. Immunity allows tolerance of levels of parasitization that would cause illness in a naive individual. Malnutrition and advanced HIV infection increase the risk of severe falciparum malaria in children. Molecular pathology, organ pathology,
and pathophysiology Pathophysiology—intravascular, asexual forms are responsible for all the pathological effects of malaria in humans. The main pathophysio- logical hallmark of severe P. falciparum infection is the cytoadherence and sequestration of parasitized red blood cells to capillary and postcapillary venular endothelium of vital organs, especially in the brain, intestines, lungs, and kidneys, resulting in reduced perfusion and tissue damage. Anaemia results from destruction/phagocytosis of both uninfected and parasitized red blood cells, as well as from dyserythropoiesis. Thrombocytopenia is attributable to splenic se- questration, dysthrombopoiesis, and perhaps endothelial mediated binding and lysis. Pulmonary oedema may result from fluid overload, but more often there is increased pulmonary capillary permeability. Clinical features Malaria causes periodic febrile paroxysms with afebrile asymp- tomatic intervals: every other day in falciparum and vivax malaria ('tertian fever'), every second day in P. malariae ('quartian fever'). Severe falciparum malaria—defined by (1) clinical features— prostration, impaired consciousness, respiratory distress/acidotic breathing, multiple convulsions, circulatory collapse, pulmonary oe- dema, and acute respiratory distress syndrome, abnormal bleeding, jaundice, and haemoglobinuria; and (2) laboratory tests—severe

 anaemia, hypoglycaemia, metabolic acidosis, hyperlactataemia, and renal impairment, which are of proven prognostic significance. Cerebral malaria—defined by coma in patients with acute P. fal- ciparum infection in whom other causes of coma, including hypo- glycaemia and transient postictal coma, have been excluded. Convulsions, dysconjugate gaze, malaria specific retinal changes, and abnormal posturing are common. So-called benign malarias, P. ovale, P. malariae, and particularly P. vivax, can cause even more severe feverish symptoms than falcip- arum malaria. P. knowlesi, one of the monkey malarias, is increasingly recognized as an important and potentially fatal zoonosis in humans in several Southeast Asian countries. Malaria in pregnancy—malaria is an important cause of maternal anaemia and death, abortion, stillbirth, premature delivery, low birth weight, and neonatal death. Chronic immunological complications of malaria—these include

quartan malarial nephrosis, tropical splenomegaly syndrome (hyper reactive malarial splenomegaly) and endemic Burkitt's lymphoma. Diagnosis The diagnosis is made by microscopy of a peripheral blood thin or thick smear or using a rapid diagnostic antigen test. Differential diagnoses include other acute febrile illness: falciparum malaria has been misdiagnosed as influenza, viral hepatitis, epilepsy, viral encephalitis, or bacterial meningitis, sometimes with fatal consequences. Treatment Uncomplicated P. falciparum malaria in malaria endemic areas—treatment is with artemisinin combination therapies. Currently used artemisinin combination therapies include artemether– lumefantrine, dihydroartemisinin-piperaquine, artesunate-mefloquine, artesunate-amodiaquine (mainly Africa), artesunate-sulphadoxin- pyrimethamine (only selected countries in Africa), and artesunate- pyronaridine (still limited use). Resistance to artemisinins, and increasingly also to the artemisinin combination therapy partner drugs, has emerged in the Greater Mekong Subregion (Cambodia, Laos, Vietnam, Thailand, and Myanmar). Further spread westward could occur over the coming years. For presumed nonimmune travellers returning to nonendemic areas with uncomplicated falciparum malaria, artemether–lumefantrine, other artemisinin combination therapies, or atovaquone–proguanil are recommended. During first trimester pregnancy, quinine combined with clindamycin is recommended. P. vivax, P. ovale, P. malariae, P. knowlesi malarias—these are treated with chloroquine. Resistant P. vivax (New Guinea, Indonesia) is treated with artemisinin combination therapies. Radical treatment in P. vivax and P. ovale malaria, eliminating the liver hypnozoites to pre- vent relapse infections, is with a 14-day course of primaquine. Severe falciparum, vivax, and knowlesi malaria—urgent parenteral antimalarial treatment with artesunate is essential. Intramuscular artemether, or quinine by intermittent or continuous intravenous infusion or intramuscular injection are second and third choice. Quinine therapy requires a loading dose. Rectal artesunate has shown benefit as a prereferral therapy in African villages. Supportive care—patients with severe malaria should be transferred to the highest possible level of care for treatment of convulsions, hypoglycaemia, severe anaemia (by blood transfusion) and organ failure. Prevention Modern malaria control and prevention aims to limit human–vector contact by indoor residual spraying and insecticide (pyrethroid) treated nets. Repellents such as diethyltoluamide are used for per- sonal protection. Intermittent preventive treatment in pregnant women with sulphadoxine–pyrimethamine in sub-Saharan Africa improves birth weight and maternal anaemia, and such treatment of infants has been implemented in several high-transmission countries in Africa. Seasonal malaria chemoprevention in children is currently rolled out in the Sahel subregion. Malarial vaccines—the RTS,S/ASO1 P. falciparum malaria vaccine has been registered recently by the European Medicines Agency. It provides short-term protection of approximately 30–50% for one year, but declines thereafter. RTS,S is now field tested on a larger scale in several African countries (2018). Travellers—prevention of malaria in people from nonmalarious areas who are visiting endemic regions has become more difficult because of resistance to antimalarial drugs. Travellers are advised to (1) be aware of the risk; (2) prevent exposure to anopheline mosqui- toes; (3) take chemoprophylaxis where appropriate—malarone, mef- loquine, or doxycycline; in Southeast Asia mefloquine resistance in prevalent (4) seek immediate medical advice in case of any feverish illness developing while abroad, or within 3 months of returning, and to mention malaria as a possibility—regardless of the precautions taken—to any doctor who sees them. Pregnant women are best ad- vised to avoid malarious areas. Introduction Malaria is a protozoan disease transmitted by the bite of infected Anopheles mosquitoes. Malaria is the most important of the para- sitic diseases of humans. It is transmitted in 106 countries containing 3 billion people and still causes approximately 2000 deaths each day. Malaria has been eliminated from the United States, Canada,

Europe, and Russia. The global mortality has decreased over the last decade as a result of substantial increases in funding for con- trol efforts, but this progress had stalled in 2017. This follows a resurgence in malaria between the 1970s and early 2000s as a re- sult of insufficient investment and support for control activities in endemic countries, increased human population movement and worsening resistance of the malaria parasites to antimalarial drugs, and of the mosquito vectors to insecticides. Occasional local transmission after importation of malaria has occurred in Europe (notably Greece) and several southern and eastern areas of the United States, indicating the continued danger to nonmalarious countries. Malaria remains today, as it has been for centuries, a heavy burden on tropical communities, a threat to nonendemic countries, and a danger to travellers. Epidemiology Malaria occurs throughout most of the tropical regions of the world. P. falciparum predominates in Africa, New Guinea, and Hispaniola (i.e. the Dominican Republic and Haiti); P. vivax is more common

8.8.2 Malaria 1397 in Central America. The prevalence of these two species is approxi- mately equal in South America, the Indian subcontinent, eastern Asia, and Oceania. P. malariae is found in most endemic areas, es- pecially throughout sub-Saharan Africa, but is much less common. P. ovale (which comprises two species) is relatively unusual outside of Africa and, where it is found, comprises less than 1% of infections. P. knowlesi malaria occurs on the island of Borneo and to a lesser extent elsewhere in Southeast Asia. Unlike the human malarias, its main hosts are the long-tailed and pig-tailed macaques (Fig. 8.8.2.1). The epidemiology of malaria is complex and can vary consid- erably even within relatively small geographic areas (Fig. 8.8.2.2). Endemicity traditionally has been defined by the prevalence of parasitaemia or palpable spleens in children 2–9 years of age (hypoendemic: <10%, mesoendemic: 11–50%, hyperendemic: 51– 75%, and holoendemic: >75%). Many countries conduct national surveys using these indices to assess control programme progress. In holo- and hyperendemic areas (e.g. parts of tropical Africa or coastal New Guinea) where there is intense P. falciparum transmis- sion, people might receive more than one infectious mosquito bite each day. They are infected repeatedly throughout their lives. As a consequence, the morbidity and mortality due to malaria are con- siderable during early childhood. But if the child survives, immunity against disease is gradually acquired and by adulthood most malaria infections are asymptomatic. Constant, frequent, year-round infec- tion is termed stable transmission. In areas where transmission is low, erratic, or focal, full protective immunity is not acquired, and symptomatic disease may occur at all ages. This is the usual situ-ation in hypoendemic areas. It is termed unstable transmission. Even in stable transmission areas, the number of malaria cases often in- crease during the rainy season, coinciding with increased mosquito breeding. In areas with unstable malaria, such as the Punjab region of northern India, the horn of Africa, Rwanda, Burundi, southern Africa, and Madagascar, sudden environmental, social, or eco- nomic changes can cause malaria epidemics. Examples are heavy P. falciparum P. vivax P. ovale P. malariae P. knowlesi Fig. 8.8.2.1 Asexual stage parasites of the different Plasmodium species infecting humans. Courtesy Dr Kesinee Chotivanich. Fig. 8.8.2.2 (a) Global epidemiology of falciparum malaria. (b) Global epidemiology of vivax malaria.

 rains following drought, or migrations of refugees or workers from a nonmalarious region to an area of high transmission together with failure to invest in malaria control activities. Breakdowns in malaria control and prevention services caused by war or civil disorder can also cause epidemics. This usually results in considerable mortality among all age

groups if the population is nonimmune. The epidemiology of malaria is determined largely by the number (density), the human-biting habits, and the longevity of the anoph- eline mosquito vectors. The c.40 species that can transmit malaria vary considerably in their efficiency as malaria vectors. Mosquito longevity is particularly important because malaria parasite devel- opment within the mosquito—from gametocyte ingestion to sub- sequent inoculation (sporogony)—takes 8–30 days, depending on ambient temperature. Thus, to transmit malaria, the mosquito must survive for at least 7 days. Sporogony is not completed at cooler tem- peratures (i.e. <16°C for P. vivax and <21°C for P. falciparum) and so transmission does not occur below these temperatures. Malaria does not occur at high altitudes either, although malaria outbreaks and transmission have occurred in the highlands (>1500 m) of east Africa, which were previously free of vectors, possibly as a result of global warming. The most effective mosquito vectors of malaria are those, which are long-lived, occur in high densities in tropical cli- mates, breed readily, and bite humans in preference to animals. The main vector in Africa, Anopheles gambiae, is a prime example. The entomologic inoculation rate (the number of sporozoite-positive mosquito bites per person per year) is the most common measure of malaria transmission and varies from less than one in some parts of Latin America and Southeast Asia to more than 300 in parts of tropical Africa. Aetiology and pathogenesis Six species of the sporozoan (apicomplexan) genus Plasmodium cause nearly all malarial infections in humans. These are P. falcip arum, P. vivax, P. ovale, P. malariae, and—in Southeast Asia—the monkey malaria parasite P. knowlesi (Table 8.8.2.1). Recent evi- dence shows that P. ovale comprises two morphologically identical sympatric species, P. ovale curtisi and P. ovale wallikeri. P. falciparum causes most malaria deaths but P. knowlesi and occasionally P. vivax can also cause severe illness. Life cycle Human infection begins when a female anopheline mosquito in- oculates plasmodial sporozoites from its salivary gland while sucking blood (Fig. 8.8.2.3). These microscopic motile malaria parasites are carried rapidly via the bloodstream to the liver, where they invade hepatic parenchymal cells and there begin asexual reproduction. By this amplification process (known as preerythrocytic schizogony or merogony), a single sporozoite eventually produces from 10 000 to Fig. 8.8.2.2 Continued

Table 8.8.2.1 Characteristics of Plasmodium species infecting humans Speciesa P. falciparum P. vivax P. ovale P. malariae P. knowlesi Duration of intrahepatic phase (days) 5.5 8 9 15 5 Number of merozoites released per infected hepatocyte 30 000 10 000 15 000 15 000 Duration of erythrocytic cycle (hours) 48 45 50 72 24 Average number of merozoites per schizont 16 16 8 8 10 Red cell preference Younger cells (but can invade cells of all ages) Reticulocytes and cells up to 2 weeks old Reticulocytes Older red cells cells Red cells of all ages Morphology Usually only ring formsb; banana-shaped gametocytes Irregularly shaped large rings and trophozoites; enlarged erythrocytes; Schüffner’s dots Infected erythrocytes, enlarged and oval with tufted ends; Schüffner’s dots Band or rectangular forms of trophozoites Young rings resemble P. falciparum, mature trophozoites resemble P. malariae Pigment colour Black Yellow-brown Dark brown Brown-black Yellow-black Parasitaemias may exceed 2% Ability to cause relapses Yes No No Yes No Yes No No Yes No a Reliable identification, particularly with low-density ring form parasitaemia, requires molecular genotyping. b P. ovale comprises two sympatric species P. ovale wallikeri and P. ovale curtesi. Salivary gland sporozoites Midgut sporozoites Oocyst Ookinete Meiosis Zygote Gametes 2 Transmission to mosquito D Sexual stages Gametocytes Asexual cycle Ring Blood stage Liver Merozoites 105 108–1012 C Liver stage Hepatocyte invasion Sporozoites B A Infection 10 Inoculation Mosquito stage 5 x 104 0–6 H 6–16 H 16–26 H 26–30 H 30–34 H 34–38 H 38–44 H 44–48 H (a) (b) Fig. 8.8.2.3 Lifecycle of Plasmodium falciparum. Female anopheline mosquitoes inoculate

around 10 motile sporozoites into the dermis (a), which invade hepatocytes within one hour (b). Within the hepatocyte, each sporozoite produces a liver schizont with 10 000 to 30 000 nuclei. After about a week, the liver schizonts ruptures, together releasing around 100 000 merozoites into the bloodstream that invade red blood cells and begin the asexual cycle (c). During the asexual cycle (48-hours in P. falciparum; inset), the parasite develops from a small ring, to a trophozoite (when malaria pigment becomes visible), to a schizont stage (when the nucleus starts to divide). At schizont rupture around 10 new erythrocytes are being infected, resulting in a multiplication factor of around 10 every 48 hours. Illness starts when total asexual parasite numbers in the circulation reach roughly 100 million. After a few cycles, some parasites develop into sexual forms (gametocytes), which are taken up by a feeding anopheline mosquito (d) and reproduce sexually, forming an ookinete, and then an oocyst in the mosquito gut. The oocyst bursts and liberates sporozoites, which migrate to the salivary glands to await inoculation at the next blood feed. The entire cycle can take roughly 1 month. Estimated numbers of parasites are shown in boxes—a total body parasite burden of 10^{12} corresponds to roughly 2% parasitaemia in an adult. Reprinted from The Lancet, Vol. 383, White NJ et al., Malaria, pages 723–735, Copyright © 2014, with permission from Elsevier.

section 8 Infectious diseases 1400 more than 30 000 daughter merozoites. The swollen infected liver cell eventually bursts, discharging the motile merozoites into the bloodstream where they invade red blood cells. They progressively consume the red cell contents and so develop from tiny ring forms into large malaria pigment-containing trophozoites, and then start nuclear division, thereby becoming schizonts. This erythrocytic life cycle takes 48 h for P. falciparum, P, vivax, and P. ovale, but 24 h for P. knowlesi, and 72 h for P. malariae. After erythrocyte schizont rupture, the released merozoites rapidly invade new erythrocytes, resulting in a multiplication rate of around 10 per cycle in non- immune hosts. When the logarithmically expanding parasite num- bers reach densities of c.50/μl of blood (c.100 million parasites in the blood of an adult), the symptomatic stage of the malaria infec- tion begins. In P. vivax and P. ovale infections, a proportion of the intrahepatic forms do not divide immediately but remain inert for a period ranging from 3 weeks to a year or longer before reproduction begins. These dormant forms, or hypnozoites, are the cause of the re- lapses that characterize infection with these two species. Merozoite invasion requires attachment to specific erythrocyte surface receptors (the glycophorins are particularly important). For P. falciparum erythrocyte invasion is dependent on the reticulocyte- binding protein homologue 5 (PfRh5), for which basigin (CD147, EMMPRIN) is the erythrocyte receptor. In P. vivax, this receptor ap- pears to be CD71 with an important supporting role from the Duffy blood-group antigen Fya or Fyb. Most West Africans and people with origins in that region have the Duffy-negative FyFy phenotype and are therefore largely resistant to P. vivax malaria. During the early stage of intraerythrocytic development, the small ‘ring forms’ of the different parasite species appear very similar under light micros- copy. But as the trophozoites grow, species-specific characteristics become evident, malaria pigment (the waste product of digested haemoglobin) becomes visible, and the parasite assumes an irregular or amoeboid shape. Then multiple nuclear divisions take place (schi zogony or merogony) before the schizont ruptures releasing 6–30 daughter merozoites, each potentially capable of invading a new red blood cell and repeating the asexual cycle. The disease malaria in human beings is caused by the direct effects of red blood cell invasion and destruction by the asexual parasite and the host’s reaction. Only in P. falciparum malaria, which causes most severe disease, erythrocytes containing the more mature asexual stage parasites sequester in the microcirculation impairing tissue flow. This process is central to pathogenesis.

After release from the liver some of the blood stage parasites develop into mor- phologically distinct, longer-lived sexual forms (gametocytes) that can transmit malaria. In falciparum malaria there is a delay of sev- eral asexual cycles before this switch to gametocytogenesis, and the developing gametocytes (stages 1 to 4) are sequestered for about one week– particularly in the bone marrow. Only the stage 5 P. fal ciparum gametocytes circulate. There are usually 3 to 5 times more female gametocytes than males in the blood. After ingestion by a feeding mosquito each male gametocyte will undergo three rounds of rapid mitosis and produce eight flagellated microgametes each capable of fertilizing a female macrogamete. In the female anopheline mosquito the male and female gametes fuse to form a zygote in the insect's midgut. This zygote matures into an ookinete, which penetrates and encysts in the mosquito's gut wall. The resulting oocyst expands by asexual division until it bursts to liberate myriad motile sporozoites, which migrate in the mosquito hemolymph to the salivary glands to await inoculation into another human at the next feeding. Pathogenesis After red cell invasion, the growing malarial parasite progressively consumes and degrades the erythrocyte proteins. By the end of the intraerythrocytic life cycle, the parasite has consumed two-thirds of the cell's haemoglobin. The potentially toxic haem is detoxified by lipid-mediated crystallization to biologically inert haemozoin (malaria pigment). The parasite also modifies the red cell mem- brane by changing its transport properties, revealing cryptic sur- face antigens, and inserting new parasite-derived proteins. The erythrocyte becomes more irregular in shape, more antigenic, and in P. falciparum infections it becomes less deformable, as most of the erythrocyte volume becomes occupied by the rigid schizont. In contrast, P. vivax enlarges the infected erythrocyte making it more deformable. In P. falciparum infections, membrane protuberances appear on the erythrocyte's surface 12–15 h after the cell's invasion. These 'knobs' extrude a high-molecular-weight, strain-specific, antigenically variant, erythrocyte membrane adhesive protein (PfEMP1) that adheres to receptors on venular and capillary endothelium—a pro- cess termed cytoadherence (Fig. 8.8.2.4). Several vascular receptors have been identified, of which endothelial protein C receptor and intercellular adhesion molecule 1 (ICAM-1) are important recep- tors on brain endothelium, chondroitin sulfate B on the placenta syncytiotrophoblast, and CD36 on the vascular endothelium of most other organs. Cytoadherence compromises blood flow in capillaries and venules and causes endothelial activation. At the same stage of parasite development, these P. falciparum-infected red cells can also adhere to uninfected red blood cells (to form rosettes) and might agglutinate with other parasitized erythrocytes. These processes of cytoadherence, rosetting, and agglutination are central to the patho- genesis of falciparum malaria. They result in the sequestration of Fig. 8.8.2.4 Electron microscopic photograph of a post-mortem brain biopsy, showing a P. falciparum trophozoite stage infected erythrocyte cytoadhered to the endothelium, causing partial obstruction of the capillary. Courtesy Dr Emsri Pongponratn.

 erythrocytes containing mature forms of the parasite in vital or- gans (particularly the brain), interfering with microcirculatory flow, tissue oxygenation, and metabolism. Sequestered parasites develop out of reach of the principal host defence mechanism: splenic pro- cessing and filtration. As a consequence, only the younger ring forms of the asexual parasites are seen circulating in the peripheral blood in falciparum malaria. This means that the level of periph- eral parasitaemia can underestimate considerably the true number of parasites within the body. Severe malaria is also associated with reduced deformability of the uninfected erythrocytes, which com- promises their passage through the partially obstructed capillaries and venules and shortens their survival. In the other human malarias, significant sequestration does not occur, and so all

stages of the parasites' development are evident on peripheral blood smears. However, all the malarias cause rosetting. Whereas P. vivax, P. ovale, and P. malariae show a marked predilec- tion for either young red blood cells (P. vivax, P. ovale) or old cells (P. malariae) and produce parasitaemias that seldom exceed 2%, P. falciparum and P. knowlesi can invade erythrocytes of all ages and can cause very high—and often lethal parasite densities. Host responses Initially, the host responds to malaria infection by activating non- specific defence mechanisms. Splenic immunologic and filtrative clearance functions are augmented in malaria, and the removal of both parasitized and uninfected erythrocytes is accelerated. The spleen is able to remove damaged ring form parasites ('pitting') and return the once infected erythrocytes to the circulation, where they have shortened survival. The parasitized cells escaping splenic removal are destroyed when the schizont ruptures. The material released by the bursting schizonts induces the activation of leuko- cytes and complement factors and the release of proinflammatory cytokines, which cause fever, and exert other pathologic effects. Temperatures of ≥40°C damage mature parasites; in untreated in- fections these temperatures further synchronize the asexual parasite cycle, with eventual production of the regular fever spikes and rigors that originally characterized the different malarias. These regular fever patterns (quotidian, daily; tertian, every 2 days; quartan, every 3 days) are seldom seen today in patients who receive prompt and effective antimalarial treatment. The global distributions of the haemoglobinopathies (thalassaemias, sickle cell disease, haemoglobins C and E, hereditary ovalocytosis) and glucose-6-phosphate dehydrogenase (G6PD) deficiency closely resemble the world map of malaria over a century ago (before large control initiatives). These genetic disorders evolved to confer protec- tion against death from malaria. For example, HbA/S heterozygotes (sickle cell trait) have a sixfold reduction in the risk of dying from se- vere falciparum malaria. HbA/S impairs parasite growth at low oxygen tensions and P. falciparum-infected red cells containing haemoglobins S and C have reduced cytoadherence because of reduced surface pres- entation and disturbed organization of the cytoadhesion molecule PfEMP1. Parasite multiplication in HbA/E heterozygotes is reduced at high parasite densities. In Melanesia, children with α-thalassemia have more frequent malaria (both vivax and falciparum) in the early years of life, and this pattern of infection appears to protect them against severe disease. In Melanesian ovalocytosis, rigid erythrocytes resist merozoite invasion, and provide a hostile intraerythrocytic milieu for the parasite. Malaria has evolved to avoid the immune response. As a result, immunity to malaria is slowly acquired and imperfect. Both hu- moral immunity and cellular immunity are necessary for protection, but the mechanisms of each are incompletely understood. Initially nonspecific host defence mechanisms stop the exponential expan- sion of malaria parasite numbers, and the subsequent strain-specific immune response later controls the infection. Eventually, with re- peated infections, exposure to sufficient numbers of strains confers protection from high-level parasitaemia and disease, but not from infection. As a result of this infection without illness (premunition), asymptomatic parasitaemia is common among adults and older children living in malaria endemic regions. The more intense the transmission, the earlier in life is this 'illness protecting' immunity acquired (Fig. 8.8.2.5). Gradually species and then strain-specific immunity is acquired against local parasites. This protects against infection. Some immunity is also gradually acquired against the preerythrocytic liver stage and the sexual stage of the infection. Immune individuals have a polyclonal elevation in serum IgM, IgG, and IgA, although much of this antibody is unrelated to protection. Antibodies to a variety of parasitic antigens limit in vivo replica- tion of the parasite. In the case of falciparum malaria, one of the most important antigens is the variant surface cytoadhesion protein PfEMP1. Passive transfer of maternal antibody contributes to the relative protection of infants from severe malaria in the first months of life. This complex

immunity to disease declines when a person lives outside an endemic area for several months or longer. Several factors slow the development of cellular immunity to mal- aria; these include the absence of major histocompatibility antigens on red cells precluding direct T cell recognition; malaria antigen- specific immune unresponsiveness; reduced formation of long-lived plasma cells and memory B-cells, the enormous strain diversity of malarial parasites, and redundancy of surface protein functions, all of which is compounded by the ability of the parasites to express Severe Mild Parasitaemia 100 80 60 40 20 0 0 5 10 15 20 25 30 35 40 45 50 Age Maximum response (%) Fig. 8.8.2.5 Clinical manifestations of P. falciparum infection in relation to age in an area of moderate to high-transmission intensity. With repeated exposure protection is acquired, first against severe malaria, then against illness with malaria, and, much more slowly, against microscopy-detectable parasitaemia. Modified with permission from Marsh K and Kinyanjui S (2009). Immune effector mechanisms in malaria. Parasite Immunology 28, pages 51–60, Copyright © 2005, John Wiley and Sons.

section 8 Infectious diseases 1402 variant immunodominant antigens on the erythrocyte surface that change during the infection. Parasites may persist in the blood for months or sometimes years (or, in the case of P. malariae, for life) if treatment is not given. These factors have all contributed to the slow progress toward an effective vaccine. Clinical features Malaria is a very common cause of fever in tropical countries. The first symptoms of malaria are nonspecific; the lack of a sense of well-being, fatigue, headache, abdominal discomfort, and muscle aches followed by fever are all similar to the symptoms of a minor viral illness. Sometimes prominent headache, chest pain, abdom- inal pain, cough, arthralgia, myalgia, or diarrhoea may suggest a different diagnosis. Although headache can be severe in malaria, there is no neck stiffness or photophobia as in meningitis. Myalgia might be prominent, but it usually milder than in dengue fever, and the muscles are not tender as in leptospirosis or typhus. Nausea, vomiting, and orthostatic hypotension are common. The classic malarial paroxysms, in which fever spikes, chills, and rigors occur at regular intervals, are relatively unusual, and suggest relapse infection with P. vivax or P. ovale. The fever is initially irregular (that of falcip- arum malaria may never become regular); in nonimmune individ- uals pyrexia often rises above 40°C with tachycardia and, sometimes, delirium. Although childhood febrile convulsions might occur with any malaria, generalized seizures are specifically associated with falciparum malaria and may herald the development of encephal- opathy (cerebral malaria). Many clinical abnormalities have been described in acute malaria, but most patients have few abnormal physical findings initially other than fever, malaise, mild anaemia, and (in some cases) a palpable spleen. This is sometimes called ‘un- differentiated fever’. Anaemia is common among young children living in areas with stable malaria transmission, particularly where antimalarial drug resistance results in recurrent infections. In acute malaria, the spleen enlarges but usually takes several days to become palpable. In malaria endemic areas splenic enlargement is found in a high proportion of otherwise healthy individuals as a result of re- peated infections. Hepatomegaly is also common, particularly in young children. Mild jaundice is common among adults; it may de- velop in patients with otherwise uncomplicated malaria and usu- ally resolves over 1–3 weeks. Malaria is not associated with a rash, differentiating it from meningococcal septicaemia, rickettsial infec- tions, enteric fever, viral exanthems, and drug reactions. Petechial haemorrhages in the skin or mucous membranes—features of viral haemorrhagic fevers and leptospirosis—develop only very rarely in severe falciparum malaria. Diagnosis The diagnosis of malaria requires demonstration of asexual forms of the parasite in suitably stained peripheral blood smears, or de- tection of blood stage antigens by rapid diagnostic tests (RDTs) (Fig. 8.8.2.6; Table

8.8.2.2). After a negative blood smear, repeat smears should be made if there is a high degree of suspicion. Both thin and thick blood smears should be examined. The thin blood smear should be air-dried rapidly, fixed in anhydrous methanol, and stained; the red cells in the tail of the film should then be examined under oil immersion (×1000 magnification). The parasite density is recorded as the number of parasitized erythrocytes per 1000 red cells. The thick blood film has the advantage of concentrating the parasites (by 40- to 100-fold compared with a thin blood film) and thus increasing diagnostic sensitivity. The thick film should be of uneven thickness. It should be dried thoroughly and stained without fixing. Both parasites and white blood cells are counted, and the number of parasites per unit volume is calculated from the total leukocyte count (or assuming a white blood cell count of 8000/µl). A minimum of 200 white blood cells should be counted under oil immersion. Interpretation of blood films requires some experience because artefacts are common. Before a thick smear is called nega- tive, 100–200 fields should be examined under oil immersion mi- croscopy. In high-transmission areas, parasite densities up to 10 000 parasites/µl of blood may be tolerated without symptoms or signs in partially immune individuals. In these areas the detection of malaria parasites is sensitive but has low specificity in identifying malaria as the cause of illness because incidental low-density parasitaemia is commonly found in other conditions causing fever. Rapid, simple, sensitive, and specific antibody-based RDTs that detect P. falciparum–specific, histidine-rich protein 2 (PfHRP2), lactate dehydrogenase or aldolase antigens in finger-prick blood samples are now being used widely in malaria control programmes (Fig. 8.8.2.6). Some of these RDTs carry a second antibody, which allows falciparum malaria to be distinguished from the less dan- gerous malarias. PfHRP2-based tests may remain positive for several weeks after acute infection. This is a disadvantage in high-transmission areas where infections are frequent, but is useful in the diagnosis of Thin film Thick film Rapid diagnostic test Result window Well for blood sample Well for buffer solution Contol line (C) Test line (T) Fig. 8.8.2.6 Giemsa stained peripheral blood slide, showing with 400x magnification in the thin film large ring stage P. falciparum parasites inside red blood cells (some with multiple invasion), and in the (haemolysed) thick film more concentrated ring stage parasites amid two white blood cells. In the lower panel, an example of a rapid diagnostic test with a positive test result.

8.8.2 Malaria 1403 severe malaria in patients who have taken antimalarial drugs and cleared peripheral parasitaemia (but in whom the PfHRP2 test re- mains strongly positive). RDTs are replacing microscopy in many areas because of their simplicity and speed, and similar sensitivity. The disadvantage is that they do not quantify peripheral blood para- sitaemia PfHRP2-based tests can be falsely negative in P. falcip arum infections with PfHRP2 gene deletions, reported mainly from South-America as well as increasingly from Africa. Prognosis In falciparum malaria patients with more than 105 parasites/µl (c.2% parasitaemia) are at increased risk of dying, but as the peripheral blood parasitaemia variably underestimates the total body parasite burden because of the sequestration which is responsible for organ dysfunc- tion, nonimmune patients may die with much lower counts. Conversely partially immune persons may tolerate relatively high parasitaemias with only minor symptoms. In severe falciparum malaria, a poorer prognosis is indicated at any parasite density by a predominance of more mature P. falciparum parasites (i.e. >20% of parasites with visible pigment) in the peripheral blood film and by the presence of phagocyt- osed malarial pigment in more than 5% of neutrophils. In P. falciparum infections, gametocytaemia peaks one week after the peak of asexual parasites. The mature gametocytes of P. falcip arum are not affected by most antimalarial drugs (whereas those of the other malarias are), so their persistence does not indicate drug resistance. Phagocytosed malarial pigment in

peripheral blood monocytes can provide a clue to recent infection if malaria parasites are not detectable. Molecular diagnosis by polymerase chain reaction (PCR) ampli- fication of parasite nucleic acid is more sensitive than microscopy or RDTs for detecting low-density malaria parasitaemia and is more ac- curate in speciation. In parts of Southeast Asia, PCR is important in the identification of P. knowlesi, which mimics P. malariae morphologic- ally. In malaria endemic areas PCR is mostly used in reference centres, although loop-mediated isothermal amplification is a low technology PCR variant adapted to the resource-poor setting. Sensitive PCR Table 8.8.2.2 Methods for the diagnosis of malariaa Method Procedure Advantages Disadvantages Thick blood filmb Round blood spot (1–2 cm2) should be of uneven thickness but sufficiently thin to read the hands of a watch through part of the spot. Stain well dried, unfixed blood spot with Giemsa, Field's, or another Romanowsky stain. Count the number of asexual parasites per 200 WBCs (or per 500 at low densities) at ×1000 magnification. Count the gametocytes separately.c Sensitive (0.001% parasitaemia); species specific; inexpensive Requires experience (artefacts may be misinterpreted as low-level parasitaemia); underestimates true count Thin blood filmd Stain fixed smear with Giemsa, Field's, or another Romanowsky stain. Count the number of RBCs containing asexual parasites per 1000 RBCs at ×1000 magnification. In severe malaria, assess stage of parasite development and count neutrophils containing malaria pigment.e Count gametocytes separately.c Rapid; species specific; inexpensive; in severe malaria, provides prognostic informatione Insensitive (<0.05% parasitaemia); uneven distribution of P. vivax, as enlarged infected red cells concentrate at leading edge Plasmodium LDH dipstick or card test A drop of blood is placed on the stick or card, which is then immersed in washing solutions. Monoclonal antibodies capture the parasite antigens and read out as coloured bands. One band is genus specific (all malarias) or P. vivax specific, and the other is specific for P. falciparum. Rapid; sensitivity similar to or slightly lower than that of thick films for P. falciparum (c.0.001% parasitaemia) Slightly more difficult preparation than PfHRP2 tests; may miss low-level parasitaemia with P. vivax, P. ovale, and P. malariae and may not speciate these organisms; does not quantitate P. falciparum parasitaemia. PfHRP2 dipstick or
card test A drop of blood is placed on the stick or card, which is then immersed in washing solutions. Monoclonal antibody captures the parasite antigen and reads out as a coloured band. Robust and relatively inexpensive; rapid; sensitivity similar to or slightly lower than that of thick films (c.0.001% parasitaemia) Detects only Plasmodium falciparum; remains positive for weeks after infectionf; does not quantitate P. falciparum parasitaemia. Increasing reports of PfHRP2 gene deltions in
P. falciparum, causing a false negative test result Microtube concentration methods with acridine orange staining Blood is collected in a specialized tube containing acridine orange, anticoagulant, and a float. After centrifugation, which concentrates the parasitized cells around the float, fluorescence microscopy is performed. Sensitivity similar or superior to that of thick films (c.0.001% parasitaemia); ideal for processing large numbers of samples rapidly Does not speciate or quantitate; requires fluorescence microscopy LDH, lactate dehydrogenase; PfHRP2, P. falciparum histidine-rich protein 2; RBCs, red blood cells; WBCs, white blood cells. a Malaria cannot be diagnosed clinically with accuracy, but treatment should be started on clinical grounds if laboratory confirmation is likely to be delayed. In areas where malaria transmission is high, low-level asymptomatic parasitaemia is common in otherwise healthy people. Thus finding a positive test for malaria does not necessarily mean it is the cause of a fever, although in this context the presence of >10 000 parasites/μl (c.0.2% parasitaemia) does indicate that malaria is the likely cause of illness. Antibody and polymerase chain reaction tests have no role in the diagnosis of malaria

except that PCR is increasingly used for genotyping and speciation in mixed infections, and for detection of low-density parasitaemias in asymptomatic residents of endemic areas. b. Clean blood slides and filtered fresh stains should be used. Asexual parasites/200 WBCs × 40 = parasite count/µl (assumes a WBC count of 8000/µl). c P. falciparum gametocytaemia may persist for days or weeks after clearance of asexual parasites. Gametocytaemia without asexual parasitaemia does not indicate active infection. d Clean blood slides and filtered fresh stains should be used. Parasitized RBCs (%) × haematocrit × 1256 = parasite count/µl. e Parasite densities of >100 000 parasites/µl (c.2% parasitaemia) are associated with an increased risk of severe malaria, but some patients have severe malaria with lower counts. At any level of parasitaemia, if >50% of parasites are tiny rings (cytoplasm width less than half of nucleus width) carries a relatively good prognosis whereas if there is visible pigment in >20% of parasites or phagocytosed pigment in >5% of polymorphonuclear leukocytes (indicating massive recent schizogony) the prognosis is worse. f Slow clearance of PfHRP2 may result in false positive results in patients who have recently recovered from malaria but fall ill again (common in high-transmission settings), but can be used to diagnostic advantage in low-transmission settings when a sick patient has already received antimalarial drugs treatment. A positive PfHRP2 test indicates that the illness is falciparum malaria, even if the blood smear is negative.

section 8 Infectious diseases 1404 detection can be used in epidemiological surveys to identify asymp- tomatic infections to guide elimination initiatives. Malaria antibody measurement using either IFA or ELISA assays may have a role in future epidemiological studies as measures of transmission intensity, but serology has no place in the diagnosis of acute malaria illness. Severe falciparum malaria Appropriately and promptly treated, uncomplicated falciparum mal- aria (i.e. the patient can swallow medicines and food) carries a mor- tality rate of less than 0.1%. However, once vital organ dysfunction occurs or the total proportion of erythrocytes infected increases to more than 2% (a level corresponding to >1012 parasites in an adult), mortality risk rises steeply. The major manifestations of severe falcip- arum malaria are shown in Table 8.8.2.3, and features indicating a poor prognosis are listed in Table 8.8.2.4. Severe malaria is a multiorgan dis- ease; and the organ systems involved vary by age group (Table 8.8.2.5, Fig. 8.8.2.7). Severe anaemia and hypoglycaemia are common mani- festations in small children whereas deep jaundice, renal failure, and pulmonary oedema are more common in adult patients. Coma and metabolic (lactic) acidosis are common in both children and adults, and have the strongest prognostic significance for death. Cerebral malaria Coma is a characteristic and ominous feature of falciparum mal- aria and, despite treatment, is associated with death rates of 15–20% among adults and 10–15% among children. Any obtundation, de- lirium, or abnormal behaviour should be taken very seriously. The onset may be gradual or sudden following a convulsion. Cerebral malaria is a diffuse symmetric encephalopathy; focal neurologic signs are unusual (Fig. 8.8.2.8). Some passive resistance to head flexion may be detected but signs of meningeal irritation are absent. The eyes may be divergent. The corneal reflexes are pre- served, except in deep coma. A pout reflex is common, but other primitive reflexes are usually absent. Muscle tone can be increased or decreased. The tendon reflexes are variable, and the plantar re- flexes can be flexor or extensor; the abdominal and cremasteric reflexes are absent. Flexor or extensor posturing might occur. On funduscopy, c.15% of patients have retinal haemorrhages, but with pupillary dilatation and indirect ophthalmoscopy the preva- lence is much higher (30–40%). Other funduscopic abnormalities (Fig. 8.8.2.9) include retinal whitening due to capillary obstruction, discrete spots of retinal opacification (30–60%), papilloedema (8% among children, rare among adults), cotton wool spots (<5%), and

decolourization of part or all of a retinal vessel of vessel (occasional cases in paediatric cases). Generalized, and often repeated, convulsions occur in c.10% of adults and up to 50% of children with cerebral malaria. More covert seizure activity is common, particularly among children, and may manifest as repetitive tonic-clonic eye movements or hypersalivation. Adults rarely suffer neurologic sequelae (in <3% of cases), but c.10% of children surviving cerebral malaria—especially those with hypoglycaemia, severe anaemia, repeated Table 8.8.2.3 Manifestations of severe falciparum malaria Signs Manifestations Major Unarousable coma/cerebral malaria Failure to localize or respond appropriately to noxious stimuli; coma persisting for >30 min after generalized convulsion. Adults: Glasgow Coma scale <11, young children: Blantyre coma scale <3 Acidaemia/acidosis Arterial pH of <7.25, plasma bicarbonate of <15 mmol/litre or venous lactate >5 mmol/litre; manifests clinically as laboured deep breathing, often termed ‘respiratory distress’ Severe normochromic, normocytic anaemia Haematocrit of <15% or haemoglobin <50 g/litre (<5 g/dl) with parasitaemia >10 000/µl Renal failure Serum or plasma creatinine level of >265 µmol/litre (>3 mg/dl) in the adult patienta. Urine output (24 h) of <400 ml in adults or <12 ml/kg in children; nonoliguric renal failure is also common;
no improvement with rehydration Pulmonary oedema/adult respiratory distress syndrome Noncardiogenic pulmonary oedema, often aggravated by overhydration Hypoglycaemia Plasma glucose <2.2 mmol/litre (<40 mg/dl) Hypotension/shock Systolic blood pressure of <50 mmHg in children 1–5 years or <80 mmHg in adults; core/skin temperature difference of >10°C; capillary refill >2 s Bleeding/disseminated intravascular coagulation Significant bleeding and haemorrhage from the gums, nose, and gastrointestinal tract and/or evidence of disseminated intravascular coagulation Other manifestations Convulsions More than two generalized seizures in 24 h; signs of continued seizure activity sometimes subtle (e.g. tonic-clonic eye movements without limb or face movement) Extreme weakness Prostration; inability to sit unaidedb Hyperparasitaemia Parasitaemia level of >5% in nonimmune patients (>10% in any patient) Jaundice Serum bilirubin level of >50 mmol/litre (>3 mg/dl) with a parasite density of 100 000/ul or other evidence of vital organ dysfunction a Normal range is lower in children so the threshold for diagnosing kidney injury in paediatric patients should be correspondingly lower. b In a child who is normally able to sit.

8.8.2 Malaria 1405 seizures, and deep coma—have an evident residual neurologic deficit when they regain consciousness; hemiplegia, cerebral palsy, cortical blindness, deafness, and impaired cognition may all occur. Most of these neurological deficits improve significantly or resolve completely within 6 months. Meanwhile the prevalence of other deficits increases; approximately 10% of children surviving cere- bral malaria have a persistent language deficit. There may also be deficits in learning, planning, and executive functions, attention, memory, and nonverbal functioning. The incidence of epilepsy is increased, and the life expectancy of paediatric cerebral malaria survivors is decreased. Hypoglycaemia Hypoglycaemia is an important and common complication of se- vere malaria. It is associated with a poor prognosis and is particu- larly problematic in children and pregnant women. Hypoglycaemia in malaria results from a failure of hepatic gluconeogenesis and an increase in the consumption of glucose mainly by the host. To compound the situation, quinine, which is still widely used for the treatment of both severe and uncomplicated falciparum malaria, is a powerful stimulant of pancreatic insulin secretion. Hyperinsulinaemic hypoglycaemia is especially troublesome in pregnant women receiving quinine treatment. In severe disease, the clinical diagnosis of hypoglycaemia is difficult: the usual physical signs (sweating, gooseflesh, tachycardia) can be absent, and the neurologic impairment caused by hypoglycaemia cannot be distin- guished from that caused by cerebral malaria. Acidosis Acidotic

breathing, often described as respiratory distress, is a sign of poor prognosis in severe malaria. It is often followed by circu- latory failure unresponsive to volume expansion or inotropic drug treatment, and ultimately by respiratory arrest. Acidosis results from accumulation of organic acids, in particular lactic acid. Lactic acid- osis is caused by the combination of anaerobic glycolysis in tissues where sequestered parasites interfere with microcirculatory flow, lactate production by the parasites, and a failure of hepatic and renal lactate clearance. Hypovolaemia is not a major contributor. Severe hyperlacataemia commonly coexists with hypoglycaemia. In adults acidosis is often compounded by coexisting renal dysfunction; in children, ketoacidosis may also contribute. Other still-unidentified organic acids are important contributors to acidosis. The plasma concentrations of bicarbonate or lactate or the 'base deficit' are the Table 8.8.2.4 Clinical and laboratory features indicating a poor prognosis in severe falciparum malaria Clinical Haematology Biochemistry Parasitology Deep coma Severe anaemia (PCV <15%) Hyperlactataemia (>5 mmol/litre) Increased mortality is associated with: parasitaemia >100 000/µl Marked agitation Leukocytosis (>12 000/µl) Acidosis (arterial pH <7.3, serum HCO3 <15 mmol/litre) High mortality at >500 000/µl Repeated convulsions Severe thrombocytopenia (<50 000/ul) Hypoglycaemia (<2.2 mmol/litre)

> 20% of parasites identified as pigment-containing trophozoites and schizonts Laboured hyperventilation (respiratory distress) Prolonged prothrombin time (>3 s) Elevated serum creatinine (>265 µmol/litre) 5% of neutrophils with visible pigment Hypothermia (<36.5°C) Prolonged partial thromboplastin time Elevated urate (>600 µmol/litre) High plasma PfHRP2 Shock Decreased fibrinogen (<200 mg/dl) Elevated transaminases (AST/ALT 3 times upper limit of normal) Bleeding Elevated total bilirubin (>50 µmol/litre) Anuria Elevated muscle enzymes (CPK ↑, myoglobin ↑) PCV, packed cell volume; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CPK, creatine phosphokinase. Table 8.8.2.5 Relative incidence of severe complications of falciparum malaria Complication Nonpregnant adults Pregnant women Children Anaemia

- ++ +++ Convulsions + + +++ Hypoglycaemia + +++ +++ Jaundice +++ +++ + Renal failure +++ +++ − Pulmonary oedema ++ +++ + Note: −, rare; +, infrequent; ++, frequent; +++, very frequent. 60% 40% 20% 0% 0 5 10 20 30 40 60 50 Age (years) Proportion of patients Jaundice Renal failure Anaemia Shock Acidosis Convulsions Hypoglycaemia Coma Pulmonary oedema ? Fig. 8.8.2.7 The different manifestations of severe falciparum malaria, according to patient age. Reprinted from The Lancet, Vol. 383, White NJ et al., Malaria, pages 723–735, Copyright © 2014, with permission from Elsevier.

 best biochemical prognosticators in severe malaria. The prognosis of severe acidosis is poor. Noncardiogenic pulmonary oedema Adults with severe falciparum malaria might develop noncardiogenic pulmonary oedema even after several days of antimalarial therapy. The pathogenesis of this form of the acute respiratory distress syn- drome is unclear. Although it is well recognized in adult patients, pulmonary oedema might be underrecognized in paediatric severe malaria. The mortality rate is more than 80% and higher in

the absence of positive pressure mechanical ventilation. Malaria non- cardiogenic pulmonary oedema can be aggravated by overly vig- orous administration of IV fluid. Pulmonary oedema can also develop in otherwise uncomplicated vivax malaria, where the prog- nosis is substantially better. Renal impairment Acute kidney injury is common in severe falciparum malaria, but oliguric renal failure is rare among children. The patho- genesis of malaria renal failure is unclear but may be related to erythrocyte sequestration and agglutination interfering with renal microcirculatory flow and oxidative damage by free haem. Clinically and pathologically, this syndrome manifests as acute tubular ne- crosis. Renal cortical necrosis never develops. Acute renal failure might occur simultaneously with other vital organ dysfunction (in which case the mortality is high) or may progress as other disease manifestations resolve. In survivors, urine flow resumes in a median of 4 days, and serum creatinine levels return to normal in a mean of 17 days. Early dialysis or hemofiltration considerably enhances the likelihood of survival. Haematologic abnormalities Anaemia results from accelerated red cell removal by the spleen, ob- ligatory erythrocyte destruction at parasite schizogony, and in re- peated infections from ineffective erythropoiesis. In severe malaria, both infected and uninfected red cells have reduced deformability, which correlates with prognosis and the development of anaemia. The survival of all red cells is shortened in severe malaria. In pa- tients with little or no pre-existing immunity, anaemia can develop rapidly, and transfusion is often required. Some patients have such severe haemolysis that haemoglobinuria results (blackwater fever). In many areas of Africa and on the island of New Guinea children have repeated malarial infections and commonly develop severe an- aemia as a result of both shortened survival of uninfected red cells and marked dyserythropoiesis. Anaemia is a common consequence of antimalarial drug resistance, which results in repeated or con- tinued infection. Moderate coagulation abnormalities are common in falciparum malaria, and mild thrombocytopenia is usual (a normal platelet count should question the diagnosis of malaria). Profound thrombo- cytopenia can occur in severe malaria (<20 000/μl). In adult patients with severe malaria, less than 5% have significant bleeding with evidence of disseminated intravascular coagulation. Hematemesis from stress ulceration or acute gastric erosions might also occur. Liver dysfunction Mild haemolytic jaundice from unconjugated bilirubin is common in malaria. Severe jaundice is associated with P. falciparum infections and is more common in adults than among children. It results from haemolysis, hepatocyte injury, and cholestasis. When accompanied by other vital organ dysfunction (often renal impairment), liver dys- function carries a poor prognosis. Hepatic dysfunction contributes to hypoglycaemia, lactic acidosis, and impaired drug metabolism. Fig. 8.8.2.8 Examples of patients with cerebral malaria. Left: adult Asian patient with unrousable coma, without signs of lateralization. Middle: African child with cerebral malaria and decerebrate posturing. Right: African child with cerebral malaria and decorticate posturing. (a) (b) Fig. 8.8.2.9 Malaria retinopathy. Left panel: indirect ophthalmoscopy picture showing small haemorrages, and peripheral retinal whitening. These areas correspond to the filling defects in the fluorescent angiogram shown in the right panel. Reprinted from The Lancet Infectious Diseases, Vol. 10, Glover SJ et al., Malarial retinopathy and fluorescein angiography findings in a Malawian child with cerebral malaria, page 440, Copyright © 2010, with permission from Elsevier.

 Occasional patients with falciparum malaria may develop deep jaundice (with haemolytic, hepatic, and cholestatic components) without evidence of other vital organ dysfunction, in which case the prognosis is good. Other complications Septicaemia may complicate severe malaria, particularly in chil- dren. Up to 20% have concomitant bacteraemia. Differentiating severe malaria from sepsis with incidental parasitaemia in child- hood is very difficult. In endemic

areas, nontyphoid Salmonella and Strep. pneumoniae bacteraemia, have been associated specifically with P. falciparum infections. Chest infections and catheter-induced urinary tract infections are common among hospitalized patients who are unconscious for more than 3 days. Aspiration pneumonia may follow generalized convulsions. HIV/AIDS and malnutrition predispose to more severe malaria. Malaria anaemia is worsened by concurrent infections with intestinal helminths (hookworm in particular). Some residents of malaria endemic areas in tropical Africa and Asia exhibit an abnormal immunologic response to repeated infec- tions that is characterized by massive splenomegaly (tropical spleno- megaly or hyperreactive malarial splenomegaly), hepatomegaly, pancytopenia with anaemia, marked elevations in serum IgM and malarial antibody, hepatic sinusoidal lymphocytosis, and (in Africa) peripheral B cell lymphocytosis. Malarial parasites can be absent in the peripheral blood smear. Patients should receive antimalarial chemoprophylaxis, which usually results in reversal of splenomegaly and the haematological abnormalities. Chronic or repeated infections with P. malariae can cause an immune-complex membranoproliferative glomerulonephritis, re- sulting in nephrotic syndrome. This quartan nephropathy usually responds poorly to treatment with either antimalarial agents or cor- ticosteroids and cytotoxic drugs. Malaria-related immune dysregulation may provoke infection with lymphoma viruses. Burkitt’s lymphoma is strongly associated with the Epstein–Barr virus. The prevalence of this childhood tu- mour is high in malarious areas of Africa. Laboratory findings in severe malaria The laboratory abnormalities in severe malaria reflect multiple vital organ dysfunction. Metabolic acidosis, with low plasma concentra- tions of glucose, sodium, bicarbonate, calcium, phosphate, and al- bumin together with elevations in plasma lactate, urea, creatinine, urate, muscle, and liver enzymes, and conjugated and unconjugated bilirubin may all occur. Normochromic, normocytic anaemia is usual. Typically, the leukocyte count is normal, although it may be raised in very severe infections. There is slight monocytosis, lymphopenia, and eosinopenia, followed by reactive lymphocytosis and eosinophilia in the weeks after the acute infection. The erythro- cyte sedimentation rate, plasma viscosity, and levels of C-reactive protein and other acute-phase proteins are all high. The platelet count is usually reduced to c.105/µl, but can be lower. Severe in- fections may be accompanied by prolonged prothrombin and par- tial thromboplastin times and by more severe thrombocytopenia. Antithrombin III is reduced even in mild infections. In uncompli- cated malaria, plasma concentrations of electrolytes, urea, and cre- atinine are usually normal. Hypergammaglobulinaemia is usual in immune and semi-immune subjects. Urinalysis is generally normal. In both adults and children with cerebral malaria, the mean opening pressure at lumbar puncture is c.160 mm of cerebrospinal fluid. The cerebrospinal fluid is usually normal or has a slightly elevated total protein level (<100 mg/dl) and cell count (<20/µl). Malaria in children Most of the 438 000 malaria deaths each year (2015 estimate) are in young African children. Convulsions, coma, hypoglycaemia, meta- bolic acidosis, and severe anaemia are relatively common among children with severe malaria, whereas deep jaundice, oliguric acute renal failure, and acute pulmonary oedema are unusual. In areas of high malaria transmission severe anaemia is the usual presentation of life-threatening falciparum or vivax malaria. Severely anaemic children may present with deep laboured breathing, previously at- tributed incorrectly to ‘anaemic congestive cardiac failure’ but in fact is usually a manifestation of metabolic acidosis. In general, children tolerate antimalarial drugs well and respond more rapidly to treat- ment than adults. Malaria in pregnancy Malaria in early pregnancy causes abortion. In areas of high mal- aria transmission, falciparum malaria in primi- and secundigravid women is associated with low birth weight (average reduction, c.170 g) and consequently increased infant mortality. In these areas infected mothers remain asymptomatic despite intense accumula- tion of parasitized erythrocytes

in the placental microcirculation. Maternal HIV infection predisposes pregnant women to more frequent and higher density malaria infections, exacerbates the reduc- tion in birth weight associated with malaria, and predisposes their newborns to congenital malarial infection. In areas with low transmission of malaria, pregnant women are prone to severe falciparum malaria. They are particularly vulnerable to high parasitaemias with anaemia, hypoglycaemia, and acute pul- monary oedema. Fetal distress, fetal death, premature labour, and stillbirth or low birth weight are common consequences. Congenital falciparum malaria occurs in less than 5% of newborns whose mothers are infected particularly if they have high parasite densities. Congenital malaria often self-terminates. P. vivax malaria in preg- nancy is also associated with a reduction in birth weight (average, 110 g), but, in contrast to falciparum malaria, low birthweight is more pronounced in multigravid than in primigravid women. About 350 000 women die in childbirth each year. Most deaths occur in low-income countries with malaria-induced anaemia, a major risk factor for maternal death from haemorrhage at childbirth. Transfusion malaria Malaria can be transmitted by blood transfusion, needle-stick in- jury, sharing of needles by infected injection drug users, or organ transplantation. The incubation period in these settings is often short because there is no pre-erythrocytic stage of development. The clinical features and management of these cases are the same as for naturally acquired infections. Radical chemotherapy with

section 8 Infectious diseases 1408 primaquine is unnecessary for transfusion-transmitted P. vivax and P. ovale infections. Treatment of malaria When a patient in or from a malaria endemic area presents with fever or a history of fever, thick and thin blood smears should be prepared and examined immediately, or a rapid test performed. Repeated blood smears should be performed if the first smears are negative and malaria is strongly suspected. Patients with severe mal- aria or those unable to take oral medicines reliably should receive prompt parenteral antimalarial therapy. If there is any doubt about antimalarial drug resistance, the infection should be considered resistant. In all endemic areas, the World Health Organization (WHO) now recommends artemisinin-based combinations (ACTs) as first- line treatment for uncomplicated falciparum malaria. They are well tolerated and are rapidly and reliably effective. ACTs are also highly effective for the other malaria species and can therefore be used as first-line treatment for all malarias. ACTs are sometimes unavailable in temperate countries, where treatment recommenda- tions are limited by the registered available drugs. Chloroquine re- mains effective for the non-falciparum malarias (P. vivax, P. ovale, P. malariae, P. knowlesi) except in Indonesia and Papua New Guinea, although resistance is increasing. Fake or substandard antimal- arials are commonly sold in many Asian and African countries. Thus, careful attention is required at the time of purchase and later, especially if the patient fails to respond as expected. Treatment of severe malaria Severe falciparum malaria is a medical emergency requiring inten- sive nursing care and careful management. The patient should be weighed if possible and, if comatose, placed on his or her side in the recovery position with frequent turning to avoid aspiration pneu- monia and decubitus pressure sores. Antimalarial treatment should be started immediately. Antimalarial treatment (Table 8.8.2.6). In the largest randomized controlled trials conducted in severe malaria, parenteral artesunate, a water-soluble artemisinin derivative, was compared with quinine— the previous treatment of choice. Artesunate reduced mortality rates in adults by 35% and by 22.5% in African children. Artesunate has, therefore, become the drug of first choice for all patients with se- vere malaria everywhere. Artesunate is usually given by IV injection but it can also be given by IM injection. Artemether and the closely related drug artemotil (β-arteether) are oil-based formulations of artemisinin derivatives given by IM injection. They are erratically absorbed and do not confer the same survival benefit as

artesunate, but they are probably more effective than quinine. If artemisinin de- rivatives are not immediately available, then treatment should start with quinine until they can be obtained. If none of these are avail- able, then the antiarrhythmic quinidine gluconate is as effective as quinine, but it is significantly more cardiotoxic and so requires close monitoring for dysrhythmias and hypotension. A rectal formulation of artesunate has been developed as a community-based prereferral treatment for patients in the rural tropics who cannot take oral medications. Prereferral administration of rectal artesunate has been shown to decrease the mortality of severely ill children without access to immediate parenteral treatment. Treatment of complications (Table 8.8.2.7). Frequent evaluation of the patient's condition is essential. Many adjunctive treat- ments including high-dose corticosteroids, urea, heparin, dextran, desferrioxamine, antibody to tumour necrosis factor, high-dose phenobarbital, mannitol, or large volume fluid or albumin bo- luses have proved either ineffective or harmful in clinical trials and should not be used. In acute renal failure or severe metabolic acid- osis, haemofiltration, or haemodialysis should be started as early as possible. Exchange transfusion might be considered for severely ill patients, although recent retrospective studies have shown no additional benefit. The rapid clearance of peripheral blood parasit- aemia achieved by exchange transfusion is also achieved by the rapid administration of parenteral artesunate. Convulsions should be treated promptly with intravenous (or rectal) benzodiazepines. The role of prophylactic anticonvulsants in children is uncertain. If re- spiratory support is not available, then a full loading dose of pheno- barbital (20 mg/kg) to prevent convulsions should not be given as it has shown to increase mortality, presumable by causing respira- tory arrest. When the patient is unconscious, the blood glucose level should be measured every 4–6 h, or at any time if the level of con- sciousness falls. All patients should receive a continuous infusion of dextrose, and blood concentrations ideally should be maintained above 4 mmol/litre. Hypoglycaemia (<2.2 mmol/litre or 40 mg/dl) should be treated immediately with bolus IV glucose. The para- site count and haematocrit level should be measured every 6–12 h. Anaemia develops rapidly in severe malaria; if the haematocrit falls to less than 20%, then whole blood (preferably fresh) or packed cells should be transfused slowly, with careful attention to circula- tory status. In endemic areas where there is limited availability of safe blood the transfusion threshold is often a haematocrit of 15%. Renal function should be checked daily. Children presenting with severe anaemia and acidotic breathing require immediate blood transfusion. Accurate assessment is vital. Management of fluid balance is difficult in severe malaria, because of the thin dividing line between overhydration (leading to pulmonary oedema) and underhydration (contributing to renal impairment). Except in hypotensive shock, fluid therapy should be restricted (e.g. 2 to 4 ml/ kg/hr). Fluid bolus therapy is contraindicated. As soon as the pa- tient can take fluids, a full three-day course of ACT should be started (except that mefloquine should not be given following cerebral malaria). In areas of high transmission where severe malaria and bacterial septicaemia commonly coexist all patients should also re- ceive broad-spectrum antibiotics. Treatment of uncomplicated malaria (See Tables 8.8.2.6 and 8.8.2.8). Malaria caused by chloroquine-sensitive P. vivax, P. knowlesi, P. malariae, and P. ovale can be treated by oral chloroquine (total dose, 25 mg base/kg divided over three days), or a three day course of an ACT (except for artesunate-sulfadoxine-pyrimethamine, P. vivax is often resistant to antifolates). Uncomplicated falcip- arum malaria should also be treated with a three-day course of an ACT. The ACTs are safe and effective in adults, children, and pregnant women. There is increasing evidence that they are also safe in the first trimester of pregnancy. The rapidly eliminated artemisinin component of ACT is usually an artemisinin deriva- tive (artesunate, artemether, or dihydroartemisinin) given for 3 days, and the partner drug is usually a more slowly eliminated

8.8.2 Malaria 1409 Table 8.8.2.6 Treatment of malaria Indication Regimen(s) Uncomplicated Malaria Known chloroquine-sensitive strains of Plasmodium vivax, P. malariae, P. ovale, P. knowlesi, P. falciparuma Chloroquine (10 mg of base/kg stat followed by 5 mg/kg at 12, 24, and 36 h or by 10 mg/kg at 24 h and 5 mg/kg at 48 h) or Any ACT (except artesunate-sulfadoxine-pyrimethamine where there is resistance) Radical treatment for P. vivax or P. ovale infection (to prevent relapse) In addition to chloroquine or an ACT give primaquine once daily for 14 days; in SE Asia and Oceania, 0.5 mg of base/kg/day elsewhere 0.25 mg/kg/day In mild G6PD deficiency, 0.75 mg of base/kg should be given once weekly for 8 weeks Primaquine should not be given in severe G6PD deficiency Sensitive P. falciparum malariab Artesunatec (4 mg/kg once daily for 3 days) plus sulfadoxine (25 mg/kg)/pyrimethamine (1.25 mg/kg) as a single dose or Artesunatec (4 mg/kg once daily for 3 days) plus amodiaquine (10 mg of base/kg once daily for 3 days)d Multidrug-resistant P. falciparum malaria Either artemether-lumefantrinec (1.5/9 mg/kg bid for 3 days with food) or Artesunatec (4 mg/kg once daily for 3 days) plus Mefloquine (24–25 mg of base/kg—either 8 mg/kg once daily for 3 days or 15 mg/kg on day 2 and then 10 mg/kg on day 3)d or Dihydroartemisinin-piperaquinec (2.5/20 mg/kg once daily for 3 days) Second-line treatment/ treatment of imported malaria Quinine (10 mg of salt/kg tid for 7 days) plus 1 of the following 3:

1. Tetracyclinee (4 mg/kg qid for 7 days)
2. Doxycyclinee (3 mg/kg once daily for 7 days)
3. Clindamycin (10 mg/kg bid for 7 days) or Atovaquone–proguanil (20/8 mg/kg once daily for 3 days with food) In of low malaria transmission, a single dose of primaquine 0.25 mg base/kg should be added to all falciparum malaria treatments to prevent transmission, except in pregnant women and infants. This is considered safe even in G6PD deficiency. Severe falciparum malariaf Artesunatec (2.4 mg/kg stat IV followed by 2.4 mg/kg at 12 and 24 h and then daily if necessary)g or, if unavailable, Artemetherc (3.2 mg/kg stat IM followed by 1.6 mg/kg once daily) or, if unavailable Quinine dihydrochloride (20 mg of salt/kgh infused over 4 h, followed by 10 mg of salt/kg infused over 2–8 h q8hi) or, if unavailable Quinidine (10 mg of base/kgh infused over 1–2 h, followed by 1.2 mg of base/kg per houri with electrocardiographic monitoring) ACT, artemisinin combination therapy; G6PD, glucose-6-phosphate dehydrogenase. See WHO guidelines for the treatment of malaria for full details: http://apps.who.int/iris/bitstream/10665/162441/1/9789241549127_eng.pdf a Chloroquine-sensitive P. falciparum malaria is now found only in Central America and Haiti. b In areas where the longer acting partner drug to artesunate is known to be effective. c Artemisinin derivatives are not readily available in some temperate countries. d Fixed-dose coformulated combinations are available. The World Health Organization now recommends artemisinin combination regimens as first-line therapy for falciparum malaria in all tropical countries and advocates use of fixed-dose combinations. e Tetracycline and doxycycline should not be given to pregnant women or to children <8 years of age. f Oral treatment should be substituted as soon as the patient recovers sufficiently to take fluids by mouth. A full course of ACT should be given, except that mefloquine should not be given following cerebral malaria. g Artesunate is the drug of choice when available. The data from large studies in Southeast Asia showed a 35% lower mortality rate than with quinine, and very large studies in Africa showed a 22.5% reduction in mortality rate compared with quinine. Children weighting <20 kg should receive a higher dose of artesunate of 3mg/kg per dose, to ensure equivalent exposure to the drug. h A loading

dose should not be given if therapeutic doses of quinine or quinidine have definitely been administered in the previous 24 h. Some authorities recommend a lower dose of quinidine. i Infusions can be given in 0.9% saline and 5–10% dextrose in water. Infusion rates for quinine and quinidine should be carefully controlled.

section 8 Infectious diseases 1410 Table 8.8.2.7 Management of complications of severe malaria Hypoglycaemia. An initial slow intravenous injection of 20% dextrose (0.5 g/kg) should be followed by an infusion of 10% dextrose (0.10 g/kg per hour). The blood glucose level should be checked regularly as recurrent hypoglycaemia is common, particularly among patients receiving quinine or quinidine. In severely ill patients, hypoglycaemia commonly occurs together with metabolic (lactic) acidosis and carries a poor prognosis. Acute renal failure. If the plasma concentrations of urea or creatinine rise despite adequate rehydration, fluid administration should be restricted to prevent volume overload. Renal replacement therapy is best performed early. Haemofiltration and haemodialysis are more effective than peritoneal dialysis and are associated with lower mortality. Some patients with renal impairment do pass small volumes of urine sufficient to allow control of fluid balance; these cases can be managed conservatively if other indications for dialysis do not arise. Renal function usually improves within days, but full recovery may take weeks. Acute pulmonary oedema. Patients should be positioned with the head of the bed at a 45° elevation and given oxygen and IV diuretics. Positive pressure ventilation should be started early if the immediate measures fail. Other complications. Patients who develop spontaneous bleeding should be given fresh blood and IV vitamin K. Convulsions should be treated with IV or rectal benzodiazepines and, if necessary, respiratory support. Aspiration pneumonia should be suspected in any unconscious patient with convulsions, particularly with persistent hyperventilation; IV antimicrobial agents and oxygen should be administered, and the airway secured. Hypoglycaemia or Gram-negative septicaemia should be suspected when the condition of any patient suddenly deteriorates during antimalarial treatment. In malaria endemic areas where a high proportion of children are parasitaemic, it is impossible to distinguish severe malaria from bacterial sepsis with confidence. In addition, severe malaria is often (ca 20%) accompanied by bacteraemia. Therefore, all children with severe malaria should be treated with both antimalarials and broad-spectrum antibiotics from the outset. Because nontyphoidal Salmonella infections and Streptococcus pneumonia are particularly common, empirical antibiotics should be selected to cover these organisms. Antibiotics should be considered for severely ill patients of any age who are not responding to antimalarial treatment. Table 8.8.2.8 Properties of antimalarial drugs Drug(s) Pharmacokinetic properties Antimalarial activity Minor toxicity Major toxicity Quinine (and quinidine) Good oral and IM absorption (quinine); Cl and Vd reduced, but plasma protein binding (principally to ∝1 acid glycoprotein) increased (90%) in malaria; quinine mean t1/2: 18h in severe malaria 16 h in uncomplicated malaria, 11 h in healthy persons; quinidine t1/2:
13 h in malaria, 8 h in healthy persons Acts mainly on trophozoite blood stage; kills gametocytes of P. vivax, P. ovale, and P. malariae (but not P. falciparum); no action on liver stage Common: ‘Cinchonism’: tinnitus, high-tone hearing loss, nausea, vomiting, dysphoria, postural hypotension; ECG QTc interval prolongation (quinine usually by <10% but quinidine by up to 25%). Rare: Diarrhoea, visual disturbance, rashes Note: Very bitter taste Common: Hypoglycaemia Rare: Hypotension, blindness, deafness, cardiac arrhythmias, thrombocytopenia, haemolysis, haemolytic-uremic syndrome, vasculitis, cholestatic hepatitis, neuromuscular paralysis Note: Quinidine substantially more cardiotoxic Chloroquine Good oral absorption, very rapid IM and SC absorption; complex pharmacokinetics; enormous Cl and Vd (unaffected by malaria); blood concentration

profile determined by distribution processes in malaria; t1/2: 1–2 months As for quinine but acts slightly earlier in asexual cycle Common: Nausea, dysphoria, pruritus in dark-skinned patients, postural hypotension Rare: Accommodation difficulties, keratopathy, rash Note: Bitter taste, well tolerated Rare: Hypotensive shock (parenteral), cardiac arrhythmias, neuropsychiatric reactions Chronic: Retinopathy (cumulative dose, >100 g), skeletal and cardiac myopathy Piperaquine Adequate oral absorption, may be enhanced by fats; similar pharmacokinetics to chloroquine; t1/2: 21–28 days As for chloroquine Epigastric pain, diarrhoea, ECG QTC prolongation None identified Amodiaquine Good oral absorption; largely converted to active metabolite desethylamodiaquine As for chloroquine Nausea (tastes better than chloroquine) Agranulocytosis (rare); hepatitis, mainly with prophylactic use; should not be used with efavirenz Primaquine Complete oral absorption; active metabolite not known; t1/2: 5–7 h Radical cure; eradicates hepatic forms of P. vivax and P. ovale; kills all stages of gametocyte development of P. falciparum Nausea, vomiting, diarrhoea, abdominal pain, hemolysis, methaemoglobinemia Massive hemolysis in subjects with severe G6PD deficiency Mefloquine Adequate oral absorption; no parenteral preparation; t1/2:
14–20 days (shorter in malaria) As for quinine Nausea, giddiness, dysphoria, fuzzy thinking, sleeplessness, nightmares, sense of dissociation Neuropsychiatric reactions, convulsions, encephalopathy Lumefantrine Highly variable absorption related to fat intake; t1/2: 3–4 days As for quinine Nausea, giddiness, dysphoria, fuzzy thinking, sleeplessness, nightmares, sense of dissociation Neuropsychiatric reactions, convulsions, encephalopathy Pyronaridine t1/2: 10 days children, 13 days adults As for quinine Nausea, vomiting, abdominal pain, diarrhoea, headache Hepatotoxicity (continued)

8.8.2 Malaria 1411 antimalarial to which P. falciparum is sensitive. Five ACT re- gimens are currently recommended by the WHO. In areas with multidrug-resistant falciparum malaria (parts of Asia and South America), artemether–lumefantrine, artesunate-mefloquine, or dihydroartemisinin-piperaquine should be used; these regimens provide cure rates of more than 90% except in Thailand and Eastern Myanmar where there is increasing resistance to mefloquine, and in Cambodia and adjacent Vietnam where there is resist- ance to piperaquine. In areas with sensitive parasites, these ACTs and also artesunate-sulfadoxine-pyrimethamine, or artesunate- amodiaquine may also be used. Artesunate-pyronaridine has been registered in a limited number of countries and appears a safe and effective alternative. Atovaquone–proguanil is also effective everywhere, although it is seldom used in endemic areas because of its high cost and the propensity for high-level atovaquone re- sistance. Of great concern is the emergence of artemisinin re- sistance in P. falciparum in the Greater Mekong subregion. Artemisinin resistant P. falciparum is now found from the coast of Vietnam to the Myanmar–India border. Infections with arte- misinin resistant parasites are cleared slowly from the blood, with parasite clearance times which typically exceed 3 days, and cure rates with ACTs are reduced. High ACT failure rates with DHA- piperaquine have been reported in Cambodia and with artesunate- mefloquine on the Thai-Myanmar border. Elsewhere these ACTs, and artemether–lumefantrine can be relied upon. Amodiaquine and sulfadoxine-pyrimethamine-resistance compromises the use of ACTs containing these antimalarials in several endemic areas. In low-transmission settings for the treatment of falcip- arum malaria a single dose of primaquine (0.25 mg/kg) should be added to the ACT as a gametocytocide to reduce transmission. Primaquine should not be given to young infants (<6 months) or to pregnant women. The 3-day ACT regimens are all generally well tolerated. Mefloquine is associated with increased rates of vomiting and minor central nervous system reactions (nausea, dizziness, dysphoria, sleep dis- turbances) are common.

The incidence of serious adverse neuro- psychiatric reactions to mefloquine treatment is c.1 in 1000 in Asia but may be as high as 1 in 200 among Africans and Caucasians. All the antimalarial quinolines (chloroquine, amodiaquine, mef- loquine, and quinine) exacerbate the orthostatic hypotension associated with malaria, and all are tolerated better by children than by adults. Several antimalarials, notably quinidine, quinine, chloroquine, amodiaquine and piperaquine prolong ventricular repolarization (QT prolongation on the electrocardiogram), but they have not been linked with dysrhythmias in the treatment of malaria. If falciparum malaria recrudesces following first-line ACT therapy, second-line treatment with a different ACT regimen may be given. An alternative is a 7-day course of either artesunate or quinine plus tetracycline, doxycycline, or clindamycin. Tetracycline and doxycycline cannot be given to pregnant women or to children less than 8 years of age. Oral quinine is extremely bitter and regu- larly produces cinchonism comprising tinnitus, high-tone deafness, nausea, vomiting, and dysphoria. Adherence is poor with the re- quired 7-day regimens of quinine. Patients should be monitored for vomiting for 1 h after the admin- istration of any oral antimalarial drug. If there is vomiting within the first half hour, the full dose should be repeated. Symptom-based Drug(s) Pharmacokinetic properties Antimalarial activity Minor toxicity Major toxicity Artemisinin and derivatives (artemether, artesunate) Good oral absorption, slow and variable absorption of IM artemether; artesunate and artemether biotransformed to active metabolite dihydroartemisinin; all drugs eliminated very rapidly; t1/2: <1 h Broader stage specificity and more rapid than other drugs; no action on liver stages; kills all but fully mature gametocytes of P. falciparum Reduction in reticulocyte count (but not anaemia); neutropenia at high doses. Following treatmen t of severe malaria with hyperparasitaemia, delayed anaemia may occur. Rare: Anaphylaxis, urticaria, fever Pyrimethamine Good oral absorption, variable IM absorption; t1/2: 4 days For blood stages, acts mainly on mature forms; causal prophylactic Well tolerated Megaloblastic anaemia, pancytopenia, pulmonary infiltration Proguanil Good oral absorption; biotransformed to active metabolite cycloguanil; t1/2: 16 h; biotransformation reduced by oral contraceptive use and in pregnancy Causal prophylactic; not used alone for treatment Well tolerated; mouth ulcers and rare alopecia Megaloblastic anaemia in renal failure Atovaquone Highly variable absorption related to fat intake; t1/2: 30–70 h Acts mainly on trophozoite blood stage None identified None identified Tetracycline, doxycyclinea Excellent absorption; t1/2: 8 h for tetracycline, 18 h for doxycycline Weak antimalarial activity; should not be used alone for treatment Gastrointestinal intolerance, deposition in growing bones and teeth, photosensitivity, candidiasis, benign intracranial hypertension Renal failure in patients with impaired renal function (tetracycline) Cl, systemic clearance; Vd, total apparent volume of distribution. ECG, electrocardiogram; G6PD, glucose-6-phosphate dehydrogenase; a Tetracycline and doxycycline should not be given to pregnant women or to children <8 years of age.
Table 8.8.2.8 Continued

section 8 Infectious diseases 1412 treatment, with tepid sponging and paracetamol (acetaminophen) administration, lowers fever and may help to prevent vomiting. Pregnant women, young children, patients unable to tolerate oral therapy, and nonimmune individuals (e.g. travellers) with sus- pected malaria should be evaluated carefully and hospitalization considered. If there is any doubt as to the identity of the infecting malarial species, treatment for falciparum malaria should be given. Nonimmune patients receiving treatment for malaria should have daily parasite counts performed until the thick films are negative. If the parasite density does not fall below 25% of the admission value in 48 h or if parasitaemia has not cleared by 7 days (and adherence is assured), drug resistance is likely, and the regimen should be changed. Radical cure

In infections with P. vivax or P. ovale infections primaquine (0.5 mg of base/kg, adult dose in Southeast Asia and Oceania, 0.25 mg/kg else- where) should be added to treatment of the blood stage treatment to eradicate persistent liver stages and prevent relapse (radical treat- ment). Primaquine should be given daily for 14 days after labora- tory tests for G6PD deficiency have proved negative. If the patient has a mild variant of G6PD deficiency, primaquine can be given in a dose of 0.75 mg base/kg (45 mg maximum) once weekly for 8 weeks. Pregnant women or infants less than 6 months with vivax or ovale malaria should not be given primaquine. Pregnant women should receive suppressive prophylaxis with chloroquine (5 mg of base/kg per week) until delivery, after which radical treatment can be given. Prevention of malaria Malaria may be contained and controlled by: insecticides to kill the mosquito vector; rapid diagnosis, and treatment of symptomatic malaria and in endemic areas, where effective and feasible; admin- istration of intermittent preventive treatments; seasonal malaria chemoprevention: or chemoprophylaxis to high-risk groups such as pregnant women, young children, and travellers from nonendemic regions. Insecticides are the cornerstone of mosquito control. The most important group are the pyrethroid insecticides which are used to impregnate mosquito nets. Insecticide treated bed-nets pro- vide protection against malaria for those sleeping under or near the nets in areas where the anopheline vectors bite at night, although increasing pyrethroid resistance threatens their future. Insecticide treated bed-nets have been shown to reduce mortality in African children by 17%. Their widespread distribution is one of the main reasons for recent reductions in global malaria mortality. Indoor re- sidual spraying (IRS) with insecticides can be highly effective against indoor resting (endophylic) Anopheles species, but sustaining high coverage has proven a challenge. It has proved very difficult to develop an effective malaria vaccine. The RTS,S/ASO1 P. falciparum malaria vaccine has been registered recently by the European Medicines Agency. This vaccine provides short-term protection of approxi- mately 30–50% for one year but declines thereafter. Protection from RTS,S in infants dropped to 16% four years after vaccination. While there is great promise for one or more malaria vaccines on the more distant horizon, prevention and control measures continue to rely on vector control and antimalarial drugs. Worryingly the recent gains in malaria control are threatened by increasing insecticide resistance and behaviour change (to avoid contact with insecticide treated bed-nets) in anopheline mosquito vectors, and spreading ar- temisinin and ACT partner drug resistance in P. falciparum. Personal protection against malaria Simple measures to reduce the frequency of infected-mosquito bites in malarious areas are very important. These include the use of insecticide treated bed-nets, avoidance of exposure to mosqui- toes at their peak feeding times (usually dusk to dawn), suitable (long-sleeve) clothing, and the use of insect repellents containing 10–35% diethyltoluamide (DEET) (or, if DEET is unacceptable, 7% picaridin). Chemoprophylaxis (See Table 8.8.2.9.) Recommendations for prophylaxis depend on knowledge of the risks of acquiring malaria and local patterns of antimalarial drug Table 8.8.2.9 Drugs used in the prophylaxis of malaria Drug Usage Adult dose Paediatric dose Comments Atovaquone/ proguanil Prophylaxis in areas with chloroquine- or mefloquine-resistant Plasmodium falciparum 1 adult tablet POa 5–8 kg: ½ paediatric tabletb once daily Begin 1–2 days before travel to malarious areas. Take once daily at the same time each day while in the malarious areas and for 7 days after leaving such areas. Atovaquone–proguanil is contraindicated in severe renal impairment (creatinine clearance rate <30 ml/min). In the absence of data, it is not recommended for children weighing <5 kg, pregnant women, or women breastfeeding infants weighing <5 kg. Atovaquone/ proguanil should be taken with food or a milky drink. ≥8–10 kg: ¾ paediatric tablet once daily ≥10–20 kg: 1 paediatric tablet once daily ≥20–30 kg: 2 paediatric tablets once daily ≥30–40 kg: 3 paediatric tablets once daily ≥40 kg: 1 adult tablet once daily Chloroquine Prophylaxis only in areas with

P. vivax only 300 mg of base (500 mg of phosphate salt) PO once weekly 5 mg/kg of base (8.3 mg of salt/kg) PO once weekly, up to maximum adult dose of 300 mg of base Begin 1–2 weeks before travel to malarious areas. Take weekly on the same day of the week while in the malarious areas and for 4 weeks after leaving such areas. Chloroquine may exacerbate psoriasis. (continued)

8.8.2 Malaria 1413 Drug Usage Adult dose Paediatric dose Comments Doxycycline Prophylaxis in areas with chloroquine- or mefloquine-resistant P. falciparumc 100 mg PO once daily ≥8 years of age: 2 mg/kg, up to adult dose Begin 1–2 days before travel to malarious areas.
Take once daily at the same time each day while in the malarious areas and for 4 weeks after leaving such areas. Doxycycline is contraindicated in children <8 years of age and in pregnant women. Mefloquine Prophylaxis in areas with chloroquine-resistant P. falciparumc 250 mg of base PO once weekly ≤9 kg: 4.6 mg of base/kg (5 mg of salt/kg) PO once weekly Begin 1–2 weeks before travel to malarious areas. Take weekly on the same day of the week while in the malarious areas and for 4 weeks after leaving such areas. Mefloquine is contraindicated in persons allergic to this drug or related compounds (e.g. quinine and quinidine) and in persons with active or recent depression, generalized anxiety disorder, psychosis, schizophrenia, other major psychiatric disorders, or seizures. Use with caution in persons with psychiatric disturbances or a history of depression. 10–19 kg: ¼ tablet once weekly 20–30 kg: ½ tablet once weekly 31–45 kg: ¾ tablet once weekly ≥46 kg: 1 tablet once weekly Primaquine For prevention of malaria in areas with mainly P. vivax 30 mg of base (52.6 mg of salt) PO once daily 0.5 mg of base/kg (0.8 mg of salt/kg) PO once daily, up to adult dose; should be taken with food Begin 1–2 days before travel to malarious areas. Take once daily at the same time each day while in the malarious areas and for 7 days after leaving such areas. Primaquine prophylaxis is contraindicated in persons with G6PD deficiency. It is also contraindicated during pregnancy and in lactation unless the infant being breast-fed has a documented normal G6PD level. Primaquine Used for presumptive antirelapse therapy (terminal prophylaxis) to decrease risk of relapses of P. vivax and P. ovale 30 mg of base PO once daily for 14 days after departure from the malarious area 0.5 mg of base/kg (0.8 mg of salt/kg), up to adult dose, PO once daily for 14 days after departure from the malarious area This is indicated for persons who have had prolonged exposure to P. vivax and/or P. ovale. It is contraindicated in persons with G6PD deficiency as well as during pregnancy and in lactation unless the infant being breast-fed has a documented normal G6PD level. a An adult tablet contains 250 mg of atovaquone and 100 mg of proguanil hydrochloride. b A paediatric tablet contains 62.5 mg of atovaquone and 25 mg of proguanil hydrochloride. c Very few areas now have chloroquine-sensitive malaria. Atovaquone–proguanil (Malarone; 3.75/1.5 mg/kg or 250/100 mg, once daily adult dose) is a fixed-combination, once daily prophylactic agent that is very well tolerated by adults and children, with fewer adverse gastrointestinal effects than chloroquine-proguanil and fewer adverse central nervous system effects than mefloquine. It is proguanil itself, rather than the antifolate metabolite cycloguanil, that acts synergistically with atovaquone. This combination is effective against all types of malaria, including multidrug-resistant falciparum malaria. Atovaquone–proguanil is best taken with food or a milky drink to optimize absorption. There are insufficient data on the safety of this regimen in pregnancy. Mefloquine (250 mg of salt weekly, adult dose) has been widely used for malarial prophylaxis because it is usually effective against multidrug-resistant falciparum malaria and is reasonably well tolerated. The drug has been associated with rare episodes of psychosis and seizures at prophylactic doses; these reactions are more frequent at the higher doses used for treatment. More common side effects with prophylactic doses of mefloquine include mild nausea, dizziness, fuzzy thinking, disturbed sleep patterns, vivid dreams, and malaise. The drug is contraindicated for use by travellers with known hypersensitivity

to mefloquine or related compounds (e.g. quinine, quinidine) and by persons with active or recent depression, anxiety disorder, psychosis, schizophrenia, another major psychiatric disorder, or seizures; mefloquine is not recommended for persons with cardiac conduction abnormalities although the evidence that it is cardiotoxic is very weak. There increasing confidence in the safety of mefloquine prophylaxis during pregnancy; in studies in Africa, mefloquine prophylaxis was found to be effective and safe during pregnancy. However, in one study from Thailand, treatment of malaria with mefloquine was associated with an increased risk of stillbirth, but this effect was not seen subsequently. Once daily administration of doxycycline (100 mg daily, adult dose) is an effective alternative to atovaquone–proguanil or mefloquine. Doxycycline is generally well tolerated but may cause vulvovaginal thrush, diarrhoea, and photosensitivity and cannot be used by children <8 years old or by pregnant women. Chloroquine can no longer be relied upon to prevent P. falciparum infections in most areas but is used to prevent and treat malaria due to the other human Plasmodium species and for P. falciparum malaria in Central American countries west and north of the Panama Canal, Caribbean countries, and some countries in the Middle East. Chloroquine-resistant P. vivax has been reported from parts of eastern Asia, Oceania, and Central and South America. This drug is generally well tolerated, although some patients cannot take it because of malaise, headache, visual symptoms (due to reversible keratopathy), gastrointestinal intolerance, or pruritus. Chloroquine is considered safe in pregnancy. With chronic administration for >5 years, a characteristic dose-related retinopathy may develop, but this condition is rare at the doses used for antimalarial prophylaxis. Idiosyncratic or allergic reactions are also rare. Skeletal and/or cardiac myopathy is a potential problem with protracted prophylactic use; they are more likely to occur at the high doses used in the treatment of rheumatoid arthritis. Neuropsychiatric reactions and skin rashes are unusual. When used continuously, amodiaquine, a related aminoquinoline, is associated with a high risk of agranulocytosis (c.1 person in 2000) and hepatotoxicity (c.1 person in 16 000); thus, this agent should not be used for prophylaxis. Primaquine (once daily adult dose, 0.5 mg of base/kg or 30 mg taken with food), an 8-aminoquinoline compound, has proved safe and effective in the prevention of drug-resistant falciparum and vivax malaria in adults. This drug can be considered for persons who are travelling to areas with or without drug-resistant P. falciparum and who are intolerant to other recommended drugs. Abdominal pain and oxidant haemolysis—the principal adverse effects—are not common as long as the drug is taken with food and is not given to G6PD- deficient persons, in whom it can cause haemolysis that is sometimes fatal. Travellers must be tested for G6PD deficiency and be shown to have a level in the normal range before receiving primaquine. Primaquine should not be given to pregnant women or neonates. The 8-aminoquinolines (primaquine, tafenoquine) given in a single dose with ACT are being considered for widespread use in treatment regimens in malaria elimination programmes because of their gametocytocidal effect on P. falciparum. In the past, the dihydrofolate reductase inhibitors pyrimethamine and proguanil (chloroguanide) were administered widely, but the rapid selection of resistance in both P. falciparum and P. vivax has limited their use. Whereas antimalarial quinolines such as chloroquine (a 4-aminoquinoline) act on the erythrocyte stage of parasitic development, the dihydrofolate reductase inhibitors also inhibit preerythrocytic growth in the liver (causal prophylaxis) and development in the mosquito (sporontocidal activity). Proguanil is safe and well tolerated, although mouth ulceration occurs in c.8% of persons using this drug; it is considered safe for antimalarial prophylaxis in pregnancy. The prophylactic use of the combination of pyrimethamine and sulfadoxine is not recommended because of an unacceptable incidence of severe toxicity, principally exfoliative dermatitis and other skin rashes, agranulocytosis, hepatitis, and pulmonary eosinophilia (incidence, 1:7000; fatal reactions, 1:18 000). The combination of pyrimethamine with dapsone (0.2/1.5 mg/kg weekly; 12.5/100 mg, adult

dose) has been used in some countries. Dapsone may cause methaemoglobinemia and allergic reactions and (at higher doses) may pose a significant risk of agranulocytosis. Proguanil and the pyrimethamine-dapsone combination are not available in the United States. There is an increasingly appreciated problem of falsified (fake, counterfeit) and substandard antimalarial drugs (and other medicines) on the shelves of pharmacies in Southeast Asia and sub-Saharan Africa; hence, travellers should purchase their preventive drugs from a reputable source before going to a malarious country. Table 8.8.2.9 Continued

---

Revision #1
Created 2026-01-22 16:46:07 UTC by Omar Ayman
Updated 2026-01-22 16:46:07 UTC by Omar Ayman