Chemotherapy of Malaria and Other Protozoal Diseases

Suresh Kumar Srinivasamurthy and Laxminarayana Kurady Bairy

Abstract

Protozoa being unicellular eukaryotic microorganisms cause several diseases, which are varied in their pathogenesis, presentation, transmission, and response to treatment. Malaria, one of the oldest diseases known to humankind, is still persistent in several countries despite effective drugs and adequate control measures. Being a vector borne Plasmodium protozoal disease, malaria poses a diverse spectrum of challenges to public health. Currently, infections among pregnant women and children residing in endemic areas are the major challenge for malaria control programs. It is further complicated by the emergence of drug resistant parasites in several countries. The antimalarial drugs for treatment and prophylaxis from quinine to artemisinin combination therapies (ACTs) are discussed in this chapter. The chemotherapeutic drugs against other protozoal infections of importance such as Leishmania, Trypanosoma, Babesia, G. lamblia, E. histolytica, Trichomonas, Toxoplasma, C. parvum, Isospora belli, Cyclospora cayetanensis, D. fragilis, Balantidium coli, Blastocystis hominis, Naegleria fowleri, and Acanthamoeba are also discussed.

Keywords

Antimalarial drugs · Antiprotozoal drugs · Anti-amebic drugs · Artemisinin combination therapy

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60.1 Introduction

- Protozoa being unicellular eukaryotic microorganisms cause several diseases. These infections in humans can be classified clinically based on their transmission. Medically important protozoa belong to the following: Apicomplexa, Kinetoplastida, Sarcodina (amebas), Ciliophora (ciliates), and other flagellates.
- Apicomplexa structurally have unique apicoplast in most of the organisms. Apicoplast takes part in crucial metabolic pathways of the organisms. Apicomplexa includes Piroplasma and Coccidia. Piroplasma consists of Plasmodium and Babesia, which can divide by binary fission and have both sexual and asexual phases. Coccidia form spore-forming intracellular obligate parasites including Toxoplasma, Cryptosporidium, and others. Spore forming Pneumocystis and microsporidia which cause opportunistic disease in immunocompromised are now considered as fungi.
- Kinetoplastida includes Leishmania and Trypanosoma. Sarcodina consists of ameba, which can cause varied diseases. Ciliophora (ciliates) consist of Balantidium coli. Other flagellates include Giardia, Dientamoeba, and Trichomonas.
- Blastocystis, earlier considered as yeast now recognized as protozoa, causes disease only in immunocompromised. It belongs to Heterokonta, which is diverse and consists mainly of diatoms and other algae (Table 60.1).

60.1.1 Historical Perspectives of Malaria

Periodic or intermittent fever has been one of the oldest diseases of the earth affecting humans. These acute paroxysmal fevers with chills were given different names as per time, geographical locations from Roman fever to Ague. The term “malaria” transliterates to “bad air” in Italian, and then considered to be caused by bad air of swampy areas as per ancient Greeks and Romans. The term “malaria” is believed to be used by Italian physician Francisco Torti during mid-eighteenth century. In 1897, British doctor Ronald Ross discovered malarial-pigmented cells in anopheles mosquito, which had fed on infected person. Later in Calcutta, Ross demonstrated through experiments in sparrows different stages of malarial parasites through mosquitoes and their transmission. He was awarded Nobel Prize for discovering stages of the parasite in mosquitoes. Concurrently, Italian scientists led by Giovanni Battista Grassi showed transmission of malaria in humans through Anopheles maculipennis by malaria parasite Plasmodium vivax. Later, H. E. Shortt and colleagues identified liver as site of initial development of Plasmodium vivax and Plasmodium falciparum in humans.

Malaria poses significant public health burden though, 2005–2015 marks significant malaria control globally. The disease burden is estimated at 228 million cases with 4,05,000 deaths in 2018. However, incidence rate of malaria persisted at 57 per
Table 60.1 The overview of mode of transmission and drugs used for protozoal infections

| Transmission                                      | Parasites                | Main drugs                                                                 |
|--------------------------------------------------|--------------------------|---------------------------------------------------------------------------|
| Arthropod bite                                   | *Piroplasma*             | Artemisinin combination therapy, quinolones                               |
|                                                  | *Plasmodium*             |                                                                           |
|                                                  | *Babesia*                | Clindamycin + quinine                                                     |
|                                                  | *Kinetoplastids*         | Liposomal amphotericin B                                                 |
|                                                  | *Leishmania*             | Paromomycin                                                               |
|                                                  |                          | Sodium Stibogluconate                                                     |
|                                                  |                          | Miltefosine                                                               |
|                                                  | *Trypanosoma*            | Suramin                                                                   |
|                                                  |                          | Melarsoprol                                                              |
|                                                  |                          | Nifurtimox                                                               |
| Enteric                                          | Other flagellates        | Metronidazole                                                             |
|                                                  | *G lamblia*              |                                                                           |
|                                                  | *Dientamoeba fragilis*   | Paromomycin                                                               |
|                                                  |                          | Metronidazole                                                             |
|                                                  |                          | Iodoquinol                                                               |
|                                                  | *Amebas* (Sarcodina)     | Metronidazole + dloxanide furoate                                        |
|                                                  |                          | Paromomycin, iodoquinol                                                  |
|                                                  | *E histolytica*          |                                                                           |
|                                                  | Coccidia (spore forming) | Pyrimethamine, sulfadiazine, folinic acid                                |
|                                                  | *Toxoplasma gondii*      | Spiramycin in first trimester                                            |
|                                                  | *Cryptosporidium parvum* | Nitazoxanide                                                             |
|                                                  |                          | Paromomycin                                                              |
|                                                  | *Isospora belli*         | Cotrimoxazole                                                            |
|                                                  | *Cyclospora cayetanensis*|                                                                           |
|                                                  | Ciliates                 | Tetracyclines                                                            |
|                                                  | *Balantidium coli*       |                                                                           |
|                                                  | *Heterokont*             | Nitazoxanide                                                             |
|                                                  | *Blastocystis hominis*   |                                                                           |
| Sexual                                           | Trichomonads (flagellates)| Metronidazole                                                             |
|                                                  | *Trichomonas*            |                                                                           |
| Freshwater aquatics contact through nasal cavity | *Ameboid to flagellates* | Amphotericin B                                                            |
|                                                  | *Naegleria fowleri*      | Fluconazole                                                               |
|                                                  |                          | Miltefosine                                                              |
| Soil and water contact with open wounds          | *Ameba*                  | Amphotericin B                                                            |
|                                                  | *Acanthamoeba*           | Cotrimoxazole                                                             |
|                                                  |                          | Fluconazole                                                              |

1000 population for five years from 2013 to 2018. Majority of cases presently are from WHO African Region (93%), then the WHO Southeast Asia Region (3.4%), and the WHO Eastern Mediterranean Region (2.1%).

The current challenges are stimulating the global malaria response again with specially designed strategies to reduce disease burden among pregnant women and children in moderate-to-high transmission countries. Insecticide-treated nets,
seasonal malaria chemoprevention in children, intermittent preventive treatment, diagnosis, and prompt treatment are the current strategies towards malaria elimination.

To date five species are shown to cause disease in humans. *Plasmodium falciparum* had shown wider geographical spread replacing *Plasmodium vivax*. Further, *P. falciparum* (Pf) is the most liable for drug resistance. The chloroquine resistance is widely reported with *P. falciparum*. *P. malariae* and *P. ovale* are the species where chloroquine can still be used. However, several countries advocate for simplified treatment guidelines involving artemisinin combination therapies (ACTs) for all species.

The most important vectors are female *Anopheles stephensi* and *Anopheles gambiae*, respectively, in India and Africa. The *P. knowlesi* is still prevalent in Southeast Asia. The *P. vivax* remains major parasite in the WHO Region of the Americas. Nevertheless, globally, half of the *P. vivax* disease burden is from the WHO Southeast Asia Region, with the majority from India.

Thus, *P. falciparum* and *P. vivax* account for most of the malarial disease burden worldwide. However, *P. falciparum* attributes for most of the malaria related deaths. The characteristic feature between Pfalciparum and P vivax is listed in Table 60.2.
60.1.2 Antimalarials Therapeutic Agents

- Antimalarial drugs are grouped based on the *Plasmodium* stage they target as shown in Fig. 60.1. The clinical utility of these drugs is listed in Table 60.3.
- The drugs with longer post-treatment effect are more likely to be used as chemopreventive agent for malaria.
- Drugs that act on red blood cell stage can be used for clinical treatment of malaria attack and as suppressive chemoprophylactic agents. The treatment should be followed by drugs, which can target the liver stages (latent hypnozoites) as well to prevent relapse. Similarly, the suppressive chemoprophylactic would be continued for at least 4 weeks after the person leaves the endemic area, to target the parasites being released from liver.
- Drugs that act on primary liver stage (pre-erythrocytic stage) can be used as causal chemoprophylactic agents that aim to prevent the primary stage of liver itself.
- Chemoprophylactic drugs are not advocated to prevent reinfection in endemic areas.
- The antimalarial agents are also grouped based on chemical structure from cinchona alkaloids to recent sesquiterpene lactones as shown in Table 60.4. The diverse list of chemical groups, which have been used since several decades against *Plasmodium*, is a testimony of changing *Plasmodium* drug susceptibility and drug resistance pattern, over location and period. It also indicates use of combination of drugs against the parasite.
- The combination of drugs is preferred than monotherapies because of the following:
  - Combination therapy prevents rapid emergence drug resistance since individual drugs combined would have different mechanism of action.
  - No single drug is effective against all stages of *Plasmodium* of all species. The effectiveness of drugs also varies with time and spread of drug resistance. Hence, combinations of drugs are essential for complete cure by targeting different stages.
  - The duration of action of each drug varies and can be grouped as in Box 60.1. Hence, by combining short acting with a longer acting drug the complete effectiveness can be maintained over the total period of therapy. Further such combinations are designed to have adequate drug levels based on asexual stages in humans, which is usually 48 h.
- Thus clinically studied and proven antimalarial therapeutic regimens depend on various factors such as
  - *Plasmodium* characteristics: susceptibility to drugs based on endemicity, species, chance of relapse involved in the life cycle.
  - Therapeutic objective (treatment or prophylaxis) determines which stage of life cycle is to be targeted. Currently there are no drugs effective against sporozoites.
Fig. 60.1 Schematic diagram of the life cycle of *Plasmodium* and prime antimalarial drugs and their probable stage of action. The latent stage in liver refers to intrahepatic hypnozoites (dormant stage) causing relapse in *P. vivax* and *P. ovale* infection (life cycle of *Plasmodium falciparum*. Credit: Enomoto et al. 2012. CCBY; modified and adopted)
- Host factors: age, body weight, area of residence, co-morbidities, physiological states such as pregnancy or lactation.
- Malaria disease status: uncomplicated or severe malaria with complications.

| Table 60.3 | Stages of antiplasmodial activity and their clinical relevance |
|-----------------|---------------------------------------------------------------|
| **The stage of antiplasmodial activity** | **Clinical utility** |
| Sporozoites | May prevent infection occurrence after infected mosquito bite |
| Hepatic stage: inhibition of pre-erythrocytic schizogony | Causal prophylactics against malaria |
| Hepatic stage: inhibition of hypnozoites of *P. vivax* and *P. ovale* | Antirelapse therapy or terminal prophylaxis (radical cure) |
| Erythrocytic stage | Treats the clinical episodes of fever and its complications; suppressive prophylaxis |
| Gametocytes | Prevents the transmission of infection from infected person |

| Table 60.4 | Classification of antimalarial drugs based on chemical structure |
|-----------------|---------------------------------------------------------------|
| **Group** | **Drugs** |
| 4-Quinoline methanol (arylamine alcohols) | Quinine (QN) (cinchona alkaloid), mefloquine (MQ) |
| 4-Aminoquinolines | Chloroquine (CQ), amodiaquine (AQ), piperaquine (PPQ) |
| 8-Aminoquinoline | Primaquine (PQ), bulaquine (BQ), tafenoquine (TQ) |
| Acridine | Mepacrine (quinacrine or atabrine), pyronaridine (PYR) |
| Biguanides | Proguanil (PG) |
| Diaminopyrimidines | Pyrimethamine (PM) |
| Other arylamine alcohols | Halofantrine (HL), Lumefantrine (LUM) |
| Sesquiterpene lactones | Artemisinin (ART), artesunate (AS), artemether (AM), arteether (AE), dihydroartemisinin (DHA), arterolane maleate (AM) |
| Naphthoquinone | Atovaquone (AV) |
| Tetracycline | Tetracycline (TET), doxycycline (DOX) |
| Pyrrolidine | Clindamycin (CL) |
| Sulfonamide | Sulfadoxine (SX) |
Box 60.1: Antimalarial Drugs Grouped Based on Elimination Half-Life (t_{1/2})

| Short acting (t_{1/2} 0-24 hrs) | Medium acting (t_{1/2} 1-7 days) | Long acting* (t_{1/2} > 7 days) |
|---------------------------------|---------------------------------|---------------------------------|
| Quinine                         | Atovaquone                      | Chloroquine                     |
| Proguanil                       | Halofantrine                    | Amodiaquine                     |
| Artemisinin and derivatives     | Sulfadoxine                     | Mefloquine                      |
| Primaquine                      | Lumefantrine                    | Piperazine                      |
| Doxycycline                     |                                | Pyrimethamine                   |
| Tetracycline                    |                                | Pyronaridine                    |
| Clindamycin                     |                                | Tafenoquine                     |

*The half-life of sulfadoxine ranges from 4 to 10 days and that of pyrimethamine ranges from 3 to 19 days. Chloroquine has half-life of 4–12 days; its active metabolite desethylchloroquine 7–12 days. Amodiaquine has a t_{1/2} of 3–12 h; however, its metabolite desethylamodiaquine has a t_{1/2} of 4–10 days.

60.1.2.1 Quinine

• As documented by an English writer William Slamon, in mid-seventeenth century, quinine is “The Peruvian bark of which the Jesuites powder is made, is an excellent thing against all sorts of Agues.”

• Since 1600s it was known that Peruvian bark from South America was the remedy for intermittent fevers. The Countess of Chinchon was then treated with the Peruvian bark, which propagated throughout Spain. During mid-eighteenth century, this tree was named as cinchona in memory of the Countess. In early nineteenth century, quinine was isolated from cinchona bark and subsequently became popular for intermittent fevers. Quinine has been the mainstay treatment for malaria since then, though treatment failures due to resistance became common during later twentieth century.

• Thus, quinine, the oldest antimalarial drug is an alkaloid from cinchona bark available as both oral and parenteral formulations. Oral quinine is distinctly bitter in taste. It acts on the food vacuole of Plasmodium by inhibiting detoxification of heme (Fig. 60.2).

• Quinidine is a stereoisomer of quinine used parenterally for severe malaria.

• Both these drugs can cause cinchonism, which involves nausea, headaches, dizziness tinnitus, and blurred vision. These effects are characteristic and occur in milder form in most of the patients and self-limiting with cessation of drugs.

• Hypersensitivity, bronchospasm, flushing, urticaria, and skin reactions also are reported less commonly.
Being drugs of narrow therapeutic margin, in overdosage, causes QT prolongation arrhythmias, hypotension, hypoglycemia, headache, deafness, and blindness.

Quinine has a short half-life unlike its later descendant chloroquine. It is given thrice a day orally. Intravenous or intramuscular quinine is the mainstay of treatment for severe malaria. However, rapid i.v. injections cause hypoglycemia, hypotension, and arrhythmias. Hence, both quinine and quinidine are given by intravenous infusion under monitoring and never intravenous bolus.

Nevertheless, during i.v. infusion monitoring for blood glucose and arrhythmias should be continued. Both the drugs are known to stimulate insulin release. Quinidine is highly cardiotoxic among these drugs and characteristically causes QT prolongation.

Resistance to quinine is documented in Brazil and Southeast Asia. It is evaluated to be due to polymorphisms among efflux transporters genes pfmdr1, pfcr1, and pfmrp1 within parasite food vacuole.

### 60.1.2.2 Chloroquine

- The Dutch had dominated cinchona cultivation from Indonesian Island during World War I. This prompted German to search for a substitute. They screened-in
Plasmochin (pamaquine) and Atabrine (quinacrine, mepacrine)—but were associated with toxicity. In 1934, Farben scientists of Germany synthesized Resochin (chloroquine), and Sontochin (3-methyl chloroquine) which belonged to 4-aminoquinolines. At the outbreak of World War II, the French captured supply of Sontochin in Tunis and transferred to Winthrop researchers. The American Winthrop researchers modified its structure and came up with chloroquine. Later, by comparing the discovered chloroquine with Resochin they understood that both were identical.

- Chloroquine and dichlorodiphenyltrichloroethane (DDT) became prime strategies for malaria control after World War II. However, chloroquine-resistant *Plasmodium falciparum* (CRPF) arose in subsequent decade from several locations.
- Chloroquine is the longer acting 4-aminoquinoline derivative of quinine. Currently threatened by the widely distributed drug resistance to *P. falciparum* in most of the countries, however still effective against *P. ovale*, *P. malariae*, and *P. vivax*.
- Oral chloroquine has high penetrability into tissues with high volume of distribution responsible for persistent drug levels for up to two months. The drug accumulates inside the food vacuole of *Plasmodium* and gets protonated.
- The ferriprotoporphyrin IX is formed because of degradation of heme by proteolytic enzymes inside the food vacuole. The protonated chloroquine enhances pH inside the food vacuole, which in turn inhibits polymerization of ferriprotoporphyrin IX (toxic heme) to hemozoin (polymerized heme). Thus, chloroquine inhibits heme detoxification.
- Common adverse reactions reported are headache, dizziness, abdominal pain, vomiting diarrhea, and pruritus. Prolonged exposure poses risk of neuromyopathy and retinopathy. Intravenous chloroquine infusion is with high toxicity hence avoided.
- Widely prevalent chloroquine resistance is due to mutations in chloroquine resistance transporter gene (PfCRT) causing 40 to 50 times increased pumping of drug out of the food vacuole of *P. falciparum*.

### 60.1.2.3 Sulfadoxine–Pyrimethamine

- Sulfadoxine–pyrimethamine (SP) is available as fixed-dose combination. The popular trade name is Fansidar.
- During World War II, a pyrimidine derivative proguanil, which modulates folate pathway, was also used for successful treatment of malaria. This led to discovery of pyrimethamine another similar drug related to blocking of folate pathway.
- Both these monotherapies documented treatment failure due to resistance. Later, sulfones and sulfonamides were explored for malaria and were combined with proguanil or pyrimethamine. Thus, sulfonamides and pyrimethamine became the most commonly used antifolate combination. However, resistance to this combination is also encountered globally.
- Both the drugs inhibit enzymes in folate pathway. Pyrimethamine targets dihydrofolate reductase (DHFR) and sulfadoxine acts on dihydropteroate
synthase (DHPS). As both drugs act on same pathway, it is not regarded as a drug combination therapy.

- Adverse effects include mild bone marrow suppression, GI disturbances, and headache. Sulfadoxine due to its sulfa moiety precipitates hemolysis in G6PD deficiency and may cause cutaneous allergic reactions including erythema multiforme, Stevens–Johnson syndrome, and toxic epidermal necrosis.

- Used as part of ACT in treatment of uncomplicated P. falciparum, however, resistance has been encountered widely due to mutations in the target enzymes. Thus, fixed dose use is restricted for preventing malaria among pregnant women in endemic countries.

60.1.2.4 Mefloquine

- The quest for alternative to quinine after World War II, coinciding with occurrence of chloroquine-resistant P. falciparum (CRPF) paved way for mefloquine a 4-quinoline methanol, by Walter Reed Army Institute of Research (WRAIR) of the USA.

- Mefloquine given orally is used as treatment or prophylaxis for susceptible malaria parasites. It is combined with artesunate for treatment of uncomplicated malaria.

- It has an elimination half-life of up to 2–3 weeks, available as 250 mg tablets of mefloquine hydrochloride.

- Adverse drug reactions include vomiting, dizziness, cardiac conduction abnormalities, and rarely pneumonitis. Divided doses are shown to reduce some of these milder symptoms. Mefloquine is characterized to cause serious neuropsychiatric symptoms such as seizures, encephalopathy, sleep disturbances, and psychosis among 1–3 patients per 1000 person years of exposure. Hence, the drug is not used in patients with history of neuropsychiatric illnesses. Gastrointestinal effects are also common and early vomiting is correlated with noncompliance with drug and treatment failure. Mefloquine is Avoided in cerebral malaria; pilots, drivers due to neuropsychiatric effects.

- Mefloquine resistance is encountered in areas of Southeast Asia and associated with polymorphisms of pfmdrl gene making lesser drug entry into parasite. Resistance to mefloquine and artesunate combination has emerged in areas of Southeast Asia.

60.1.2.5 Amodiaquine

- Amodiaquine is structurally similar to chloroquine and shares cross-resistance but may show some activity against chloroquine-resistant Plasmodium.

- Usually co-formulated with artesunate and combination is used for chloroquine-resistant infections in endemic areas. Amodiaquine is also used with SP for seasonal malaria prevention.

- Amodiaquine is well absorbed orally and converted to active metabolite desethylamodiaquine through CYP2C8 in the liver. The elimination half-life of active metabolite is 4–10 days.
• Adverse reactions of amodiaquine include nausea, vomiting, skin reactions, pruritus, neutropenia, and eye disorders affecting cornea, accommodation, and rarely retina. Prolonged exposure for prevention of malaria among travelers has documented agranulocytosis and hepatotoxicity. Thus, amodiaquine has been withdrawn from market in countries such as the USA.

60.1.2.6 Piperaquine
• Piperaquine is a bisquinoline and structurally similar to chloroquine and amodiaquine.
• It is used in combination with dihydroartemisinin (DHA-PQ) for treatment and prevention of malaria. With a half-life of 2–3 weeks, piperaquine provides extended post-treatment prophylaxis for chloroquine-resistant parasites.
• Adverse reactions include QT prolongation.

60.1.2.7 Primaquine
• Primaquine is the first in group 8-aminoquinolines for clinical use, predominantly used to prevent relapse in P. vivax and P. ovale attributed to its good activity against dormant hypnozoites.
• Primaquine thus shows efficacy against pre-erythrocytic stage, gametocytes, and exoerythrocytic (hypnozoites) stage in case of P. vivax and P. ovale. No evidence of apparent resistance has been documented.
• Primaquine as such is not active but after metabolism in liver produces reactive intermediates which causes mitochondrial toxicity in Plasmodium.
• Primaquine causes hemolysis in G6PD deficiency, this condition needs to be excluded before administration of the drug. Further electrocardiogram monitoring is also ensured in patients with preexisting cardiac disease such as long QT syndrome, due to their proneness to risk of arrhythmias.
• Contraindicated in severe G6PD deficiency, pregnancy, and breastfeeding.
• WHO recommends single dose primaquine following an ACT regimen intending to further reduction of gametocyte carriage and period of infectivity in P. falciparum malaria.
• Many long acting analogues were developed for clinical use. One such is bulaquine (also known as elubaquine) is a primaquine prodrug developed by Central Drug Research Institute (CDRI), Lucknow, and approved from India. Recently long acting tafenoquine is approved in the USA for the radical cure (prevention of relapse) of Plasmodium vivax and prophylaxis.

60.1.2.8 Mepacrine
• An acridine derivative developed as alternative for quinine, known for yellowing of skin, which may not be related to jaundice. Adverse reactions include dizziness, abdominal discomfort, headache, and hepatotoxicity.
• Later superseded by chloroquine which is more effective and tolerable. Used for off-label indications including giardiasis and rheumatoid arthritis.
60.1.2.9 Pyronaridine

- Pyronaridine chemically consists of a 9-aminoacridine nucleus with side chain resembling amodiaquine. The drug was synthesized in China and has been used as single agent against malaria since 1970. It is available as 175 mg tetraphosphate, which is equivalent to 100 mg freebase.

- Pyronaridine has recently been used as a partner drug in ACTs. Artesunate and pyronaridine are used as 3:1 combination. The additive and synergistic property have been reported from combination of artesinin and pyronaridine also.

- It is shown to target food vacuole of erythrocytic stage of parasites and inhibits formation of hemozoin (beta-hematin) similar to chloroquine. Further, it can also form complexes with hemozoin and turn it toxic to the parasite. The drug also inhibits glutathione dependent heme metabolism. The activity is most for ring forms, schizonts, and trophozoites.

- Pyronaridine is metabolized by CYP1A2, CYP2D6, CYP3A4 and has elimination half-life of 11–13 days.

- Adverse reactions include gastrointestinal discomfort, nausea, vomiting, dizziness, and pruritus.

60.1.2.10 Atovaquone-Proguanil

- Disrupts two different pathways in the biosynthesis of pyrimidines. Atovaquone targets cytochrome b of mitochondrial electron transport chain. It inhibits Plasmodium mitochondrial electron transport chain and proguanil is converted to active cycloguanil, which blocks *Plasmodium* dihydrofolate reductase. Proguanil also directly enhances action of atovaquone, hence used as a combination.

- This combination is not used in malaria endemic areas due to rapid development of resistance. It is usually used for prophylaxis. The combination is effective against hepatic stage, blood stage, and gametocytes of all species.

- Oral absorption is increased by fat meal.

- Atovaquone–proguanil is shown to be safe in pregnancy. Vomiting, diarrhea, abdominal pain, headache, pruritus are reported frequently.

- Atovaquone resistance is attributed to mutations in cytochrome b gene, which could appear even in parasites not exposed to the drug. Nevertheless the clinical efficacy in both prevention and treatment is retained.

60.1.2.11 Halofantrine

- Halofantrine is a phenanthrene methanol used as blood schizonticide, effective against chloroquine-resistant and SP-resistant *P. falciparum*. It is also used in *P. vivax* infection.

- Halofantrine shows cross-resistance with mefloquine.

- Oral absorption is increased by fat meal. The elimination half-life of active metabolite lasts up to 3 days.

- Abdominal pain, itching rashes, rise in liver enzymes, and QT prolongation have been reported as adverse reactions. The QT prolongation poses the risk of sudden cardiac mortalities in susceptible patients.
60.1.2.12 Lumefantrine
• Lumefantrine is a synthetic aryl-amino alcohol structurally and mechanistically related to others such as halofantrine, quinine, and mefloquine. It was developed as benflumetol from China for drug resistant falciparum. Currently used with artemether in ACTs.
• Oral absorption is fat dependent and increased with fat meal. It has elimination half-life of 4–5 days, providing shorter post-treatment prophylaxis.
• Nausea, vomiting, sleeping dysfunction, and neurological disturbances are reported.

60.1.2.13 Tetracycline and Doxycycline
• Tetracyclines are shown to disrupt apicoplast activity in the progeny of treated Plasmodium parasites. They act during cycle of cell division, hence slower in showing activity. Doxycycline especially is long acting with half-life of 8–22 h. Thus, they are combined with fast acting antimalarials such as quinine. Doxycycline is used commonly as primary chemoprophylaxis of malaria.
• Resistance to the antimicrobials has not been detected among Plasmodium.
• Gastrointestinal disturbances, esophageal ulcers, photosensitivity, candidiasis are adverse effects. Tetracyclines also deposit in bones and teeth, hence avoided during pregnancy. Further, they cause permanent tooth discoloration, hence cautiously used in children less than 8 years.
• Nevertheless, doxycycline has been shown to bind less readily to body calcium and recommended as part of antimalarial therapy for less than 21 days in all age group children.

60.1.2.14 Clindamycin
• Clindamycin could be an alternative among children but not advocated in chemoprophylactic regimens. Clindamycin is one of the old drugs against malaria since its introduction in the 1970s.
• It is also active against anaerobic bacteria, toxoplasmosis, Babesia, Pneumocystis.
• It probably targets the apicoplast and causes protein synthesis inhibition.
• The drug accumulates slowly but has elimination half-life of 3–6 h. The antimalarial action is slower in onset, needs at least 3 days of drug administration. It is often combined with fast acting quinine, thus taking advantage of both the drugs, which show synergistic effect.
• Adverse reactions include diarrhea, allergic reactions, and perioral rashes.
60.1.2.15 Artemisinin

- Artemisinin also known as the Chinese herbal medicine qing-hao (sweet wormwood) was used to treat fevers with chills for more than 2000 years. In fourth century AD, Chinese scholar, Ge Hang had documented that to relieve fever, “take a handful of sweet wormwood, soak it in a sheng of water, squeeze out the juice and drink it all.”
- Subsequently, in 1972, Chinese scientists mainly led by Tu Youyou extracted artemisinin sesquiterpene lactones from Artemisia annua (sweet wormwood) and later confirmed to be useful for malaria in humans. Thus, artemisinin became mainstay drug for chloroquine resistance. All artemisinin derivatives are short acting in nature and have risk of recrudescence of infection due to unaffected parasites if used alone.
- Structurally they are sesquiterpene lactone containing distinct endoperoxide 1, 2, 4-trioxane ring, very distinct from any other available antimalarials then. Eventually derivatives that are more active were synthesized.
- The part of 2015 Nobel Prize in Physiology and Medicine was awarded to Tu Youyou for her significant contribution in reducing the disease burden of malaria.

60.1.2.16 Artemisinin Derivatives

- Artemisinin derivatives are the principle part of artemisinin combination therapy (ACT) which is the mainstay treatment for widely prevalent *P. falciparum*.
- Sesquiterpene lactone containing distinct endoperoxide 1, 2, 4 trioxane ring binds to iron of heme by releasing these peroxide bridges, causing release of free radicals which leads to oxidative damage of the parasite proteins.
- Evidence also suggest this carbon centered free radicals mediated alkylation of heme and proteins could be a random, nonspecific process.
- They are fastest acting with rapid clearance of blood stages of all *Plasmodium* species. The elimination half-life is less than 24 h (Table 60.5).
- Further, because of their good activity against gametocytes, they also reduce malaria transmission.
- Intravenous artesunate is the mainstay acute treatment for severe malaria and found to be superior to quinine. Rectal artesunate is used in remote endemic areas for severely ill cases as prereferral treatment before they are transported to health

| Drug                   | Route of administration               | Elimination half-life |
|------------------------|---------------------------------------|-----------------------|
| Artemisinin            | Oral, suppository                      | 2–5 h                 |
| Artesunate             | Oral, intravenous, intramuscular       | Less than 1 h         |
| Artemether             | Oral, intramuscular                    | 5–7 h                 |
| Artemotil (arteether)  | Intramuscular                          | 20 h                  |
| Dihydroartemisinin     | Oral                                  | 1.5–2.5 h             |
| Arterolane             | Oral                                  | 2–4 h                 |
facilities. Artemisinins have short half-life and therapy in severe malaria should be followed by longer acting oral antimalarials regimens.

- Further, monotherapy with artemisinin for less than five days results in recurrent parasitemia due to residual parasites, referred as recrudescence. Moreover, emergence of resistance is of concern. Hence, oral artemisinin-based monotherapies are withdrawn based on WHO guidelines.
- Complete parasite clearance is achieved within 48 h of therapy. Monotherapies of artemisinin as injections and rectal formulations are allowed only in severe malaria cases.
- Artesunate and artether are prodrugs and dihydroartemisinin is the active metabolite form, which is available itself as a formulation.
- Artesunate is water-soluble hemisuccinate derivative. Artether and arteether (artemotil) are oil-based derivatives. Arteether is an ethyl ether derivative of artemisinin with long half-life. Arterolane, a synthetic ozonide with both a trioxolone group and an adamantane group is developed as a part of fixed-dose combination for \textit{P. falciparum} malaria. It is approved in Asian countries for uncomplicated \textit{P. falciparum} malaria among adults. Emerging evidence suggest the use of arterolane–piperaquine fixed dose for uncomplicated \textit{P. falciparum} malaria in children.
- Artesinin group of drugs is usually well tolerated; however, cases of allergy, transient neurological disturbances such as nystagmus are reported. At higher doses artesunate is documented to cause transient neutropenia.
- Limited studies have shown no adverse pregnancy outcomes when artemisinin is administered in first trimester; however, animal studies have documented risk of teratogenicity when drug is given during organogenesis.

60.1.2.17 Artemisinin Combination Therapy (ACTs)

- The Artemisinin combination therapies (ACTs) act on wider parasite stages than other drugs. They are potent and rapid acting. However, drug resistance is emerging and in Greater Mekong Subregion (GMS), parasite has shown to be resistant to all the partner drugs.
- The ACTs comprise short acting artemisinin derivatives and longer acting partner drug to reduce rapid emergence of resistance and cause sustained reduction of \textit{Plasmodium} and thereby reducing disease spread.
- Longer acting partner clears the remaining parasites being released from liver. They also provide post-treatment prophylaxis.
- The combination given for 3 days is shown to be effective in clearing parasites and reduces rapid development of resistance to artesunate. The 3-day regimen could aptly target two asexual cycles, which is usually 48 h each. The various ACTs are listed in Table 60.6.
The patient with previous use of amodiaquine should be monitored for treatment response to artesunate + amodiaquine.

Artesunate–sulfadoxine, pyrimethamine is not available as fixed-dose combination. Artesunate tablets are given with sulfadoxine–pyrimethamine fixed-dose formulations.

Piperaquine is shown to produce lower drug levels in children; hence, higher dose per body weight is advocated with no increased drug levels and evidence of toxicity. Thus, dihydroartemisinin (4 mg/kg) and piperaquine (18 mg/kg) once a day for 3 days in adults and pediatric population ≥25 kg are standard regimen. In children below 25 kg dihydroartemisinin (4 mg/kg) and piperaquine (24 mg/kg) once a day for 3 days are advocated.

The adverse reaction of QT prolongation is documented with piperaquine and hence, avoided in congenital QT prolongation.

WHO has considered artesunate–pyronaridine, the first ACT specifically used for treatment of both P. falciparum and P. vivax blood-stage parasites in adults and children weighing more than 5 kg, for uncomplicated malaria to include in malaria control programs. However, the concern for risk of hepatotoxicity prevails with pyronaridine.

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**Table 60.6 Artemisinin combination therapies (ACTs) for the treatment of uncomplicated *P. falciparum* malaria**

| Drugs                               | Schedule                                                                 | Comments                                                                 |
|-------------------------------------|--------------------------------------------------------------------------|--------------------------------------------------------------------------|
| Artemether+ lumefantrine            | Artemether 80 mg + lumefantrine 480 mg twice a day for 3 days            | Fat meals increase the absorption                                         |
| Artesunate+ amodiaquine             | Artesunate 200 mg + amodiaquine 540 mg once a day for 3 days             | Avoided concurrent use with zidovudine, cotrimoxazole, due to risk of neutropenia |
| Artesunate + mefloquine             | Artesunate 200 mg + mefloquine 440 mg daily for 3 days                  | Concurrent rifampin has shown to reduce mefloquine levels                 |
| Artesunate + sulfadoxine–pyrimethamine | Artesunate 200 mg daily for 3 days Sulfadoxine–pyrimethamine (1500/75) mg single dose on day 1 | High dose folic acid (5mg) daily reduces the efficacy                     |
| Dihydroartemisinin + piperaquine    | Dihydroartemisinin 160 mg + piperaquine 1280 mg once a day for 3 days   | High fat diet is avoided as it can precipitate piperaquine toxicity       |
| Artesunate + pyronaridine           | Artesunate 240 mg + pyronaridine 720 mg once a day for 3 days            | Raised alanine aminotransferase (ALT) is documented without significant risk of hepatic failure |
| Arterolane maleate + piperaquine    | Arterolane 150 mg + piperaquine 750 mg once a day for 3 days            | Vomiting and gastrointestinal disturbance reported adverse reactions       |

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- The patient with previous use of amodiaquine should be monitored for treatment response to artesunate + amodiaquine.
- Artesunate–sulfadoxine, pyrimethamine is not available as fixed-dose combination. Artesunate tablets are given with sulfadoxine–pyrimethamine fixed-dose formulations.
- Piperaquine is shown to produce lower drug levels in children; hence, higher dose per body weight is advocated with no increased drug levels and evidence of toxicity. Thus, dihydroartemisinin (4 mg/kg) and piperaquine (18 mg/kg) once a day for 3 days in adults and pediatric population ≥25 kg are standard regimen. In children below 25 kg dihydroartemisinin (4 mg/kg) and piperaquine (24 mg/kg) once a day for 3 days are advocated.
- The adverse reaction of QT prolongation is documented with piperaquine and hence, avoided in congenital QT prolongation.
- WHO has considered artemesrin–pyronaridine, the first ACT specifically used for treatment of both P. falciparum and P. vivax blood-stage parasites in adults and children weighing more than 5 kg, for uncomplicated malaria to include in malaria control programs. However, the concern for risk of hepatotoxicity prevails with pyronaridine.
• The concern of risk of hepatotoxicity was judged by independent expert review in 2018. Currently the WHO model list of essential medicines recommends artemether–pyronaridine.
• The fixed-dose combination of arterolane maleate and piperaquine in the dose of 150–750 mg is approved in some countries as a simple 3-day once a day regimen.

60.1.2.18 Tafenoquine
• Tafenoquine is a long acting analogue of primaquine (8-aminoquinoline) targeting both the hepatic and blood stages of Plasmodium of all species. It also has good activity against gametocytes of all species of Plasmodium. It has prolonged half-life of 14–28 days.
• Single dose is approved in 2018 for the prevention of relapse following P. vivax treatment. It is also used to prevent malaria as chemoprophylactic agent against all species.
• In a small study it is shown to be more efficacious than primaquine in preventing relapse.
• Also precipitates hemolysis in G6PD deficient patients. Owing to its long duration of action, hemolysis may be prolonged; hence, care should be taken to rule out G6PD deficiency before therapy.
• As antirelapse it is given as single dose 300 mg on 1st or 2nd day of therapy. As chemoprophylactic agent in travelers, it can be given orally 200 mg daily for 3 days before travel; then orally maintained dose 200 mg once a week throughout the stay; and continued for one more week after return from the travel.

60.1.3 Chemotherapeutic Regimens of Uncomplicated P. falciparum Malaria
• Uncomplicated falciparum malaria as per WHO is referred to “symptomatic P. falciparum infection with a positive test and parasitemia <4%, with no features of severity and or evidence of organ dysfunction.”
• ACT regimens consist of 3 days-treatment schedule and are choice of therapy (Box 60.2).
• Recurrence of infection could be due to reinfection or recrudescence. Fever and parasitemia occurring within 28 days of therapy are considered recrudescence or treatment failure. They are treated with an alternative ACT. Fever and parasitemia occurring after 28 days are considered reinfection and treated with an ACT. Mefloquine-based ACT is avoided within 60 days of initial use due to more risk of neuropsychiatric adverse effects.
• A single dose of primaquine (0.25 mg/kg) is shown to be safe even in G6PD deficiency. It is advocated to reduce the transmission of malaria in the geographical area. This strategy is efficient only if high number of malaria treated patients receive primaquine and in areas of low reservoir of parasite burden.
• ACTs are recommended for uncomplicated P. falciparum malaria in second and third trimester. The safety profile is also good with no apparent safety issues.
Among them, dihydroartemisinin + piperaquine is associated with maximum post-treatment effect and safety profile. Hence, this combination is also used as intermittent preventive treatment for malaria in pregnancy. Artemether-lumefantrine is shown to cause lesser adverse effects.

### Box 60.2: Therapeutic Regimens for Uncomplicated *P. falciparum* Malaria in Nonpregnant Adults and Children

| Treatment of uncomplicated *P. falciparum* malaria | Any one of the following ACTs: |
| Children and adults (except pregnant women in first trimester) | • Artemether + lumefantrine |
| | • Artesunate + amodiaquine |
| | • Artesunate + mefloquine |
| | • Dihydroartemisinin + piperaquine |
| | • Artesunate + sulfadoxine–pyrimethamine (SP) |
| | • Artesunate + pyronaridine |

| Gametocidal drug to reduce the transmission of treated *P. falciparum* | Single dose of 0.25 mg/kg primaquine is given in low transmission areas |
| Except pregnant women, infants aged < 6 months and women breastfeeding infants aged < 6 months | G6PD testing is not required |

Data modified and adopted from World Health Organization guidelines for the treatment of malaria 3rd edition 2015 available at Accessed March 18, 2020

### 60.1.4 Antimalarial Regimen for Severe Malaria

- Severe malaria is commonly reported from *P. falciparum*; however, it can occur with *P. vivax* and *P. knowlesi* infections also. It is characterized with microvascular obstruction due to sequestration of infected red blood cells compromising blood supply and leading to end organ failure.
- Artesunate is the drug of choice for severe malaria based on a landmark SEQUAMAT trial, and subsequent studies as shown in Box 60.3.
- Further, artemether is considered only if artesunate is not available. A recent systematic review showed that artemether is inferior to artesunate in treating severe malaria in adults. However, artemether is proved better than quinine in both children and adults.
- Artesunate dose need not be adjusted in renal or liver dysfunction. Quinine needs dose adjustment according to renal parameters. Mefloquine is contraindicated in patients with epilepsy or neuropsychiatric disorders.
### Box 60.3: Therapeutic Regimens for Severe Malaria

| Adults, pregnant women children | Initial therapy | After 24 h and able to eat and drink |
|----------------------------------|-----------------|--------------------------------------|
| **First line**                   | Artesunate IV 2.4 mg/kg per dose at hour 0, 12, 24, and then every 24 h (if less than 20 kgs artesunate IV 3.0 mg/kg per dose to be given) | Artemisinin-based combination therapy orally for 3 days (not mefloquine) Travel history to countries with artemisinin resistance: intravenous artesunate PLUS intravenous quinine |
| **Alternate initial therapy**    | Artemether intramuscular injection 3.2 mg/kg loading dose, then 1.6 mg/kg every 24 h • Quinine dihydrochloride IV infusion 20 mg/kg loading dose over 4 h then maintenance dose 10 mg/kg over 2 h every 8 h | |

Data modified and adopted from World Health Organization guidelines for the treatment of malaria 3rd edition 2015 available at Accessed March 18, 2020

### 60.1.5 Other Therapeutic Regimens for Uncomplicated Malaria

The therapeutic regimens for other clinical scenarios such as first trimester pregnancy and malaria; malaria in infants; uncomplicated falciparum malaria in HIV are listed in Table 60.7. The malaria occurring from *P. vivax*, *P. ovale*, and *P. malariae* is also listed.

### 60.1.6 Chemoprevention of Malaria Among High-Risk Group in Endemic Areas and Seasonal Prevention of Malaria

- Chemoprevention is the use of antimalarial drugs either for prophylaxis in travelers or for preventive malaria among high-risk group in the endemic area and a specific season of risk.
- The rationale for chemoprevention is maintaining adequate drug levels in blood during the period of maximum risk. Hence, antimalarial drugs are started before the risk ensues in high-risk people for ensuring drug levels also assessing the tolerability.
- Intermittent preventive therapy (IPT) is recommended in areas of moderate-to-high transmission of malaria, where malarial parasite is still susceptible to SP as indicated by 50% or lesser prevalence of the Pfdrps 540 mutation.
- IPT for malaria is suggested in pregnancy in endemic areas as shown in Table 60.8. Intermittent preventive treatment in pregnancy (IPTp) with SP is
| Specific scenario                                      | Therapeutic regimen                                                                                                                                                                                                 |
|-------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| First trimester uncomplicated *P. falciparum* malaria  | Quinine (10 mg/kg) 8th hourly and clindamycin (10 mg/kg) twice a day orally for 7 days                                                                                                                                  |
| Infants below 5 kg body weight uncomplicated *P. falciparum* malaria | ACT at same bodyweight target dose (mg/kg) as for children weighing 5 kg                                                                                                                                             |
| Patients co-infected with HIV uncomplicated *P. falciparum* malaria | Avoid artesunate + SP, if patient is also receiving cotrimoxazole  
Avoid artesunate + amodiaquine if patient is also receiving efavirenz or zidovudine                                                                                                                                   |
| Non-immune travelers with *P. falciparum* malaria      | Travelers returning to non-endemic areas are treated with an ACT                                                                                                                                                     |
| Uncomplicated hyperparasitemia                        | They are at risk of treatment failure, severe malaria, and death; ACT to be administered; closely monitored                                                                                                           |
| If malaria species is not known with certainty        | Treat as for uncomplicated *P. falciparum* malaria                                                                                                                                                                    |
| In areas with chloroquine susceptible infections      | Any one of the two regimens  
1. Chloroquine  
   - Base 25 mg/kg divided over 3 days  
   - Day 1: 10 mg base/kg  
   - Day 2: 10 mg base/kg  
   - Day 3: 5 mg base/kg  
2. ACT (except pregnant women in first trimester)                                                                                                           |
| In areas with chloroquine-resistant infections        | ACT (except pregnant women in first trimester)                                                                                                                                                                        |
| Chloroquine-resistant *P. vivax* infection in first trimester | Quinine (10 mg salt/kg) 8 hourly for 7 days                                                                                                                                                                            |
| Antirelapse therapy in *P. vivax, P. ovale* malaria    | Adults and children (except G6PD deficient patients, pregnant women, infants < 6 months, women breastfeeding infants < 6 months, women breastfeeding older infants unless they are known not to be G6PD deficient)  
Primaquine 14-day course 0.25–0.5 mg/kg body weight, daily                                                                                                     |
| Antirelapse therapy in *P. vivax, P. ovale* malaria: with G6PD deficiency | Primaquine base 0.75 mg/kg once a week for 8 weeks under supervision and monitoring for hematological toxicity                                                                                                        |
| Antirelapse therapy in *P. vivax, P. ovale* malaria: unknown G6PD status and testing not available | Primaquine (based on assessment of risks of use against benefits)                                                                                                                                                   |
| Antirelapse therapy in pregnant and breastfeeding women | Consider weekly chemoprophylaxis with chloroquine (300 mg base) until delivery and breastfeeding are completed; then based on G6PD status give primaquine to prevent relapse                                                                 |

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well studied in endemic areas of Africa. Several trials have showed that when administered three or more doses during second trimester at interval of one-month apart, SP increases mean birth weight of infants, reduces low-birth-weight infants, placental parasitemia, and maternal parasitemia. However the data of these benefits in third or later pregnancy is limited.

• Similarly in areas of moderate-to-high transmission of malaria, where infection is acquired mostly in childhood or infancy, SP-IPTi is recommended for infants (<12 months) at the time of vaccination against diphtheria, tetanus, pertussis (DTP), and measles immunization—usually 10 weeks, 14 weeks, and 9 months of age. The pooled analysis of randomized placebo controlled trials had shown significant protection against clinical malaria, anemia, and all cause hospital admissions for up to 35 days following each dose.

• SP-IPTi is not recommended in infants who had already received sulfa drugs for any other ailments such as for opportunistic infections in HIV.

• Evidence is emerging for safety and tolerability of monthly dihydroartemisinin–piperazine (DP) as IPT in infants, children, and pregnant women. The monthly DP for 3 days, given for up to 6 months to be safe, effective in lowering

| Chemoprevention                                                                 | Special risk groups                                                                 |
|---------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| Intermittent preventive treatment of malaria in pregnant women (IPTp) in moderate-to-high malaria stable transmission areas in Africa | • Sulfamethoxazole and pyrimethamine (SP-IPTp) to all women during their first or second pregnancy  
• Dosing during antenatal visits starting second trimester  
• Sulfadoxine (1500 mg)/pyrimethamine (75 mg)—atleast three doses are received 1 month apart |
| Intermittent preventive treatment in infants (IPTi) residing in moderate–high malaria stable transmission areas in Africa | • Sulfamethoxazole and pyrimethamine (SP-IPTi) to all infants (<12 months) at the time of second and third doses of DTP vaccination and during measles  
• The dose is half tablet of sulfadoxine (500 mg) + pyrimethamine (25 mg) in infants weighing more than 5 kg and one fourth the tablet in infants less than 5 kg |
| Seasonal malaria chemoprevention (SMC) in areas of highly seasonal malaria transmission in sub-Sahel region of Africa | • Amodiaquine + SP monthly for all children <6 years (3–59 months) during every transmission season for maximum of four doses  
• Dose in 3–11 months: half tablet of 153 mg AQ base once daily for 3 days + half tablet of sulfadoxine 500 mg/pyrimethamine 25 mg, once  
• Dose in 12–59 months: 153 mg AQ base once daily for 3 days + sulfadoxine 500 mg/pyrimethamine 25 mg, once |

Data modified and adopted from World Health Organization guidelines for the treatment of malaria 3rd edition 2015 available at Accessed March 18, 2020
symptomatic malaria, as well as asexual and sexual stage parasites. This strategy may reduce malaria transmission in endemic areas.

- Seasonal malaria chemoprevention (SMC) consists of intermittent administration of full course of antimalarial drugs to children during the season in areas with highly seasonal malaria transmission in sub-Saharan region only. This is because most mortality and morbidity among children occur during rainy season during which malaria transmission is more.
- SMC is given by administering sulfadoxine–pyrimethamine and amodiaquine. It is shown to reduce the incidence of malaria in areas of extended seasonal transmission among children. If SMC is employed in the region, IPTi is withheld.
- Complete course of monthly amodiaquine + SP for all children below 6 years of age (3–59 months) is administered for maximum of four doses.
- Treatment of P. falciparum infections during the period of SMC should include alternative antimalarial drug regimens which do not include amodiaquine and SP.
- It is shown that SMC protects against occurrence of malaria episodes including severe malaria episodes.

60.1.6.1 Chemoprophylaxis Among Travelers

- With widespread malaria infection globally, there is a risk for international travelers to the malaria endemic areas.
- Malaria in travelers account for significant amount of disease burden, also posing other challenges like delayed diagnosis and treatment in malaria free areas.
- Further, malaria parasite is dynamic with respect to its distribution, susceptibility to drugs, and human immunity. This global malaria scenario is further complicated by malaria occurring among travelers.
- Waning of immunity occurs over a period of six months once the person moves to malaria free areas.
- Preventive strategies include being aware, avoid being bitten, chemoprophylaxis, diagnose, and treat fever one week or more after residing in endemic area and three months after leaving the high risk area and avoid swampy environments during dusk and nights.
- Fever in a traveler within three months of leaving an endemic country is medical emergency and malaria should be ruled out. Standby emergency treatment (SBET) is indicated in such cases in the absence of definitive diagnosis.
- Chemoprophylaxis provides significant reduction in fatality of disease. The regimen is selected based on data on malarial parasite and its drug sensitivity. Some of the regimens are listed in Table 60.9.
- Non-immune traveler to endemic areas during transmission seasons exposed to mosquito bites especially during dusk to dawn is at risk of disease.
- The drugs that inhibit pre-erythrocytic, liver stage of malaria parasites are causal prophylactic agents. These agents like atovaquone + proguanil or primaquine are continued until person stays in endemic areas and stopped after leaving the zone.
Table 60.9 Chemoprophylactic regimens of malaria for travelers to endemic areas

| Drugs       | Regimen                                      | Instructions                                                                 |
|-------------|----------------------------------------------|------------------------------------------------------------------------------|
| Atovaquone–proguanil | One dose of 250 mg atovaquone + 100 mg of proguanil, daily | One day before departure and continue for 7 days after return                |
| Chloroquine | One dose of 300 mg chloroquine base weekly: 5 mg base/kg weekly or 600 mg chloroquine base weekly divided over 6 daily doses of 100 mg base; 10 mg base/kg weekly divided over daily doses (with one drug-free day per week) | One week before departure and continue for four weeks after return If following daily dosing start one day before |
| Doxycycline | One dose of 100 mg daily                      | Start one day before departure and continue for four weeks after leaving the high risk area |
| Mefloquine  | 5 mg/kg weekly one dose of 250 mg weekly      | Start two to 3 weeks before departure and continue four weeks after return   |
| Primaquine  | Primaquine 30 mg base, once a day after       | 2 days prior to travel, daily during travel, and for 7 days after leaving (not to be used in G6PD deficiency) |

- The drugs that inhibit erythrocytic, asexual stage of parasites are suppressive prophylactic agents. These drugs are taken during stay in endemic areas and continued after at least 4 weeks after leaving the zone to eliminate all parasites moving out from the liver.

60.1.6.2 Chemoprophylaxis in Pregnant and Children Travelers
- In pregnancy, it is advisable to avoid traveling to malaria endemic areas. However, if travel is inevitable proper guidance and counseling are to be given. Chemoprophylaxis includes chloroquine-based prophylaxis, if the endemic area is with exclusively P. vivax transmission. Travelling to areas endemic with P. falciparum transmission should receive mefloquine prophylaxis.
- Similarly, infants and young children should be avoided from travel to endemic areas. Chloroquine and mefloquine-based regimens based on body weight doses need to be given.

60.1.6.3 Standby Emergency Treatment (SBET)
- Standby emergency treatment is self-administration of antimalarial drugs in case of symptoms of malaria, as a first-aid, if travelers are staying in remote areas with lack of medical access (Table 60.10).
- SBET is indicated only if not possible to reach medical center within 24 hours of fever. Clear written instructions on identifying symptoms and how to take the drugs before they reach medical centers should be precisely given to travelers.
- Definitive treatment for malaria once medical center is accessed should be with drug not used as SBET.
Vomiting within 30 min of drug intake should be followed by another full dose. Vomiting occurring 30–60 min of drug intake should be followed by additional half dose.

Full course of SBET should be completed and antimalarial chemoprophylaxis should be resumed 1 week after starting SBET.

### Table 60.10 Standby emergency treatment (SBET) regimens for malaria chemoprophylaxis

| Regimens                  | Regimen                                                                 | Comments                                           |
|---------------------------|-------------------------------------------------------------------------|----------------------------------------------------|
| Artemether–lumefantrine    | 6 doses in total over 3 days                                            | Apparently safe in children                        |
|                           | Each dose consists of 80 mg of artemether + 480 mg of lumefantrine      | Limited data                                       |
|                           |                                                                         | Limited data in first trimester                    |
| Atovaquone–proguanil      | One dose daily for three days                                           | Safe in children (limited data)                    |
|                           | 1 g atovaquone + 400 mg proguanil                                       | No data in pregnancy                               |
| Chloroquine               | 25 mg base/kg divided over 3 days                                       | Safe in children and pregnancy                     |
|                           | Day 1: 10 mg base/kg                                                    |                                                    |
|                           | Day 2: 10 mg base/kg                                                    |                                                    |
|                           | Day 3: 5 mg base/kg                                                    |                                                    |
| Clindamycin               | 300 mg dose 4 times daily for 5 days                                    | Safe in children and pregnancy                     |
| Dihydroartemisinin + piperaquine | One dose daily for 3 days            | Limited data in first trimester                    |
|                           | Dihydroartemisinin 4 mg/kg per day                                      | Safe in children > 5 kg                            |
|                           | Piperaquine 18 mg/kg per day                                            |                                                    |
| Quinine                   | 8 mg base/kg                                                            | Safe in pregnancy and children                     |
|                           | 3 times daily for 7 days                                                |                                                    |

- Vomiting within 30 min of drug intake should be followed by another full dose. Vomiting occurring 30–60 min of drug intake should be followed by additional half dose.
- Full course of SBET should be completed and antimalarial chemoprophylaxis should be resumed 1 week after starting SBET.

### 60.1.7 Antimalarial Therapeutics: Future Perspectives

#### 60.1.7.1 Artemisinin and Partner Drug Resistance
- Malaria parasites resistant to more than two different chemical groups of drugs are multidrug resistant. Usually such parasites are resistant to chloroquine and SP. However, resistance to mefloquine and artemisinins is also being reported.
- PfKelch13 mutations are the molecular markers for partial artemisinin resistance mainly from Greater Mekong subregion (GMS) Guyana, Papua New Guinea, and Rwanda. In WHO Southeast Asia Region, such markers are found in Bangladesh, India, Myanmar, and Thailand. Emerging failure rates of treatment with first line ACT against P. falciparum are reported to be highest in Thailand.
- Recent evidence suggest triple drugs artemisinin-based combination therapies (TACTs), where three drugs are combined as in dihydroartemisinin–piperaquine
and mefloquine, and artemether-lumefantrine and amodiaquine, show promise in countries with artemisinin and ACT partner drug resistance. Both these combinations were efficacious and tolerated for acute uncomplicated P. falciparum malaria, though the later combination has risk of prolonging QT interval.

- Safety and efficacy of adding methylene blue (MB) or primaquine (PQ) both being gametocidal agents to existing ACTs in children with uncomplicated falciparum malaria to decrease malaria transmission are also being explored.

### 60.1.7.2 Mass Drug Administration to Control Vector Transmission of Malaria

- The newer concept of mass drug administration of systemic insecticides such as ivermectin is evolving to control the vector. This forms drug based vector control by the use of systemic insecticides also known as endectocides.
- The first cluster-randomized trial has given evidence that ivermectin mass administration every 3 weeks during rainy season would significantly reduce the incidence of malaria in young children.
- Ivermectin is shown to affect both mosquito mortality and sporozoite transmission during mosquitoes bite. Further, this strategy also enhances the control of other tropical neglected diseases such as lymphatic filariasis where ivermectin and albendazole mass administration are already in place.

### 60.1.7.3 Malaria Vaccine

- Antisporozoite vaccines are being studied for the prevention of malaria. However, the development of immunity to malaria infection is complicated by several factors such as two reproductive cycles, different stages within these phases, different target cells in each of these stages, genetic variability associated with the parasite.
- Recombinant protein vaccine such as RTS, S elicits good IgG antibodies response to P. falciparum circumsporozoite protein (CSP), the crucial protein of the pre-erythrocytic (PE) stage sporozoite.
- RTS, S/AS01B and RTS, S/AS02A both were shown to be effective and safe at 50% and 32%, respectively, in a phase 2 trials among adults. Similarly, RTS, S/AS01E evaluated in Africa has showed moderate efficacy against clinical and severe malaria among children.
- In spite of these studies, several studies have shown high parasitemia even in protected individuals and high genetic variability of CSP protein. In view of these developments, WHO has showed concern on uncertainties and reproducibility of efficacy and safety of RTS, S to implement for routine use.
- WHO suggests pilot implementation of 4-dose booster schedule in children residing in moderate-to-high transmission areas of sub-Saharan Africa. The schedules for pilot implementation consist of a 3-dose initial series from 5 to 9 month of age with a minimum interval between doses of 4 weeks, followed by a 4th dose at 15–18 months.
- WHO also recommends further studies to enhance the efficacy of the RTS, S.
### 60.1.7.4 Investigational Drugs in Clinical Development

- **Cipargamin (KAE609)**
  Cipargamin is a synthetic antimalarial spiroindolone analog which disrupts parasite plasma membrane Na-ATPase and shown to be active against sexual and asexual stages. The clinical development is ongoing for both *P. falciparum* and *P. vivax* malaria. It shows good parasite clearance and tolerability. The elimination half-life being nearly 20 h, it can be adopted for once a day regimens.

- **Artefenomel (OZ439)**
  Artefenomel is synthetic peroxide with long duration of action. It is shown to be efficacious and tolerable in a clinical study against both *P. falciparum* and *P. vivax*. It has elimination half-life of 46–62 h possibly may be useful for single dose regimens for malaria in the future.

- **KAF156**
  KAF156 is an imidazolopiperazine which targets pre-erythrocytic liver parasites and blood stages by unknown mechanism. It has shown good activity against *P. falciparum* and *P. vivax* during clinical development. Efficacy against artemisinin-resistant parasites is also evaluated.

- **Dihydroorotate Dehydrogenase Inhibitor**
  DSM265 is the first in class inhibitor of enzyme dihydroorotate dehydrogenase (DHODH) of pyrimidine biosynthetic pathway. DSM265, chemically triazolopyrimidine, is being explored in clinical trials for *P. falciparum* and drug resistant *Plasmodium*. It is predicted to be of long elimination half-life. A related compound DSM 421 is also explored for single dose cure of malaria.

- **Ferroquine**
  Ferroquine is a 4-aminoquinoline which is structurally related to chloroquine and showed activity against chloroquine-resistant *P. falciparum*, when given as combination with artesunate (Table 60.11).

### 60.2 Babesiosis

- Babesiosis is characterized by exposure to tick bites, fever, anemia, splenomegaly, and demonstration of parasites inside red blood cells. The disease is usually self-limited with parasitemia over months to years. In older subjects and those with splenectomy, the progression is rapid with hemolytic anemia, thrombocytopenia, hemoglobinuria, disseminated intravascular coagulation, and renal failure.

- Important species is Babesia microti transmitted by ticks *Ixodes scapularis* which also spread Lyme disease and anaplasmosis. Other species such as Babesia venatorum, Babesia duncani, and Babesia divergens are also known to cause Babesiosis.

- Atovaquone, azithromycin, quinine clindamycin are used in therapeutic regimens as shown in Table 60.12. Plasmapheresis and red blood cell exchange transfusion
| Drug       | Mechanism                                                                 | Indication                                                                 | Adverse reactions                                                                 |
|------------|---------------------------------------------------------------------------|----------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| Quinine    | Alkaloid from Cinchona bark  
L-stereoisomer of quinidine  
Inhibits parasite heme detoxification inside food vacuole  
Kills large ring form and trophozoites asexual | Parenteral indicated in severe malaria. Oral is used in uncomplicated malaria especially in first trimester pregnancy Alternately if ACT is not available | Cinchonism: dizziness, tinnitus, hearing impairment, headache, nausea, vomiting, altered vision, vertigo, abdominal pain, diarrhea, hyperinsulinemia, hypoglycemia, QTc interval prolongation Hypersensitivity: urticaria, bronchospasm, thrombocytopenia, and hemolytic anemia Oxidative hemolysis in G6PD deficiency IV bolus: hypotension and cardiac arrest IV: venous thrombosis IM: pain, necrosis, abscess Overdose: retinal toxicity and cardiac toxicity (arrhythmias, angina, cardiac arrest) |
| Chloroquine| 4-amino quinoline  
Inhibits heme detoxification in the parasite  
Disrupts nucleic acid synthesis | Treatment for uncomplicated malaria due to *P. vivax*, *P. ovale*, *P. knowlesi*, *P. malariae*, and prevention of *P. vivax* infection | Considered safe in pregnancy  
Pruritus  
Hepatitis  
Headache  
GI disturbances  
Slight QT prolongation  
CNS toxicity-convulsions  
Chronic use: keratopathy, retinopathy |
| Amodiaquine| Converted to active metabolite desethylamodiaquine accumulating inside | In combination with artesunate for uncomplicated *P. falciparum*, *P. malariae* | GI disturbances such as nausea, vomiting, loss of appetite, abdominal pain, |

(continued)
Table 60.11 (continued)

| Drug       | Mechanism                                      | Indication                                      | Adverse reactions                                   |
|------------|------------------------------------------------|-------------------------------------------------|-----------------------------------------------------|
|            | food vacuole and disrupts heme detoxification | *vivax*, and other species Follow-on therapy for severe malaria (this combination is not used for prophylaxis due to risk of hepatotoxicity) In combination with SP at monthly intervals for seasonal malaria chemoprevention to children 3–59 months | fever, cough, anorexia, fatigue, weakness, neutropenia, hepatotoxicity, arrhythmias, bradycardia, transient accommodation disorders, corneal opacification, extrapyramidal effects, and pruritus |
| Pyronaridine| Inhibits formation of hemozoin (beta-hematin) It can also form complexes with hemozoin and turn it toxic to the parasite | Combined with artemesunate for uncomplicated *P falciparum* malaria | Include gastrointestinal discomfort, nausea, vomiting |
| Mefloquine | Inhibition of heme detoxification Inhibition of endocytosis of cytosol in parasite | Chemoprophylaxis of malaria for all species treatment of uncomplicated malaria | Neuropsychiatric effects such as anxiety, dizziness, confusion, seizures, depression, hallucinations, vomiting, hepatitis, thrombocytopenia |
| Primaquine | 8-aminoquinoline Reactive intermediate metabolites lead to toxic intracellular oxidative process Disruption of mitochondria and electron transport in parasite | In combination with ACT or chloroquine (*vivax*, *ovale*) Radical cure: *P vivax*, *P ovale* Presumptive antirelapse: (terminal prophylaxis) *P vivax*, *P ovale* decreases onward transmission *P falciparum* monotherapy alternate for primary prophylaxis against all malaria | GI disturbances, abdominal pain, nausea, vomiting |

(continued)
Table 60.11 (continued)

| Drug                     | Mechanism                                                                 | Indication                                              | Adverse reactions                                     |
|--------------------------|---------------------------------------------------------------------------|---------------------------------------------------------|-------------------------------------------------------|
| Sulfadoxine–pyrimethamine| Blocking of folic acid synthesis by inhibition of dihydropterotate synthetase (sulfadoxine) and dihydrofolate reductase (pyrimethamine) | SP + artesunate for uncomplicated malaria SP + amodiaquine chemoprevention among children in areas with high seasonal transmission Intermittent preventive treatment in I and II trimester and in infants in areas with moderate-to-high transmission | GI disturbances, dizziness, skin reactions Leukopenia, thrombocytopenia, megaloblastic anemia, hemolytic anemia Crystalluria, hematuria, hepatitis |
| Atovaquone–proguanil     | Atovaquone–hydroxynaphthoquinone Inhibits transport of several parasites enzymes Interferes cytochrome electron transport chain Disrupts mitochondrial membrane potential Proguanil Biguanide active metabolite cycloguanil acts by inhibiting dihydrofolate reductase | Prophylaxis of malaria In combination with artesunate and primaquine as an alternative treatment for uncomplicated malaria treatment of uncomplicated malaria in travelers outside malaria endemic areas (not used in endemic areas due to emergence of resistance) | Safe in pregnancy Cough GI disturbances Dizziness Oral ulceration Neutropenia and anemia Skin reactions Hepatitis |
| Lumefantrine             | Prevents heme detoxification in parasite food vacuole Accumulation of toxic heme complex Not used as monotherapy | Oral as FDC artemether with lumefantrine for uncomplicated malaria caused by any of the species of malaria follow-on treatment after severe malaria (this is not indicated for prophylaxis) | Nausea, dizziness, headache |
| Doxycycline              | Inhibits protein synthesis Disrupts apicoplast in parasites               | Prophylaxis of malaria in combination for uncomplicated malaria and follow- | GI disturbances Dysphagia, dry mouth stomatitis, esophageal ulcers Enamel hypoplasia, (continued) |

(continued)
Table 60.11 (continued)

| Drug                  | Mechanism                                                                 | Indication                                                                 | Adverse reactions                                                                 |
|-----------------------|---------------------------------------------------------------------------|----------------------------------------------------------------------------|---------------------------------------------------------------------------------|
| Clindamycin           | Lincosamide                                                               | In combination with artesunate or quinine in uncomplicated or severe malaria | Discoloration of teeth                                                             |
|                       | Inhibition of protein synthesis and peptide chain initiation               |                                                                            | Regarded as safe in pregnancy                                                     |
|                       |                                                                            |                                                                            | Pseudomembranous enterocolitis                                                     |
|                       |                                                                            |                                                                            | GI disturbances                                                                  |
|                       |                                                                            |                                                                            | Metallic taste in mouth                                                           |
|                       |                                                                            |                                                                            | Allergic reactions                                                               |
|                       |                                                                            |                                                                            | Blood dyscrasias                                                                 |
|                       |                                                                            |                                                                            | Hepatotoxicity                                                                   |
|                       |                                                                            |                                                                            | Gasping syndrome in neonates due to “benzyl alcohol” in parenteral formulations   |
| Artesunate            | Hemisuccinate derivative of dihydroartemisinin                           | Uncomplicated malaria of any of species                                     | Possible risk of teratogenicity in first trimester (limited studies in humans);   |
|                       | Cation mediated formation of reactive intermediates and reduction of peroxy | P. falciparum, P. vivax, P. ovale, P. knowlesi, P. malariae                  | still used for severe malaria                                                     |
|                       | bridge                                                                     | Artesunate—amodiaquine, artesunate—mefloquine, artesunate-SP                | Safely used in second and third trimester of pregnancy                             |
|                       |                                                                            | Parenteral artesunate (IV, IM) in severe malaria                            | Hypersensitivity reactions, GI disturbances, rashes, cough delayed hemolysis      |
|                       |                                                                            | Rectal artesunate—prereferral treatment in severe malaria                   | Neutropenia                                                                       |
| Artemether            | Methyl ether derivative of dihydroartemisinin                            | Oral as FDC with lumefantrine for uncomplicated malaria caused by any of the | Hypersensitivity reactions, GI disturbance                                        |
|                       |                                                                            | species of malaria follow-on treatment after severe malaria (this is not indicated for prophylaxis) IM as an alternative for parenteral artesunate severe malaria prereferral | Dizziness                                                                         |
|                       |                                                                            |                                                                            | Neutropenia                                                                       |
|                       |                                                                            |                                                                            | Raised liver enzymes                                                             |
|                       |                                                                            |                                                                            | Bradycardia, Slight QT prolongation                                               |

(continued)
are advocated for severe parasitemia and rapidly progressive disease in asplenic patients.

Table 60.11 (continued)

| Drug                | Mechanism                                                                 | Indication                                      | Adverse reactions               |
|---------------------|---------------------------------------------------------------------------|-------------------------------------------------|---------------------------------|
| Dihydroartemisinin–Piperaquine | Dihydroartemisinin Active metabolite of artesunate and artemether Cation mediated formation of reactive intermediates Piperaquine accumulates and inhibits heme detoxification in food vacuole; causes deposition of toxic heme complex | Treatment of uncomplicated malaria \( P \text{ falciparum, } P \text{ vivax, } P \text{ knowlesi, } P \text{ malariae} \) Follow-on therapy for severe malaria after parenteral regimen | Diarrhea, nausea, vomiting Anemia Dizziness Headache Cough Slight QT prolongation |

Table 60.12 Therapeutic regimens for Babesiosis

| Babesiosis    | Regimens                                                                 |
|---------------|--------------------------------------------------------------------------|
| Mild to moderate | Atovaquone 750 mg twice daily + azithromycin 600 mg once a day for 7 days |
| Severe disease | Quinine 650 thrice a day + clindamycin 600 mg thrice daily for 7 days    |

60.3 Trypanosomiasis

60.3.1 Human African Trypanosomiasis (HAT) (Sleeping Sickness)

- Hemoflagellates of \( \text{Trypanosoma brucei rhodesiense} \) and \( \text{Trypanosoma brucei gambiense} \) gain entry into human body by bites of tsetse flies found in shaded areas along streams especially in sub-Saharan Africa.
- \( T. b. gambiense \) causes West African trypanosomiasis, in which humans are main mammalian hosts. Rarely, chancre occurs at the bite sites but initial period is asymptomatic. Then hemolymphatic disease characterized by irregular fever, joint pain, rashes, headache, edema, lymphadenopathy with characteristic rubbery nodes over the months is seen. This stage progresses to meningoencephalitis with features of somnolence, severe headache, personality changes, parkinsonism, and coma.
T. b. rhodesiense causes East African trypanosomiasis, which is primarily a zoonosis of cattle. Painful chancres occur at bite sites along with lymph node enlargement rapidly progressing to hemolymphatic stage, which could also cause myocarditis. This stage progresses to meningoencephalitis without treatment.

Trypanosoma develops in tsetse fly for 18-35 days before entry into body through the bite.

Pentamidine and nifurtimox + eflornithine are the mainstay drugs for early and later stage of West African trypanosomiasis (Table 60.13). Alternatively, suramin + eflornithine combination is used for early trypanosomiasis. Melarsoprol is used as alternative in meningoencephalitis stage.

Suramin and melarsoprol are the mainstay drugs for early and late stages of East African trypanosomiasis, respectively. Pentamidine can be used as an alternative for early stage of East African trypanosomiasis.

Fexinidazole, introduced in 2018, was the first oral therapy for HAT. It is given once a day for ten days. It is a heterocyclic compound similar to nifurtimox and benznidazole undergoes reductive activation (nitro reduction) with the enzyme nitroreductase leading to cytotoxicity.

Benzoxaborole-6-carboxamides are being explored in clinical trials as a breakthrough single oral therapy for meningoencephalitic stage of HAT. Acoziborole is the first drug in this class and in phase III clinical trials with some early signs of positive results. The drug affects parasite polyadenylation specificity factor subunit 3 (CPSF3) disrupting methionine metabolism.

### Table 60.13 Therapeutic regimens for different stages of Human African Trypanosomiasis (HAT)

| Disease          | Early stage                                                                 | Meningoencephalitic stage                                                                 |
|------------------|-----------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|
| West African     | Pentamidine 4mg/kg intramuscular or intravenously every day or alternate days for 7 days | Nifurtimox–eflornithine combination therapy (NECT) Eflornithine intramuscular or intravenously (400 mg/kg/day in two divided doses for 7 days) and oral nifurtimox (15 mg/kg/day in three doses for 10 days) |
| East African     | Suramin (100–200 mg test dose, then 20 mg/kg [maximum up to 1 g] intravenously on days 1, 3, 7, 14, and 21 or weekly for five doses) | Melarsoprol (three periods of 3.6 mg/kg/day intravenously for 3 days, with 7-day breaks between the periods or a 10-day intravenous course with 0.6 mg/kg on day 1, 1.2 mg/kg on day 2, and 1.8 mg/kg on days 3–10) |

#### 60.3.1.1 Pentamidine

- Pentamidine belongs to the group of diamidine. It is useful against *L. donovani*, Trypanosomes, and *Pneumocystis jirovecii*.
- It causes DNA damage and also alters mitochondrial membrane potential.
Pentamidine is strongly basic in nature and causes histamine release, hypoten-
sion, palpitation, vomiting, and fever after intravenous injection. Hence, it is
given intramuscularly to lessen these acute reactions. Other adverse effects
include renal and hepatic damage. Pentamidine also causes cytolysis of pancreatic
cells, with initial hypoglycemia and later insulin-dependent diabetes mellitus.
• Effective in leishmaniasis (kala azar) even for antimony-resistant parasites; how-
ever, pentamidine resistance has also emerged. It is also effective only for first
stage *Trypanosoma brucei gambiense* before CNS involvement.

**60.3.1.2 Eflornithine**
• Eflornithine is a high cost drug given slow intravenous infusion for prolonged
periods.
• Used for second stage disease only but ineffective against *T. b. rhodesiense*.
• It is an ornithine decarboxylase inhibitor also being explored for tumors. It is also
used topically as cream to reduce the facial hair growth in women.
• Adverse reaction includes vomiting, bone marrow toxicity, and septicemia.

**60.3.1.3 Nifurtimox–eflornithine combination therapy (NECT)**
• Given intravenously for second stage disease.
• Eflornithine is combined with nifurtimox, a nitrofuran compound, which
produces free radical metabolites in the body.
• NECT is better tolerated than monotherapy of eflornithine, further this combina-
tion is advocated for slowing the emergence of resistance.
• Adverse effects reported are fever, convulsions, and confusion.

**60.3.1.4 Suramin**
• Suramin is used since 100 years and still retains its action against *Trypanosoma*.
• Effective only for first stage *Trypanosoma brucei rhodesiense*.
• Highly toxic drug, given intravenously.
• Being highly negatively charged, it is taken inside of *Trypanosoma* by receptor-
mediated endocytosis through a glycoprotein and LDL receptor. The mechanism
of suramin is postulated to be broad spectrum. Inside the protozoa, suramin is
shown to disrupt vesicular transport. It interferes the several metabolic pathways
such as glycolysis and disrupts mitochondrial membrane potential and finally
reducing cellular ATP.
• Adverse reaction includes myalgia, irritability, nausea, vomiting, mouth ulcers,
vision disturbances, tingling sensation of skin, rashes, numbness, tenderness of
extremities, renal failure.

**60.3.1.5 Melarsoprol**
• Highly toxic arsenic compound, known to cause drug-induced reactive encepha-
lopathy, convulsions, fever, bloody diarrhea, renal and cardiac abnormalities.
• Used for second stage disease.
• Melarsoprol is a prodrug which converts to melarsen oxide and produces adducts with several enzymes, inhibits trypanothione reductase, and causes mitosis defects.
• Given intravenously, high incidence of drug resistance.

60.3.2 American Trypanosomiasis (Chagas Disease)

• The protozoan parasite *Trypanosoma cruzi* infects animals and sometimes humans. The regions with Chagas disease include continental Latin American countries from Southern South America to Southern United States.
• The transmission of disease to humans is through contact with feces and/or urine of infected blood sucking triatomine bugs, which live in roof cracks or walls of sparsely constructed houses. The bugs bite and defecate close to bitten spot, in humans during night.
• Chagas disease can also be transmitted through blood, blood products organ transplantation from infected person, and intake of food contaminated with infected vector feces. Congenital disease is by mother to child transmission.
• The *T. cruzi* after entry into body, from bloodstream gains into several organs such as heart, brain, intestines causing progressive diseases over decades.
• Acute infection is sparsely seen characterized by fever, inflammation at the site of inoculation with lymphadenopathy (Chagoma of skin), hepatosplenomegaly, myocarditis, and parasitemia.
• This phase is followed by asymptomatic latent phase, which may last lifelong with some patients going for symptomatic disease many years after initial infection.
• Chronic infection is characterized by abnormalities in smooth muscle function and heart.
• The presentation ranges from dysphagia, mega esophagus, aspiration, megacolon, abdominal pain, constipation, cardiomyopathy, arrhythmias, heart failure to meningoencephalitis.

| Table 60.14 | The therapeutic regimens for American trypanosomiasis |
|-------------|---------------------------------------------|
| Drugs       | Mechanism                                   | Schedule                                      | Adverse reactions                     |
| Benznidazole| Nitroimidazole, undergoes reductive activation and produce reactive metabolites which causes DNA damage | Oral doses of 5 mg/kg/day in two divided doses for 60 days | Rashes, fever, peripheral neuropathy Bone marrow suppression, granulocytopenia |
| Nifurtimox  | Nitrofuran derivative undergoes reduction and forms nitro-anion radical metabolites which causes DNA breakdown | 8–10 mg/kg/day in four divided oral doses for 90–120 days | Anorexia, loss of weight, psychiatric abnormalities, excitability, ataxia, sleepiness, nausea, and vomiting |
Benznidazole and nifurtimox are the trypanocidal drugs effective against parasitemia, hence used in acute stage in children, congenital infections, reactivated infections, and young adults with chronic disease. The therapeutic drugs are summarized in Table 60.14.

Both the drugs being nitroheterocyclics undergo anaerobic enzymatic reduction of nitro group producing reactive metabolites and cause DNA damage of trypanosomes, which are considered as facultative anaerobes.

Benznidazole is preferred due to its better efficacy and safety. Either of them is not effective in preventing progression of disease during chronic phase of Chagas disease. Still drugs are recommended for all patients with T. cruzi infection irrespective of clinical disease stages including in childbearing women to prevent vertical transmission as per the latest guidelines from Pan American Health Organization (PAHO).

Anorexia, weight loss, and peripheral neuropathy are common adverse reactions reported with both benznidazole and nifurtimox. Adverse fetal effects are not reported with either of the drugs. These drugs are not recommended in adults over 50 years with chronic infection with established organ damage due to marginal benefits.

### Table 60.15 Summary of drugs used in treatment of leishmaniasis

| Agents                      | Regimen and indications                                                                 | Adverse reactions                                         |
|-----------------------------|-----------------------------------------------------------------------------------------|-----------------------------------------------------------|
| Liposomal amphotericin B    | 3 mg/kg/day intravenously on days 1–5, 14, and 21                                          | Infusion related reactions, fever, chills, dyspnea, hypotension, hepatotoxicity, renal toxicity |
| Pentavalent antimonials      | 20 mg/kg/day intravenous or intramuscular once a day for 28 days (Visceral and mucocutaneous disease) and 20 days for cutaneous leishmaniasis | Gastrointestinal disturbances, fever, headache, myalgias, pancreatitis, arrhythmias |
| Sodium stibogluconate       | Visceral, mucocutaneous, and cutaneous leishmanias                                         |                                                           |
| Meglumine antimoniate       | Visceral leishmanias                                                                      |                                                           |
| Miltefosine                 | Oral doses of 2.5 mg/kg in two divided doses for 28 days Visceral, New world cutaneous leishmanias | Vomiting diarrhea, abnormalities in liver and renal function tests |
| Paromomycin                 | 11 mg/kg/day intramuscular for 21 days in Visceral leishmanias                            | Nephrotoxicity, ototoxicity, elevation of liver enzymes, and renal toxicity |
60.4 Leishmaniasis

- Spectrum of diseases caused by protozoan parasites Leishmania transmitted by insect female phlebotomus sandfly through bites; depending on species of leishmania three different forms of diseases are identified: cutaneous, visceral (kala-azar), and mucocutaneous. The pharmacotherapy is outlined in Table 60.15.
- Most people with parasite infection remain asymptomatic without development of leishmaniasis.
- Old world cutaneous leishmaniasis caused by Leishmania tropica, Leishmania major, and Leishmania aethiopica (Mediterranean, Middle East, Africa, Central Asia, and Indian subcontinent).
- New world cutaneous leishmaniasis by Leishmania mexicana, Leishmania amazonensis, Leishmania braziliensis, Leishmania panamensis, and Leishmania peruviana (Central and South America) can progress to mucocutaneous disease.
- Mucocutaneous leishmaniasis: Leishmania braziliensis, Leishmania panamensis, and Leishmania peruviana (lowland forest of America).
- Visceral leishmaniasis caused by Leishmania donovani (Indian subcontinent and East Africa), Leishmania infantum (Mediterranean, Middle East, China, parts of Asia, and Africa), and Leishmania chagasi (South and Central America) characterized with fever, progressing hepatosplenomegaly, pancytopenia, wasting, and has high case fatality.

60.4.1 Amphotericin B

- Amphotericin B is effective in Leishmania due to high ergosterol content in their membranes. Currently this drug has highest cure rates.
- Highly toxic and needs monitoring.
- Liposomal formulation is more effective, well tolerated but expensive, and needs intravenous administration. Thus, liposomal amphotericin B is first line of drug for visceral leishmaniasis because of effectiveness, shorter course, and lower toxicity.

60.4.2 Pentavalent Antimonials

- Pentavalent antimonials such as sodium stibogluconate and meglumine antimoniate are given parenterally.
- Sodium stibogluconate has been first line drug for visceral leishmaniasis (kala-azar means “black” (kala) “fever” (azar) in Hindi) with emergence of resistance in parts of India. It is given parenterally usually intramuscular injections. The plasma half-life is usually 6–12 h. However, the drug is accumulative in the tissues.
• The sulfhydryl metabolic enzymes of amastigotes are inhibited. It also blocks glucose and fatty acid metabolism. It can also cause oxidative damage by reducing pool of reduced thiols in parasites.
• Treatment in kala-azar needs up to 28 days.
• Highly toxic with feature such as nausea, metallic taste, abdomen pain, cough, abscess, pancreatitis, ECG changes, renal and hepatic damage.

60.4.3 Miltefosine

• Only oral drug for visceral leishmaniasis.
• It causes DNA damage and mitochondrial toxicity.
• Adverse effects include vomiting, diarrhea, renal and hepatic impairment.
• Emergence of treatment failure is reported with miltefosine also.
• Highly teratogenic drug.

60.4.4 Paromomycin

• An aminoglycoside given as intramuscular injection has shown to be useful for stibogluconate-resistant leishmania. It is available as topical preparation for cutaneous lesions.
• Good efficacy has been demonstrated with 21-day course.
• Adverse reactions include nephrotoxicity, raised hepatic enzymes, injection site pain, and ototoxicity.

60.4.5 Combination of Drugs for Visceral Leishmaniasis

• With emergence of resistance to existing drugs, combination is being used in many countries as follows:
• Single dose of liposomal amphotericin + 7-day course of miltefosine
• Single dose of liposomal amphotericin B + 10-day paromomycin
• Course of 10-day of miltefosine + paromomycin

60.4.6 Topical Therapy for Cutaneous Leishmaniasis

• Topical drugs include intralesional antimonials or pentamidine; paromomycin ointment, cryotherapy, and surgery.
• Oral fluconazole has also shown some efficacy for cutaneous leishmaniasis (Fig. 60.3)
60.5 Coccidiosis

- Coccidiosis are caused by Cryptosporidium parvum, Cryptosporidium hominis, Isospora belli, Cyclospora cayetanensis, Sarcocystis.
- Coccidian oocysts act as infective form transmitted by ingestion of contaminated food.
- Cryptosporidiosis often seen as community outbreaks of gastroenteritis and one of the common causes of childhood diarrhea. It is also commonly encountered in AIDS causing chronic watery diarrhea.
- Cryptosporidiosis pharmacotherapy is useful in some patients only. Restoring immunity by antiretroviral drugs in AIDS helps in the treatment. Commonly used drugs are paromomycin and nitazoxanide.
- The other parasites, Isospora belli and Cyclospora cayetanensis cause severe form of diarrhea and fever and weight loss in immunocompromised. Cotrimoxazole (trimethoprim + sulfamethoxazole, TMP-SMZ) is used as therapeutic regimen as shown in Table 60.16.
- No specific drugs are established for sarcocystosis, a course of albendazole or cotrimoxazole has been tried.
- Ocular disease is treated with systemic albendazole, topical fumagillin, and corticosteroids.
Blastocystis hominis were earlier described as yeasts, currently classified as protozoa. The parasite is known to cause disease only in immunocompromised. The infection is spread by feco-oral route with ingestion of cysts forms. The dogs and pigs form the natural hosts of the parasite. Most of the symptoms are mild or self-limiting, with watery diarrhea, abdominal pain, loss of appetite, and bloating. Metronidazole, tinidazole, nitazoxanide, cotrimoxazole, paromomycin have been used as drugs.

Amebiasis is one of the leading causes of severe diarrhea globally. Entamoeba histolytica, the species, which cause clinical disease, may occur as avirulent intestinal commensal or can lead to serious disease. Other two species E. dispar and E. moshkovskii appear as avirulent commensals, of which E. dispar are most commonly encountered. Disease is caused by penetration of the intestinal wall, then causing diarrhea, and with progression leading to dysentery or extraintestinal disease, most commonly liver abscess. Humans are the only established host of E. histolytica with transmission between them. Flies can act as mechanical vectors for contamination of food from feces. The cyst in the fecally contaminated food gets into the body through ingestion. Thus, poor sanitation and crowding contribute significantly for propagation of E. histolytica.
• Most of the people with E. histolytica remain as asymptomatic carriers capable of spreading the disease.
• Symptomatic disease, which occurs in 10–20% of infected, starts with diarrhea, abdominal pain, leading to dysentery with bloody stools in severe cases. High fevers, hypotension, abdominal tenderness, hyperperistalsis, and hepatomegaly occur in disseminated extraintestinal infections. Fulminant colitis could occur in 1–2% of infected, rapidly progresses to necrotizing colitis with hemorrhage and intestinal perforation. The mortality exceeds more than 50% in cases of fulminant disease.
• The evidence for other mode of transmission such as direct contact and sexual route due to oral–anal sexual practices is emerging.
• Chronic infection leads to ameboma presenting with obstructive intestinal symptoms. Amebic liver abscess is most common presentation of extraintestinal disease with fever, tender liver, and weight loss. Severity of disease is most pronounced in malnourished children, pregnant women, and intake of corticosteroids.
• Antiamoebic drugs can be divided based on their clinical utility as luminal agents, tissue amebicides, and both luminal and tissue amebicides (Table 60.17). All drugs especially nitroimidazoles are effective in amoebiasis and are widely used. The therapeutic regimen based on stage of disease is given in Fig. 60.4.
• The asymptomatic cases are treated only with luminal agents. Moderate to severe disease is treated with metronidazole and emetine. The emetine dihydrochloride hydrate, derived from ipecac root is rarely used due to its toxicity including cardiotoxicity. Dehydroemetine is the synthetic congener of emetine with similar adverse reactions, including renal failure and cardiotoxicity.
• Metronidazole and tinidazole are the first line drugs for amebic liver abscess. The chloroquine has advantage of gaining good concentration in liver and is added in cases of treatment failure with metronidazole. In severe and complicated liver abscess, imaging-guided needle aspiration and drainage are preferred in addition to pharmacotherapy. The mechanism of action of various antiamoebic drugs is illustrated in Fig. 60.5.

Table 60.17  Amebicide groups and their drugs

| Types of amebicides                        | Drugs used                                              |
|-------------------------------------------|---------------------------------------------------------|
| Both luminal (intestinal) and tissue       | Nitroimidazoles (metronidazole, tinidazole, ornidazole, secnidazole), thiazolides (nitazoxanide), emetine, dehydroemetine |
| Tissue (extraintestinal) amebicides        | Chloroquine                                             |
| Luminal amebicides                         | Diloxanide furoate, paromomycin, iodoquinol, quiniodochlor, tetracycline |
**Fig. 60.4** Summary of therapeutic regimens for treatment of amebiasis

**Fig. 60.5** Schematic diagram of drugs acting on *Entamoeba histolytica*, trophozoite, and cyst forms. *Diloxanide furoate has activity against luminal trophozoites also; ROS reactive oxygen species*
60.7.1 Nitroimidazoles: Metronidazole

- Metronidazole is a prototype drug introduced in the 1950s, effective orally and intravenously.
- Metronidazole is drug of first line for anaerobic microorganisms including amebiasis, amebic liver abscess, trichomoniasis, giardiasis, bacterial vaginosis, and pseudomembranous enterocolitis. It is also effective against Bact. fragilis, Fusobacterium, Clostridium perfringens, Helicobacter pylori, Campylobacter, peptococci, spirochetes, and anaerobic Streptococci.
- Luminal amebicides are often combined with metronidazole for intestinal amebiasis as little of drug reaches colon after systemic absorption in proximal intestine. Further, nitroimidazoles do not completely eradicate cysts in the lumen.
- Metronidazole undergoes reductive activation by ferredoxin oxidoreductase (PFOR)-1 and/or PFOR 2 (ferredoxin (fd) as a cofactor); nitroreductase-1 (cofactor being flavin mononucleotide (FMN)) or by thioredoxin reductase (cofactor being flavin adenine dinucleotide (FAD)). In the process, metronidazole is converted to reactive oxygen species and other nitro radicals, which cause oxidative damage. Thus, metronidazole interferes in electron transport chain of anaerobic organisms and shows no effect on aerobic organisms as shown in Fig. 60.6.
- The drug is well absorbed from intestines and widely distributed. It undergoes oxidation and glucuronidation in liver and excreted in urine. The plasma half-life is nearly 8 h.
- Adverse drug reactions include nausea, metallic taste, glossitis, dizziness, abdominal cramps, neutropenia, thrombophlebitis of injected veins, and disulfiram-like reactions in alcoholics.
- The alcohol antabuse syndrome (disulfiram-like reaction) is seen with most of nitroimidazoles and due to inhibition of alcohol dehydrogenase. The symptoms consist of vomiting, flushing, sweating, abdominal cramps, and hypotension. Hence, alcohol-containing products should be avoided during and for atleast, 48–72 h post-dose of nitroimidazoles therapy.

![Fig. 60.6](image)

**Fig. 60.6** Schematic of mechanism of metronidazole in microaerophilic, amitochondriate protozoa (*Entamoeba, Giardia, and Trichomonas*). PFOR-1: ferredoxin oxidoreductase, *FMN* flavin mononucleotide, *FAD* flavin adenine dinucleotide
Long-term exposure can cause nervous system adverse reactions such as seizures and neuropathies.

Asymptomatic pregnant women who are known to pass of cysts could have therapy delayed until after 14 weeks or until delivery. For symptomatic mild to severe infection, the risk–benefit should be judged before the use of metronidazole and paromomycin. Metronidazole is teratogenic during first trimester with risk of cleft lip in the newborn. Hence, during first trimester least absorbed amebicide like paromomycin, which is considered safe in pregnancy, is used.

Enzyme inducers such as phenobarbitone and rifampin enhance metabolism of metronidazole and reduce its therapeutic effects. The enzyme inhibitors like cimetidine can precipitate toxicity.

Other nitroimidazoles including tinidazole, secnidazole, and ornidazole are long acting, thus requiring less frequent dosing schedule. There is limited data evidence for better effectiveness of tinidazole as compared to metronidazole in amebiasis.

Tinidazole has a plasma half-life of about 12 hours hence used in once a day regimens. The adverse effects are similar to metronidazole but with lesser incidences.

Ornidazole has a plasma half-life of about 12–14 h, with similar efficacy and adverse effect profile as that of metronidazole.

Secnidazole has an even longer half-life of 17–29 h with better maintenance of minimum inhibitory concentrations (MIC) over longer duration.

Satranidazole is another longer action with 14 h half-life. It is claimed to have much lesser adverse reactions including disulfiram-like reactions.

60.7.2 Thiazolides

Nitazoxanide is a broad-spectrum agent useful against wide range of organisms including anaerobic bacteria, helminths, protozoa, and viruses.

It is converted to the active form tizoxanide, which disrupts energy metabolism by interfering with pyruvate: ferredoxin/ flavodoxin oxidoreductase (PFOR)-mediated electron transport chain of anaerobic metabolism.

The drug has shown some evidence of effectiveness in both intestinal and hepatic amebiasis in smaller clinical studies. It is advocated as an alternative to metronidazole in amebic colitis at the dose of 500 mg orally twice a day for 3 days.

60.7.3 Emetine and Its Derivatives

An alkaloid with good amebicide activity against trophozoites. It acts by inhibiting protein synthesis. It is given parenterally as subcutaneous or...
intramuscular injections. Emetine is accumulated in liver, kidney, and lungs for up to 2 months.

- Adverse effects are high with local injection reactions, nausea, vomiting, diarrhea, muscle weakness, myositis, and myocarditis. The drug is contraindicated for cardiac and renal impairments and also during pregnancy.
- Dehydroemetine, a derivative of emetine, is shown to be less cumulative and less toxic and preferred.

### 60.7.4 Chloroquine

- Chloroquine is effective for amebic hepatic abscess due to its high accumulation in liver. It is not used for intestinal disease. With a better safety profile as compared to emetine, chloroquine is preferred for elimination of trophozoites in liver.

### 60.7.5 Diloxanide Furoate

- Effective luminal amebicide with lytic actions on trophozoites and cysts.
- Though absorbed from intestines it has minimal tissue amebicide activity.
- Used for asymptomatic intestinal amebiasis and carriers in areas where infections are not common. Not used solely for extraintestinal infections.
- Flatulence, vomiting, and itching are commonly reported.

### 60.7.6 Paromomycin

- Aminoglycoside used for intestinal parasitic infections such as luminal amebiasis, cryptosporidiosis, and leishmaniasis.
- Drug of first line for asymptomatic intestinal amebiasis and carriers in areas where infections are not common.
- Considered first line drug for amebiasis and giardiasis in pregnancy.

### 60.7.7 Iodoquinol and Quiniodochlor

- Iodoquinol and quiniodochlor belong to the group of 8-hydroxyquinolines and are effective luminal amebicides with no action on tissue forms.
- These compounds can cause thyroid enlargement in toxic doses. Other adverse reactions include nausea, diarrhea, and pruritus.
- Long-term use also causes iodism characterized by mucous membrane inflammation, due to iodine overload. Some compounds especially quiniodochlor can cause subacute myelo optic neuropathy (SMON), which was in an endemic form in Japan during the 1970s.
60.8 Giardiasis

- Flagellate protozoa Giardia lamblia infect upper small intestines and regarded as the most common intestinal protozoa of the USA and Europe.
- G. lamblia and microsporidia share similarities with bacteria and are considered as evolutionary transition between eukaryote and prokaryotes. However, microsporidia is now recognized as fungi.
- Infection is transmitted through ingestions of contaminated water and food with dormant cysts of G. lamblia. In the small intestine, these cysts develop into trophozoites, which are attached to the lumen of small intestine.
- Trophozoites are anaerobic in nature and undergo asexual replication and also produce cysts which pass through feces transmitting another mammal.
- Several mammals act as host for this infection such as human, sheep, cattle, and dogs.
- Mild infection in humans is common. Up to 10% of infected people become asymptomatic cyst passers.
- Acute diarrhea is seen in 25–50% of infected with profuse watery diarrhea, usually leading to chronic phase with malaise, malabsorption, anorexia, bloating, and abdominal cramps.
- Common regimens include metronidazole 250 mg three times daily for 5–7 days; tinidazole 2g once; albendazole 400 mg orally once daily for 5 days; nitazoxanide 500 mg orally twice daily for 3 days; furazolidone 100 mg four times a day for 7 days.
- Paromomycin 500 mg orally three times a day for 7 days is also useful especially during pregnancy due to its better safety data.
- Emerging evidence suggest superiority of single dose tinidazole compared to metronidazole and albendazole for symptomatic and asymptomatic giardiasis in both children and adults.

60.8.1 Nitazoxanide

- Nitazoxanide is a congener of niclosamide, an antihelminthic drug.
- It is converted to the active form tizoxanide, which disrupts anaerobic energy metabolism.
- Nitazoxanide interferes with inhibition of pyruvate: ferredoxin/flavodoxin oxidoreductase (PFOR)-mediated electron transport chain of anaerobic metabolism.
- Other mechanisms reported are inhibition of glutathione-S-transferase (GST), modulation of chloride channel, disruption of cell membrane, inhibition of viral hemagglutinin, and transcription factor immediate early 2 (IE2). Nitazoxanide is also explored to be an antiviral agent including SARS-CoV-2 infection.
- Nitazoxanide is approved for Giardia lamblia and Cryptosporidium parvum in patients above 1 years. It is also useful in E. histolytica, T. vaginalis, Ascaris, H. pylori. It is shown to be effective against metronidazole-resistant anaerobic parasites also.
- Metabolism of tizoxanide is by conjugation and excreted in urine and bile.
Adverse effects are mild and include gastrointestinal disturbances, vomiting, and headache.

**60.9 Trichomoniasis**

- *Trichomonas vaginalis* is very commonly seen in sexually transmitted disease. The protozoa survives in moist conditions for many hours diagnosed by demonstration of motile trichomonads on wet mount.
- The usual presentation is non-foul smelling, copious vaginal discharge with vulvovaginal symptoms in females, and nongonococcal urethritis with minimal discharge in males.
- The drugs commonly used are tinidazole or metronidazole; both can be used as oral single dose of 2 g; tolerability of tinidazole is better than metronidazole.
- Metronidazole is also used as oral 500 mg twice daily for 7 days regimen to improve tolerability, currently suggested for treatment in HIV patients. Evidence shows multidose metronidazole to be more efficacious as compared to single dose regimen.
- Asymptomatic infection also needs to be treated to limit the progression of disease.

**60.10 Toxoplasmosis**

- *Toxoplasma gondii* is an intracellular protozoan found in many species of mammals including humans and birds.
- Toxoplasmosis is identified by isolation of Toxoplasma gondii or identification of tachyzoites in tissue or body fluids. Cats are the definitive hosts and transmitted by ingestion of cysts in raw meat and oocysts in food and water.
- Primary disease is characterized by malaise, fever, sore throat, and lymphadenopathy.
- Mother to fetal transmission leading to congenital toxoplasmosis characterized by CNS abnormalities and retinochoroiditis.
- Immunocompetent individuals developing primary infections usually recover by themselves. Treatment is indicated for only severe, persistent, visceral disease for 2 to 4 weeks. Primary infections during pregnancy and in immunocompromised persons are treated with drugs. In patients with persistent immunodeficiency such as HIV, treatment is continued after the full course of therapy as maintenance. These HIV positive patients are treated with chemoprophylaxis even in the absence of symptoms or signs.
- Pharmacotherapy works only against tachyzoites and do not eradicate infection.
- Pyrimethamine, sulfadiazine, and folinic acid form first line of treatment; folinic acid is added to reduce bone marrow suppression as shown in Table 60.18. The adverse reactions of this regimen include sulfonamide sensitivity reactions such as rashes, hepatotoxicity, gastrointestinal disturbances, nephrotoxicity, bone marrow suppression.
Congenital infection in child is also treated with pyrimethamine, sulfadiazine, and folinic acid for 12 months to reduce the progression of disease.

Trimethoprim/sulfamethoxazole (TMP/SMX) is the only efficient combination for prophylaxis in patients at risk for Toxoplasma reactivation (CD4+ T cells < 200/μL).

Spiramycin, a macrolide, is preferred in pregnancy of gestation period less than 14 weeks. It is advocated only to prevent vertical transmission. Established fetal infection does not benefit from spiramycin as it does not cross the placental barrier.

Conversely, pyrimethamine–sulfadiazine definite therapy is avoided before 14 weeks of gestation due to the teratogenic potential of sulfadiazine.

Blood count should be monitored weekly for bone marrow suppression.

Alternative regimens include replacing sulfadiazine in the regimen with clindamycin, or trimethoprim–sulfamethoxazole.

### Table 60.18 Therapeutic regimens for toxoplasmosis

| Scenario | Regimen |
|----------|---------|
| Acute infection in immunocompromised | 6 week-induction treatment (until clinical and radiological improvement) Combination of pyrimethamine (200 mg loading dose on day 1, then 75 mg/day if patient weighs ≥ 60 kg or 50 mg/day if patient weighs < 60 kg), plus sulfadiazine (3000 mg twice a day if patient weighs ≥ 60 kg or 2000 mg twice a day if patient weighs ≥ 60 kg) and folinic acid (10–15 mg/day) Maintenance regimen until CD4 count stays above 200/mm³ Pyrimethamine 50 mg/day Sulfadiazine 2000 mg twice a day |
| Acute toxoplasmosis in pregnancy (no proof of fetal infection) gestational age less than 14 weeks | Spiramycin (SPI) oral 1 g for three times a day until amniocentesis |
| Acute toxoplasmosis in pregnancy with fetal toxoplasmosis | Oral pyrimethamine 50 mg/d + sulfadiazine 4–6 g/d + folinic acid 50 mg/week until delivery |

- Congenital infection in child is also treated with pyrimethamine, sulfadiazine, and folinic acid for 12 months to reduce the progression of disease.
- Trimethoprim/sulfamethoxazole (TMP/SMX) is the only efficient combination for prophylaxis in patients at risk for Toxoplasma reactivation (CD4+ T cells < 200/μL).
- Spiramycin, a macrolide, is preferred in pregnancy of gestation period less than 14 weeks. It is advocated only to prevent vertical transmission. Established fetal infection does not benefit from spiramycin as it does not cross the placental barrier.
- Conversely, pyrimethamine–sulfadiazine definite therapy is avoided before 14 weeks of gestation due to the teratogenic potential of sulfadiazine.
- Blood count should be monitored weekly for bone marrow suppression.
- Alternative regimens include replacing sulfadiazine in the regimen with clindamycin, or trimethoprim–sulfamethoxazole.

### 60.11 *Naegleria*

- *Naegleria fowleri* is the free-living ameba with mitochondria seen in warm freshwater. They can gain entry into human body through nasal cavity.
The infection of brain is very aggressive causing primary amebic meningoencephalitis (PAM) notoriously giving the name “brain eating ameba” to the parasite.

Intravenous amphotericin B, fluconazole, and rifampin are the mainstay treatment, which has shown some success for the fatal disease. Recently, miltefosine has also been shown to be useful in therapeutic regimens.

60.12 Acanthamoeba

Acanthamoeba is a mitochondria bearing free-living ameba, rarely causes disease after infection. The spread is through direct contact with wounds, cuts, or through contact lenses. The parasite is ubiquitously found in soil and water. Acanthamoeba can occur in healthy individuals and can progress to blindness because of keratitis.

Acanthamoeba keratitis is treated with a biguanide antiseptic polymer, polyhexamethylene biguanide (0.02% PHMB) eye drops. The other topical antiamebic therapies include propamidine (diamidine) or chlorhexidine, used either as monotherapy or in combination.

Granulomatous amebic encephalitis (GAE) is a fatal infection involving central nervous system usually in immunocompromised. Combinations of fluconazole, flucytosine, amphotericin, albendazole, pentamidine, sulfadiazine, and clarithromycin have been tried along with surgical resection of lesions.

The infection could be disseminated to multiple organs including skin, sinuses, and lungs in the immunosuppressed patients.

60.13 Dientamoeba

*Dientamoeba fragilis* is one of the causes for traveler diarrhea, though many individuals may remain asymptomatic.

The trophozoite stage is highly fragile and hence difficult to isolate from the stool samples. Further, dientamebiasis is often associated with E vermicularis infection (pinworm).

Severe symptomatic disease is treated with Iodoquinol, paromomycin, and metronidazole, along with albendazole for E vermicularis.

60.14 Balantidium

*Balantidium coli* is the only ciliate protozoa known to infect humans.

The parasite commonly resides in pigs and transmitted through contaminated water and feco-oral route.

The infection is aggressive only in immunocompromised.
| Drug                          | Mechanism                                                                 | Indication                                      | ADRs                                                                 |
|------------------------------|---------------------------------------------------------------------------|-------------------------------------------------|----------------------------------------------------------------------|
| Metronidazole and other     | In anaerobic mitochondrial protozoa undergoes reductive activation, free radicals are formed which cause DNA damage | Giardiasis                                      | Vertigo, nausea, headache, neuropathy, pancreatitis, Metalic taste, leukopenia, antabuse effect |
| nitroimidazoles              |                                                                            | Trichomoniasis                                  |                                                                      |
|                              |                                                                            | Amebiasis                                       |                                                                      |
| Diloxanide furoate           | Protein synthesis inhibitor                                               | As luminal amebicide                            | Vomiting, nausea, itching, flatulence                                |
| Paromomycin                  | Protein synthesis inhibitor                                               | Luminal amebicide                               | Vomiting, nausea gastrointestinal disturbances                        |
|                              |                                                                            | Luminal amebicide, amebiasis, and giardiasis in pregnancy |                                                                      |
| Iodoquinol                  | Probable chelation of ferrous ion                                        | Luminal amebicide                               | Vomiting, nausea, headache, thyroid swelling, gastrointestinal disturbances |
| Pentamidine                  | DNA damage and mitochondrial toxicity                                      | Kala-azar                                       | Fever, hypotension, renal and hepatic damage                         |
| Suramin                      | Depletion of ATP                                                          | Early stage of human African trypanosomiasis   | Myalgia, irritability, nausea, vomiting, tingling sensation of skin, rashes, numbness, tenderness of extremities, renal failure |
| Melarsoprol                  | Mitotic defect                                                            | Later stage of trypanosomiasis                 | Reactive encephalopathy, convulsions, fever, bloody diarrhea, renal and cardiac abnormalities |
| Nifurtimox                   | Mitochondrial damage                                                     | American trypanosomiasis (Chagas disease)      | Nausea, anorexia, abdomen pain, weight loss, neuropathy, thrombocytopenia |
| Liposomal amphotericin B     | Micropores in cell membranes                                             | Leishmaniasis                                   | Nausea, vomiting, anemia, renal failure, infusion reactions, hypokalemia, hypomagnesemia |
| Sodium stibogluconate        | Pentavalent antimony compound reduced to trivalent acts by inhibiting glycolysis in parasite | Leishmaniasis                                   | Arthralgia, myalgia, raise in liver enzymes, prolongation of QT interval |
| Miltefosine                  | DNA fragmentation mitochondrial toxicity                                   | Leishmaniasis                                   | Nausea, thrombocytopenia, raised liver enzymes                        |
| Nitazoxanide                 | Inhibition of pyruvate: ferredoxin/flavodoxin oxidoreductase (PFOR)       | Cryptostrongium parvum, Giardia intestinalis    | Gastrointestinal disturbances, flu like symptoms, colored urine     |
| Pyrimethamine                | Inhibition of dihydrofolate reductase, folic acid synthesis               | Toxoplasma                                      | Teratogenic, bone marrow toxicity, renal failure, liver failure     |

(continued)
The treatment consists of tetracycline 500 mg (four times a day for 10 days), metronidazole 500 mg thrice a day for 5 days, or iodoquinol 650 mg thrice a day for 20 days (Table 60.19).

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