Malaria: An Update on Treatment

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Disclosure Information

I have no financial relationship to disclose.

I will discuss the following FDA off-label use and/or

investigational use in my presentation:

- off-label malaria treatment

Objectives

- Discuss the epidemiology of malaria, including its global distribution and risk factors.
- Explain the treatment options for malaria, including antimalarial drugs and supportive care.
- Identify the challenges and future directions in malaria control and elimination.

Malaria

- Manifestations of malaria vary widely
  - Region
  - Village
  - Person
- Due to:
  - Mosquito biting habits
  - Mosquito breeding habits
  - Parasite species
  - Genetic and acquired resistance of person
  - Compliance with treatment

Global Epidemiology and US Incidence

- ~263 million malaria cases and ~597,000 deaths worldwide (2023).
- Majority of transmission in sub-Saharan Africa, Southeast Asia, and South America.
- Vulnerable populations: young children, pregnant women, travelers from non-endemic to endemic regions.
- U.S.: ~2,000 imported cases/year; *2023*: 10 locally acquired (autochthonous) cases (FL, TX, MD, AR); *2024*: no confirmed autochthonous cases as of November.
- Highest risk in U.S.: travelers visiting friends and relatives (VFRs) in endemic areas

WHO World Malaria Report 2024
CDC Yellow Book 2026

Risk Factors for Malaria Acquisition

- Residence or extended travel in endemic regions.
- Poor adherence to/absence of chemoprophylaxis.
- Lack of access to vector control (bed nets, indoor spraying).
- Genetic factors: lack of sickle cell trait or G6PD deficiency increases risk.
- Age <5 years, pregnancy, immunocompromised status.
- Rapid waning of immunity in migrants after leaving endemic areas.
- VFR traveler populations: highest U.S. risk profile

Malarial Management

- All patients will need antimalarial treatment
- Many patients will need antipyretics and analgesics
  - APAP or Ibuprofen
  - Avoid ASA in children
- Assess ABCs

Malarial Management

- Treat hypoglycemia
- Watch for bacterial co-infection
- Treat dehydration
- Oxygen/mechanical ventilation
- Inotropic therapy

Artemisinin-based combinations therapies (ACTs)

- Treatment of choice for uncomplicated falciparum malaria globally
- Combo of artemisinin derivative and another antimalarial

- Reduces spread of resistance, but resistance is increasing in Southeast Asia and Africa
- Same principle as treatment of HIV/AIDs and TB
- Resistance to artemisinin – delayed parasite clearance
- Non-artemisinin based combo therapies are not recommended

WHO Preferred Regimens for Uncomplicated Malaria

- Artemisinin-based Combination Therapies (ACTs) are first-line worldwide:
  - Artemether-lumefantrine (AL)
  - Dihydroartemisinin-piperaquine (DHA-PPQ)
  - Artesunate-amodiaquine (ASAQ)
  - Artesunate-mefloquine (ASMQ)
  - Artesunate-sulfadoxine-pyrimethamine (AS+SP; restricted in pregnancy)
  - Artesunate-pyronaridine (APS; avoid in liver disease)
- All regimens: ACT for 3 days.
- For *P. vivax*, *P. ovale*: add primaquine or tafenoquine (check G6PD status).

Artemether + lumefantrine

- Indication
  - Uncomplicated falciparum malaria
- Dose – artemether 20mg/lumefantrine 120mg tabs
  - Adult: > 35 kg, 4 tabs at 0 h, 8 h, 24 h, 36 h, 48 h, and 60 h
  - Peds:
    - 25-34kg, 3 tabs per dose
    - 15-24kg, 2 tabs per dose
    - 5-14kg, 1 tab per dose
  - Take with milk or fat-containing food

Artemether + lumefantrine

- Side effects
  - HA, palpitations, fever, chills, GI, sleep disturbances
- Contraindications
  - QT prolongation
- Children
  - Use appropriate dose
- Pregnancy
  - Use Caution
- Lactation
  - Use Caution
- Availability
  - US and Worldwide

Review

Which of the following recommendations should be made for someone who is receiving artemether + lumefantrine?

A. Take with milk or fat containing food
B. Take on an empty stomach

Dihydroartemisinin-piperaquine

- Indication: Uncomplicated falciparum malaria
- Dose:
  - Adults ≥36 kg: 3 tablets (DHA 40 mg + PPQ 320 mg per tablet) once daily x 3 days
  - Pediatrics: use weight-based dosing per WHO chart

Dihydroartemisinin-piperaquine

- Side effects:
  - Headache, GI upset (nausea, vomiting, diarrhea), QT prolongation (monitor ECG in at-risk patients)
  - Mild elevation of transaminases
- Contraindications:
  - QT prolongation, underlying cardiac disease
  - Avoid in pregnancy (first trimester)
- Children: Use appropriate dosing
- Pregnancy/Lactation: Avoid in first trimester; may use if no alternatives in second/third
- Availability:
  - Widely available in malaria-endemic countries; not FDA approved, must contact CDC for use in U.S.

Artesunate + amodiaquine

- Indication
  - Uncomplicated falciparum malaria
  - Only suitable for areas where amodiaquine monotherapy 28 day cure rate > 80 % (predominantly only West Africa)
- Dose
  - Adults: > 13 yo: 200/540mg qd x 3 days
  - Peds:
    - 7-13 yo: 100/270mg qd x 3 days
    - 1-6 yo: 50/125mg qd x 3 days
    - < 1 yo: 25/67.5mg qd x 3 days

Artesunate + amodiaquine

- Side effects
  - GI, sleep disturbances
- Contraindications
  - Previous problems with amodiaquine
- Children
  - Use appropriate dose
- Pregnancy
  - Not 1st trimester
- Lactation
  - Probably ok
- Availability
  - Limited to western Africa

Review

If an area in Western Africa has a known amodiaquine monotherapy cure rate of 60% for malaria then which of the following statements is CORRECT?

A. Amodiaquine + artesunate is a good choice of meds to use
B. Amodiaquine + artesunate is NOT a good choice of meds to use

Artesunate + mefloquine

- Indication
  - Uncomplicated falciparum malaria
- Dose
  - Adults: > 13 yo: artesunate 200mg qd x 3 days, mefloquine 1000mg on day 2 and 500mg on day 3
  - Peds:
    - 7-13 yo: artesunate 100mg qd x 3 days, mefloquine 500mg day 2, 250mg day 3
    - 1-6 yo: artesunate 50mg qd x 3 days, mefloquine 250mg day 2
    - 5-11 months: 25mg qd x 3 days, mefloquine 125mg day 2

Artesunate + mefloquine

- Side effects
  - GI, sleep disturbances
- Contraindications
  - QT prolongation
- Children
  - Use appropriate dose
- Pregnancy
  - Unknown, but some teratogenicity seen in animals
- Lactation
  - unknown
- Availability
  - Artesunate
    - Must contact CDC for US use (only IV though)
    - Readily available in larger cities of endemic areas
  - Mefloquine – widely available

Artesunate + Sulfadoxine-pyrimethamine (SP)

- Indication
  - Uncomplicated falciparum malaria
  - Only where 28 day cure rates to SP alone are > 80% (some of Africa)
- Dose
  - Adults: > 13 yo: artesunate 200mg qd x 3 days, SP 1500mg/75mg on day 1
  - Peds:
    - 7-13 yo: artesunate 100mg qd x 3 days, SP 1000/50mg day 1
    - 1-6 yo: artesunate 50mg qd x 3 days, SP 500/25mg on day 1
    - 5-11 months: artesunate 25mg qd x 3 days, SP 250/12.5 on day 1

Artesunate + Sulfadoxine-pyrimethamine (SP)

- Side effects
  - GI predominantly, headache
- Contraindications
  - Sulfa allergy, renal failure, hepatic failure
- Children
  - Use appropriate dose
- Pregnancy
  - contraindicated
- Lactation
  - contraindicated
- Availability
  - SP is widely available except in US (Fansidar was discontinued)

Artesunate - Pyronaridine

- Indication: Uncomplicated falciparum malaria (and some non-falciparum species if ACT is needed)
- Dose:
  - Adult: Artesunate 60 mg + Pyronaridine 180 mg x 3 tablets once daily x 3 days
  - Pediatrics: weight-based dosing per WHO chart

Artesunate-Pyronaridine

- Side effects:
  - GI upset, mild elevation of liver enzymes (monitor ALT/AST)
  - Headache, dizziness
- Contraindications:
  - Known liver dysfunction or severe hepatic impairment
  - Avoid in pregnancy (limited safety data)
- Children: Use appropriate dose
- Pregnancy/Lactation: Limited data—avoid unless no alternative
- Availability:
  - Not FDA approved; widely used in endemic settings, U.S. providers must contact CDC

Review

- A 14-year-old child visiting from Nigeria is diagnosed with uncomplicated Plasmodium falciparum malaria in the U.S. According to current WHO guidelines, which of the following regimens is preferred?
  A. Chloroquine
  B. Artemisinin-based combination therapy (e.g., artemether-lumefantrine)
  C. Mefloquine monotherapy
  D. Primaquine alone

What about non-falciparum species?

- P. vivax, P. ovale
  - Use ACT or chloroquine, depending on regional resistance
  - Follow with G6PD testing and consider an anti-relapse treatment with primaquine or tafenoquine

Second-line Antimalarials for Falciparum Malaria

- Used in cases of treatment failure < 14 days after ACT tx
  - An alternative ACT regimen OR
  - Artesunate (2mg/kg qd) plus either tetracycline (4mg/kg q6h) or doxycycline (2mg/kg qd) or clindamycin (10mg/kg q12h) x 7 days OR
  - Quinine (10mg salt/kg q8h) plus either tetracycline (4mg/kg q6h) or doxycycline (2mg/kg qd) or clindamycin (10mg/kg q12h) x 7 days
- Quinine is poorly tolerated with poor adherence
- Doxy/tetra should not be used during pregnancy or in peds < 8 yo

Treatment of Severe Malaria

- Should start immediately
- Parenteral (IV or IM) artesunate is preferred
- IM artemether is second-line alternative
- IM or IV quinine should be reserved for neither is available
- Continue until patient is well enough to take oral follow-on treatment and the full oral treatment should be continued after parenteral.

Treatment of Severe Malaria - Artesunate

- Artesunate 2.4mg/kg IV or IM at 0h, 12 h, 24h, then QD
- WHO recommended therapy in low transmission or non-malaria endemic areas and a recommended therapy in high transmission areas
- Associated with a 35% relative reduction in mortality as compared with quinine

Treatment of Severe Malaria - Artemether

- Artemether 3.2mg/kg IM then 1.6mg/kg IM QD
- Erratic absorption
- WHO recommended tx in high transmission areas

Treatment of Severe Malaria - Quinine

- Quinine 20mg salt/kg loading dose then 10mg salt/kg q8h thereafter
- Give by rate controlled IV infusion over 4 hours or by divided IM injection
- WHO recommended therapy in high transmission areas when artesunate unavailable
- Associated with hypoglycemia especially in pregnant women
- Use caution in renal failure or hepatic dysfunction

Treatment of Severe Malaria - Quinidine

- Not really recommended anymore due to toxicity
- Quinidine 15mg base/kg infused IV over 4 hours, followed by 7.5mg/kg over 4 hours every 8 hours.
- Requires cardiac monitoring
- Dose adjustments necessary in renal failure/hepatic dysfunction
- Convert to oral ASAP

Treatment of Severe Malaria - Pregnancy

- Give recommended parenteral agent used locally for severe malaria in full doses
- Artesunate is 1st choice in 2nd/3rd trimester
- Artemether is 2nd choice in 2nd/3rd trimester
- Little evidence for best choice in 1st trimester
- Quinine can cause severe hypoglycemia in pregnant patients

Treatment of Severe Malaria – Follow-on Treatment

- Once patient is well enough to take oral meds
- Complete 7 days treatment with an oral formulation of the parenteral drug + 7 days treatment with doxycycline (or clindamycin in children and pregnancy).
- Alternatively a full course of oral ACT therapy could be given

Primaquine

- Indication
  - Treatment of malaria caused by P. vivax or P. ovale
  - Treatment of liver-stage malaria to give a radical cure
- Dose
  - Adults:
    - Malaria – 0.25mg/kg daily for 14 days
    - Liver stage – 0.25-0.5mg/kg daily for 14 days
  - Peds:
    - > 4 years old - 0.25-0.5mg/kg daily for 14 days

Treatment of Malaria in US?

- 2023 saw first cases of locally-acquired malaria in the US in 20+ years (10 cases) but most cases of malaria (about 2000 annually) in the US are in travelers
- Many drugs are not available readily in the US and must be obtained directly from the CDC
- Treatment guidelines published by the CDC for Treatment of Malaria in the US are different than WHO guidelines

Vaccines

- Development is difficult
- RTS,S/AS01 and R21/Matrix-M received WHO endorsement in 2023 and approximately 24 million doses delivered to multiple African countries by summer 2025
- RH5.1/Matrix-M and Semalvac6 that target blood-stage has shown promising phase-II trial results
- SE36/cVLP entering first-in-human trials

https://www.gavi.org/news/media-room/guinea-introduces-malaria-vaccine-routine-immunization

Key Challenges in Malaria Control and Elimination

- *Emergence of Drug Resistance*: Increasing resistance to artemisinin and partner drugs, especially in sub-Saharan Africa and Southeast Asia.
- *Insecticide Resistance*: Mosquito vectors developing resistance to commonly used insecticides, reducing effectiveness of bed nets and sprays.
- *Health System Barriers*: Limited access to diagnostics, treatment, and consistent supply chains in endemic areas.
- *Surveillance Gaps*: Insufficient monitoring for drug resistance, case detection, and outbreak response.
- *Socioeconomic Factors*: Poverty, migration, and instability hinder prevention efforts.
- *Substandard/Counterfeit Medicines*: Circulation of poor-quality drugs fosters resistance and lowers treatment success rates.

https://www.sciencedirect.com/science/article/pii/S0924857925001980

Future Directions for Malaria Control and Elimination

- *Novel Therapeutics*: Development and deployment of new antimalarial drugs active against resistant parasites.
- *Vaccine Rollout*: Expanded use of WHO-approved vaccines (e.g., RTS,S/AS01, R21/Matrix-M), further clinical evaluation of new candidates (e.g., Semalvac6, monoclonal antibodies).
- *Integrated Vector Control*: Use of new-generation insecticide-treated bed nets (pyrethroid-chlorfenapyr) and enhanced environmental strategies.
- *Digital Surveillance*: Mobile technologies and regional data sharing for real-time case and resistance tracking.
- *Community Engagement*: Targeted education and outreach to travelers, high-risk groups, and local populations.
- *Global Funding & Collaboration*: Ongoing investment and multi-sector partnership to sustain progress and adapt to emerging threats.

Review Slide

- Which of the following is currently considered the most significant threat to global malaria control and elimination?
  A. The discovery of new mosquito vectors
  B. The development of new antimalarial drugs
  C. The emergence and spread of drug-resistant Plasmodium species
  D. Declining interest in malaria vaccine research

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Evaluation QR Code

Key References

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- WHO Initiative for Vaccine Research http://www.who.int/immunization/research/development/malaria/en/