Montefiore
HEALTH SYSTEM, INC.

Montefiore Malaria Treatment Guideline for Adults

(2023-2024)

Introduction:

Malaria is caused by the *Plasmodium* parasite transmitted by the anopheles mosquito. There are approximately 2,000 cases of malaria reported every year in the United States. And approximately 3.2 billion people live in areas at risk for malaria transmission in 106 countries and territories. Malaria can cause high morbidity and mortality, therefore, it should be strongly considered in patients coming from endemic countries or returning travelers from high risk areas.

There are five known species of Plasmodium associated with malaria, including *P. falciparum, P. vivax, P. ovale, P. malariae* and *P. knowlesi.* Depending on the species, the incubation period ranges from 10-14 days (*P. falciparum*) up to several months (*P. vivax, P. ovale*, etc.) after exposure to parasite from a mosquito bite. Malaria usually presents with fever, chills, weakness, malaise, myalgia, nausea, vomiting, diarrhea, cough, headache, back pain, and confusion. In severe cases, it can also cause organ failure, coma, and death.

Diagnosis:

Primary diagnosis is made microscopically by thin and thick blood smears. Thick smears help with initial diagnosis due to the higher volume of blood, which increases sensitivity. Thin smears are useful in identification and quantification of the parasite. Ideally three sets of blood smears obtained every 12 to 24 hours help to increase sensitivity of the test especially for patients with low parasitemia. Three negative sets will rule out the diagnosis of malaria.

BinaxNOW, a rapid diagnostic test (RDT) for malaria, is used at our institution. It can detect two malaria antigens. One antigen is for all plasmodium species, and the second antigen is specifically for *P. falciparum*. Results are available in 15 minutes and if positive, will be reported as *P. falciparum* infection, non-*P. falciparum* infection, or possible co-infection with multiple species. The sensitivity of the test for *P. falciparum* is 99.7% and specificity is 94.2%. This test CANNOT inform about percentage of parasitemia. The RDT is performed as a reflex test in all cases of suspected malaria with negative smears. For any questions regarding test results, please page the Moses microbiology supervisor at 917-956-3012 from 9 am-5 pm, or page the pathology resident on call from 5 pm-9 am.

Treatment:

Treatment is started after confirming diagnosis ideally, but it should be given presumptively when there is a high clinical suspicion of malaria, especially if the patient meets criteria for severe disease. Treatment options are guided by 1) species of *Plasmodium*, 2) percentage of parasitemia,

3) clinical status, 4) history of prior use of antimalarial medications and presumptive drug susceptibility based on area where infection was acquired. Please see tables 2 and 3 for treatment guidance.

Treatment issues to consider:

1) **Plasmodium species**: *P. falciparum and P. knowlesi* are known to cause severe disease. The majority of *P. falciparum* cases come from Sub-Saharan Africa. *P knowlesi* cases are only reported in Malaysia and are rarely seen. *P. ovale* and *P. vivax* can have liver dormant forms called hypnozoites that require specific treatment (see treatment tables).

2) **Clinical status:** Malaria is classified as uncomplicated or severe disease. Recognition of severe malaria is essential when choosing the appropriate treatment regimen. **Severe malaria presents with one or more of the following criteria and requires intravenous treatment**.

- **IV artesunate is now the only IV option** available (see page 5 for instructions)
- INITIAL ORAL THERAPY IS STRONGLY RECOMMENDED FOR ALL SEVERE MALARIA CASES WHILE AWAITING IV ARTESUNATE. THEREFORE NG TUBE PLACEMENT AND IV ANTIEMETIC ADVISED

Severe Malaria Criteria
Impaired consciousness/coma or seizures
Severe anemia with Hb <7 gm/dL
Acute renal failure
Pulmonary edema or ARDS
Hypotension or shock
Disseminated intravascular coagulation
Spontaneous bleeding
Acidosis (e.g. HCO3 < 15 mmol/L)
Hemoglobinuria
Jaundice
Parasitemia ≥5%

3) **Resistance***:* For *P. falciparum,* chloroquine-sensitive regions are Central America west of Panama Canal, Haiti, the Dominican Republic, and most of the Middle East. All other regions are chloroquine resistant. For *P. vivax,* most regions are chloroquine sensitive, except Papua New Guinea or Indonesia. For *P. malariae, P. knowlesi,* and *P. ovale*, chloroquine remains an effective choice. For further information about the list of chloroquine sensitive regions, please visit cdc.gov/malaria.

4) If malaria disease occurs despite the use of chemoprophylaxis, the **same medication should NOT be used** as part of the treatment. If there is difficulty in identifying the species once the malaria diagnosis is made, treatment for possible chloroquine resistant *P. falciparum* is recommended.

According to epidemiologic data provided by the Montefiore microbiology lab, a total of 114 malaria cases were reported between May 18th 2014 to February 2nd 2018 from inpatient services and

outpatient clinics at Montefiore. Among these cases, **104 (91.2%) cases were *P. falciparum*.**

What history is important to obtain from patient?

- What is the patient's country of origin and when was the last time the patient visited the country?
- Which country or countries did the patient travel to? How long was the stay? What date did the patient return from an endemic region?
- Did the patient take prophylaxis? If so, which medications? Was the patient compliant?
- Does the patient have a previous history of malaria?
- Can the patient take oral medications?

What labs are needed to help determine the severity of malaria illness?

- *Serial CBC* to monitor hemoglobin and platelets
- *Serial Chemistry*
    - BUN/Creatinine – to evaluate renal function
    - Bicarbonate and lactate – to evaluate for presence of acidosis
    - Bilirubin and LDH – to evaluate for hemolysis
- **Bicarbonate < 20 mEq/L is concerning**. Consider placing patient in a highly monitored setting; must repeat labs to see the trend within 4 to 6 hours.
- *Serial blood smears* to speciate and obtain parasitemia percentage. BinaxNOW (quick diagnostic antigen test) will help you differentiate *P. falciparum* from *non-falciparum*. **Please follow the percentage of parasitemia every few hours to make sure it is declining.**

Considerations when choosing treatment

Treatment is primarily based on plasmodium species, percentage of parasitemia and clinical severity (see treatment tables). **For severe infection with any type of plasmodium species, give one dose of artemether/lumefantrine (Coartem) or oral quinine. *If there is a delay in acquisition of IV artesunate, follow with second dose 8 hours after administration of first dose of oral anti-malarial.***

***See Appendix on page 8 for tables on:**

- Malaria Medication/Strengths as per MMC Formulary

- Renally Adjusted Antimalarial Medication Doses

Malaria Treatment Guideline for Adults (Adapted from CDC guidelines, modified based on MMC formulary)

TABLE 1: Treatment for *Plasmodium Falciparum* Malaria or for Species Not Yet Identified [1-2]

	Chloroquine-resistant or Unknown Resistance (All countries known to have *P. falciparum* malaria are chloroquine resistant except the countries listed as chloroquine sensitive in the next column)	**Chloroquine-sensitive** (For *P. falciparum* only: Central America west of the Panama Canal, Haiti, Dominican Republic, Middle East). **For updates in malaria sensitivities, check cdc.gov/Malaria**
Uncomplicated Malaria *-Infectious Disease team MUST be consulted*	**1) Artemether-lumefantrine (Coartem®)** **Dose for >35 kg patient weight: 4 tablets/dose (1 tablet = 20 mg artemether and 120 mg lumefantrine). A 3-day treatment schedule with a total of 6 oral doses as follows: initial dose, second dose 8 hours later, then 1 dose twice a day for the following 2 days.(Note: 6 doses = 24 tablets)** **OR** **2) Quinine sulfate + either doxycycline or clindamycin** (quinine sulfate combination with doxycycline is preferred) **Dose: Quinine 648 mg salt (two 324 mg salt-capsules = 542 mg base) PO Q8 H x 3 days (7 days if infection is acquired in South East Asia)** **+** **Doxycycline[3] 100 mg PO Q12 H x 7 days** ***Or*** **Clindamycin 20 mg/kg/DAY PO divided in 3 doses x 7 days** -Artemether-lumefantrine or quinine plus doxycycline or clindamycin are equivalent options -See footnote[4-5] for other alternative options	**1) Chloroquine phosphate** **Dose: 1000 mg salt (two 500 mg salt-tablets = 600 mg base) initial dose PO followed by 500 mg salt (= 300 mg base) PO at 6, 24, and 48 hours for a total dose of 2500 mg salt (= 1500 mg base)** **OR** **2) Hydroxychloroquine** (if chloroquine not available) **Dose: 800 mg salt (four 200 mg salt-tablets = 620 mg base) initial dose PO followed by 400 mg salt (two 200 mg salt-tablets = 310 mg base) PO at 6, 24 and 48 hours for a total dose of 2000 mg salt (= 1550 mg base)** -Chloroquine and hydroxychloroquine are equivalent alternatives
Uncomplicated *Plasmodium falciparum* malaria in PREGNANCY[3] *-Infectious Disease team MUST be consulted* Pregnancy itself is not part of severe malaria criteria but pregnant patients are at increased risk for severe disease, therefore close monitoring for progression of symptoms are required	**1) Artemether-lumefantrine (Coartem®)** **Dose for >35 kg patient weight: 4 tablets/dose (1 tablet = 20 mg artemether and 120 mg lumefantrine). A 3-day treatment schedule with a total of 6 oral doses as follows: initial dose, second dose 8 hours later, then 1 dose twice a day for the following 2 days.(Note: 6 doses = 24 tablets)** **OR** **2) Quinine sulfate + Clindamycin** **Dose: Quinine 648 mg salt (two 324 mg salt-capsules = 542 mg base) PO Q 8 H x 3 days (7 days if infection is acquired in South East Asia)** **+** **Clindamycin 20 mg/kg/DAY PO divided in 3 doses x 7 days** -Artemether-lumefantrine or quinine plus doxycycline or clindamycin are equivalent options Mefloquine[5] is another option for pregnant females. It's a non-formulary medication and less frequently used due to CNS and psychiatric side effects.	**1) Chloroquine phosphate** **Dose: 1000 mg salt (two 500 mg salt-tablets = 600 mg base) initial dose PO followed by 500 mg salt (= 300 mg base) PO at 6, 24, and 48 hours for a total dose of 2500 mg salt (= 1500 mg base)** **OR** **2) Hydroxychloroquine** (if chloroquine not available) **Dose: 800 mg salt (four 200 mg salt-tablets = 620 mg base) initial dose PO followed by 400 mg salt (two 200 mg salt-tablets = 310 mg base) PO at 6, 24, and 48 hours for a total dose of 2000 mg salt (=1550 mg base)** -Chloroquine and hydroxychloroquine are equivalent alternatives

1. Treat for *P. falciparum* if species of plasmodium is not yet specified at time of diagnosis.
2. If a patient develops malaria while taking chemoprophylaxis, the same medication should NOT be chosen for treatment
3. In pregnancy: DO NOT use doxycycline (only can be used if no other options are available). There are no sufficient data for atovaquone-proguanil & artemether-lumefantrine during 1st trimester of pregnancy.
4. Atovaquone-proguanil and mefloquine are alternative options (they are non-formulary medications). Avoid mefloquine use due to CNS and psychiatric side effects.
5. Mefloquine should not be used in patients acquiring infection in South East Asia due to resistance and it is less commonly used due to psychiatric side effects.

Severe Malaria -**Severe disease can be caused by any plasmodium species but in the US, *P. falciparum* is most common** -Severe malaria treatment criteria is the same regardless of the region of acquisition *-Infectious Disease team MUST be consulted for severe malaria*	**Severe malaria can progress rapidly and must be treated as soon as possible with IV artesunate.** **ACQUIRING ARTESUNATE:** ID-ASP/Pharmacy **MUST** be notified when there is a consideration for using IV artesunate to ensure timely acquisition. Please refer to list below to contact the respective antimicrobial stewardship team at each campus to facilitate the process. Please note: depending on campus and available stock, delivery times will vary and can take up to 24 hours. Moses- Epic secure chat "Moses Antimicrobial Stewardship ASP" Wakefield- Epic secure chat "Wakefield Antimicrobial Stewardship ASP" Weiler- Epic secure chat "Weiler Antimicrobial Stewardship ASP" **WHILE WAITING FOR ARTESUNATE:** Fast-acting oral antimalarials (listed below) should be administered while waiting for IV artesunate to arrive. *If patient cannot take PO or unable to tolerate an oral antimalarial due to nausea and vomiting, nasogastric tube and IV antiemetics must be utilized to facilitate PO administration of antimalarial.* For comatose patients, a nasogastric tube can be considered. IV Clindamycin or IV doxycycline act slowly and SHOULD NOT BE USED. IV quinidine is no longer manufactured. 1) **Artemether/lumefantrine (Coartem®):** 1 tablet=20 mg artemether and 120 mg lumefantrine. Give initial dose-4 tablets (patient weight >35kg), then if still needed, follow with second dose of 4 tablets 8 hours later. **OR** 2) **Quinine:** 650 mg (salt) every 8 hours. **ARTESUNATE ADMINISTRATION AND FOLLOW UP MEDICATIONS:** Once IV artesunate is begun, the oral medications should be stopped. **IV artesunate Dose:** 2.4 mg/kg/dose at 0 hour, 12 hours, and 24 hours; thereafter administered once daily Follow parasitemia, continue until <1% (max 7 days) After the course of IV artesunate is completed, **a full course of PO drug must be administered.**[6,7] Use either: 1) **Artemether/lumefantrine (Coartem®):** 1 tablet=20 mg artemether and 120 mg lumefantrine. **Dose:** A 3-day treatment schedule with a total of 6 oral doses as follows: initial dose, second dose 8 hours later, then 1 dose twice a day for the following 2 days. Dosing as above. **OR** 2) **Doxycycline:** **Dose:** 100 mg twice a day for 7 days. Pregnant women can receive artemether/lumefantrine OR clindamycin 20 mg base/kg/day divided three times a day for 7 days. *For those patients that still cannot tolerate oral medications after completing artesunate treatment, several treatment options are available. The most suitable course of treatment should be selected by the attending clinicians in consultation with CDC. Potential options include the following:*

	• *Continue IV artesunate, 1 dose daily (see above for dosing) not to exceed a total course of 7 days.* • *Switch to treatment with IV doxycycline (7 days) or IV clindamycin (7 days), dosing as above.* Persons treated for severe malaria with IV artesunate should be monitored for up to 4 weeks after that treatment for evidence of hemolytic anemia, which is a rare complication of artesunate treatment.

6. Artesunate can also be followed by atovaquone-proguanil or mefloquine (they are both non-formulary).

7. Mefloquine should not be used in patients acquiring infection in South East Asia due to resistance; it is less commonly used due to CNS and psychiatric side effects.

For any questions regarding test results, please page the Moses microbiology supervisor at 917-956-3012 from 9am-5pm, or page the pathology resident on call from 5pm-9am. For any questions regarding medications, please call pharmacy: Moses at 718-920-4103, Weiler at 718-904-2838 and Wakefield at 718-920-9631.

Malaria Treatment Guideline for Adults (Adapted from CDC guidelines, modified based on MMC formulary)

TABLE 2: Treatment of Uncomplicated Malaria for Species Other Than *Plasmodium Falciparum*

	Chloroquine-resistant For P. vivax only, chloroquine resistance can be seen in infections acquired in Papua New Guinua or Indonesia	**Chloroquine-sensitive** For P. malaria, P. knowlesi, or P. ovale, there is little to no concern for chloroquine resistance
Plasmodium malaria or knowlesi	Given no concern for chloroquine resistance for these species, please see treatment for chloroquine sensitive *P. malaria* or *P. knowlesi*	**Chloroquine phosphate** **Dose: 1000 mg salt (two 500 mg salt-tablets = 600 mg base) initial dose PO followed by 500 mg salt (= 300 mg base) PO at 6, 24, and 48 hours for a total dose of 2500 mg salt (= 1500 mg base)** **OR** **Hydroxychloroquine** (if chloroquine not available) **Dose: 800 mg salt (four 200 mg salt-tablets = 620 mg base) initial dose PO followed by 400 mg salt (two 200 mg salt-tablets = 310 mg base) PO at 6, 24, and 48 hours for a total dose of 2000 mg salt (= 1,550 mg base)** -Chloroquine and hydroxychloroquine are equivalent alternatives. Treatment options for chloroquine resistant *P. falciparum* also can be used.
***Plasmodium malaria or knowlesi in* PREGNANCY**	Given no concern for chloroquine resistance for these species, please see treatment for chloroquine sensitive *P. malaria* or *P. knowlesi*	**Chloroquine phosphate OR Hydroxychloroquine (dosing as above)**
Plasmodium ovale -Primaquine is essential when treating *P. ovale* for liver dormant forms	Given low concern for chloroquine resistant *P. ovale,* use chloroquine sensitive *P. ovale* treatment options	**Chloroquine phosphate (dosing as above) + Primaquine phosphate: 30 mg base PO daily x 14 days (two 26.3 mg-tablets = 30 mg base)[9]** **OR** **Hydroxychloroquine** (if chloroquine not available) **(dosing as above) + Primaquine phosphate: 30 mg base PO daily x 14 days (two 26.3 mg-tablets = 30mg base)[9]** ***-MUST check for G6PD deficiency prior to starting primaquine due to risk of hemolytic anemia***
Plasmodium vivax -Primaquine is essential when treating *P. vivax* for liver dormant forms	*If patient acquired infection in Papua New Guinea or Indonesia* **Quinine sulfate + doxycycline[3] (dosing as in *P. falciparum* chloroquine resistant treatment section)** **+** **Primaquine phosphate: 30 mg base PO daily x 14 days (two 26.3 mg-tablets = 30mg base)** See footnote[8-9] for alternative options	
***Plasmodium ovale and vivax* in PREGNANCY [10-12]** -For *P. ovale,* always use chloroquine sensitive treatment options -For *P. vivax,* treat according to region where infection was acquired as recommended above	**Quinine sulfate + clindamycin (for dosing and duration see *P. falciparum* and pregnancy section)** **AND** **After completing treatment, patient should be maintained on chloroquine prophylaxis (ppx) for the duration of the pregnancy** **Chloroquine ppx dose is 500 mg (= 300 mg base) PO once a week** **AND** **After delivery and only if not G6PD deficient, start primaquine phosphate 30 mg base PO daily x 14 days (as detailed above)**	**Chloroquine phosphate OR Hydroxychloroquine (dosing as above)** **AND** **After completing treatment, patient should be maintained on chloroquine ppx for the duration of the pregnancy** **Chloroquine ppx dose is 500 mg (=300 mg base) PO once a week** **AND** **After delivery and only if not G6PD deficient, start primaquine phosphate 30 mg base PO daily for 14 days (as detailed above)**

8. Primaquine + either atovaquone-proguanil or mefloquine are treatment options (they are non-formulary medications). Avoid mefloquine use due to CNS and psychiatric side effects.
9. For patients with borderline G6PD deficiency, consider treating with primaquine 45mg (3 tablets of 15 mg base) orally once a week x 8 weeks. For complete deficiency, do NOT use primaquine, and please monitor for signs and symptoms of reactivation of malaria to treat active disease.
10. Check G6PD deficiency for newborns prior to starting treatment for the mother because primaquine can be excreted in breast milk.
11. Mefloquine can be used in pregnant females (non-formulary medication). It's less frequently used due to CNS and psychiatric side effects.
12. In pregnancy, DO NOT use primaquine and doxycycline (can only be used if no other options are available). There is insufficient data for atovaquone-proguanil & artemether-lumefantrine during 1st trimester of pregnancy

For any questions regarding test results, please page the Moses microbiology supervisor at 917-956-3012 from 9am-5pm, or page the pathology resident on call from 5pm-9am. For any questions regarding medications, please call pharmacy: Moses at 718-920-4103, Weiler at 718-904-2838 and Wakefield at 718-920-9631.

Appendix

TABLE 3: Malaria Medication/Strengths as per MMC Formulary

Dosing at MMC of quinine, chloroquine and hydroxychloroquine is based on the salt formulation

Medication Name	Strength
Quinine sulfate capsule	*324 mg salt (=269 mg base)
Artemether-lumefantrine (Coartem) tablet	20 mg artemether/120 mg lumefantrine
Chloroquine phosphate tablet	*250 mg salt (=150 mg base), 500 mg salt (=300 mg base)
Hydroxychloroquine tablet	*200 mg salt (=155 mg base)
Primaquine tablet	26.3 mg salt (=15 mg base)

TABLE 4: Renally Adjusted Antimalarial Medication Doses

Medication	Dose adjustment
Artemether-lumefantrine (Coartem)	No adjustment. Use with caution in renal failure (has not been studied)
Artesunate	No adjustment
Chloroquine	**-CrCl >10 ml/min or CRRT:** no adjustment **-CrCl <10 ml/min, HD or PD:** 500 mg salt initial dose followed by 250 mg salt PO at 6, 24 and 48 hours
Clindamycin	No adjustment
Doxycycline	No adjustment
Hydroxychloroquine	No adjustment
Primaquine	No adjustment
Quinine	For mild to moderate malaria: **-GFR >50 ml/min:** no dose adjustment -**GFR 10-50 ml/min or CRRT:** 648 mg salt Q8 or 12H **-GFR <10 ml/min or PD:** 648 mg salt Q24H **-HD:** no dose adjustment needed, administer dose after HD

CRRT: continuous renal replacement therapy, HD: hemodialysis, PD: peritoneal dialysis