Malaria 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

- To review the current treatment of malaria in and outside of the US.
- To describe how to control symptoms of a malaria patient.
- Discuss current research on a malaria vaccine.

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

Epidemiology

- Estimated 216 million cases of malaria in 2010.
- Estimated 655,000 deaths in 2010.
- Malarial transmission dependent on:
  - Mosquito lifespan
  - Ambient temperature
  - Population density
  - Mosquito's biting habits
  - Host immune response
  - Drug activity

http://www.who.int/malaria/world_malaria_report_2011/en/

Malarial Transmission

- Two distinct patterns of transmission occur
  - Stable malaria
    - Intense year-round transmission
    - Predominantly affects young children and pregnant women
    - Adults may have positive blood smears but rarely ill
    - Leads to problematic control as interventions that decrease transmission impair development of naturally acquired immunity, which leads to unstable disease
  - Unstable malaria
    - Affects all ages and occurs in areas of seasonal or low transmission

Innate Immunity

- Certain genetic variants of the red blood cell may lead to at least partial protection
  - Sickle cell anemia
  - Glucose 6-phosphate dehydrogenase-deficiency (G6PD)
  - Thalassemia
  - Ovalocytosis

Acquired Immunity

- Believed to require repeated exposure to malarial infection
- Areas of stable transmission allows neonates to be protected for the first 6 months or so of life due to maternal antibodies
- Adults tend to get less severe bouts of the disease
- Without reinfection immunity wanes after about 5 years
- Pregnancy, severe illness, and surgery decrease immunity

Pregnancy

- Infection may be asymptomatic or severe
- Decreased birth weight
- Watch for:
  - Anemia
  - Hypoglycemia
  - Pulmonary edema
  - Fetal distress
  - Premature labor
  - Stillbirths

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
- Combo of artemisinin derivative and another antimalarial
- Reduces spread of resistance
- Same principle as treatment of HIV/AIDs and TB
- No known resistance to artemisinin drugs, but be aware of resistance to "partner drugs"
- Non-artemisinin based combo therapies are not recommended

Currently Recommended ACTs

- Artemether + lumefantrine (Co-artem™, Riamet ™)
- Artesunate + mefloquine
- Artesunate + sufadoxine-pyrimethamine
- Artesunate + amodiaquine
- Many in development

Artemether + lumefantrine (Co-artem ™, Riamet ™)

- 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 (Coartem ™, Riamet ™)

- 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

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 + sufadoxine-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 + sufadoxine-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 + 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

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

Review

Which of the following statements is CORRECT regarding artemisinin-based compounds for treatment of malaria?

A. Lots of resistance worldwide
B. Lots of resistance in the US
C. Should only be used if a patient cannot tolerate mefloquine
D. Generally more effective if given with another antimalarial

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

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
- Continue until patient is well enough to take oral follow-on treatment

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 - 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
- Associated with hypoglycemia especially in pregnant women
- Use caution in renal failure or hepatic dysfunction

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 - Quinidine

- 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
- Use if other recommended drugs not available in parenteral form (US)

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

Treatment of Malaria in US?

- 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 vastly different than WHO guidelines

Vaccines

- Development is difficult
- Currently no commercial vaccine available
- RTS,S/AS01 currently in Phase 3 trials and showed a 51% efficacy in reducing falciparum malaria in infants 5-17 months
- Currently there are at least 20 other malaria vaccines that are in early testing; they are at least 5-10 years behind RTS,S

Questions??

Key References

- WHO World Malaria Report 2011 http://www.who.int/malaria/world_malaria_report_2011/en/
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