How do you solve a problem like Malaria?

Mark Corden – Children’s Hospital Los Angeles
Sarah White – Children’s Hospital Los Angeles
Mark Travassos – University of Maryland

Disclosure

• We have no relevant financial relationships to disclose.
Objectives

1) Recall the classic signs and symptoms of uncomplicated malaria and contrast diagnostic measures

2) Review the approach to seizures in cases of malaria

3) Apply treatment principles for severe malaria based on guidelines and evidence-based medicine

4) Identify prognostic factors to predict outcomes in cases of malaria

Global Targets (GTS 2016-2030):
- Reduce mortality by >90%
- Eliminate malaria in >35 countries
Case

- You are working in a hospital in sub-Saharan Africa.
- A 5-year-old girl presents with fever, chills and malaise x 2 days. This morning she woke up and vomited once, and her father witnessed a 2-minute generalized tonic-clonic seizure.
- He brings her to the nearest hospital. On arrival she is alert and is tired but generally well-appearing.

You suspect which of the following?

A. Complicated malaria
B. Uncomplicated malaria
C. Influenza
D. Shigella gastroenteritis
E. Not enough information to answer
You suspect which of the following?

A) Complicated malaria
B) **Uncomplicated malaria**
C) Influenza
D) Shigella gastroenteritis
E) Not enough information to answer
Uncomplicated Malaria
- Fever
- Fatigue & Lassitude
- Nausea and vomiting
- Muscle and joint pain
- Cough
- Diarrhea

Given that you are in a malaria endemic area you think uncomplicated malaria is likely. Your options for malaria testing include:

A. Thick and thin film microscopy
B. Only thick film microscopy
C. Immunochromatographic Rapid Diagnostic Tests (RDTs)
D. Nucleic acid PCR
E. Malaria Binding Protein Assay (MBPA)
Given that you are in a malaria endemic area you think uncomplicated malaria is likely. Your options for malaria testing include:

A) **Thick and thin film microscopy**
B) Only thick film microscopy
C) Immunochromatographic Rapid Diagnostic Tests (RDTs)
D) Nucleic acid PCR
E) Malaria Binding Protein Assay (MBPA)
Suspected malaria: Nonspecific Sx’s

- Whenever possible parasite testing should be done
  * Do not rely on clinical diagnosis

Where malaria transmission is HIGH, test when:
- Hx of fever or T>37.5 w/o other obvious cause
- Children with “pallor” or Hgb<8

Where malaria transmission is LOW:
- More discretion should be used prior to parasitological diagnosis

<table>
<thead>
<tr>
<th></th>
<th>Thick Film Microscopy</th>
<th>Thin Film Microscopy</th>
<th>RDTs</th>
<th>Nucleic acid PCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>+++</td>
<td>+</td>
<td>+/- *</td>
<td>+++</td>
</tr>
<tr>
<td>Specificity</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Identification</td>
<td>+</td>
<td>+++</td>
<td>+/- *</td>
<td>+++</td>
</tr>
<tr>
<td>Quantification</td>
<td>-</td>
<td>+++</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Other
- Most sensitive method routinely available
- Allows quantification and identification
- Easy
- Minimal training
- Improves time to treatment
- No electricity required!
- Detection of drug resistance patterns.
- Not available rapidly or in most LMICs

* Depending on the type of RDT, some only detect p.f.
Case

- You are working in a hospital in sub-Saharan Africa.
- A 5-year-old girl presents with fever, chills and malaise x 2 days. This morning she woke up and vomited once and her father witnessed a 2-minute generalized tonic-clonic seizure.
- He brings her to the nearest hospital. On arrival she is sleepy and hypotonic.
Differential Dx?

- Idiopathic
- Febrile Seizure
- Hypoglycemia
- Malaria
- Uremia?
- Meningitis?

Seizures

- Most common neurological complication of acute *P falciparum* malaria
  - simple tonic-clonic
  - partial convulsive episodes
  - clinically silent electrical status
    - excess salivation
    - irregular respiratory pattern
Definitions
## Definitions

- **Neuro**
  - ALOC: GCS < 11 (adults) / BCS < 3 (children)
  - Prostration
  - Seizures: >2 in 24h

- **Resp**

- **CVS**

- **Heme**

- **Renal**

- **ID**

- **Metabolic**

- **Pulmonary**
  - Edema: CXR/O2sat < 92% with RR > 30

- **CVS**
  - Shock: CRT > 3 sec / SBP < 70 (decomp)

- **Metabolic**
  - Acidosis: BD > 8 / HCO3 < 15 / Lactate > 5

- **Hypoglycemia**: < 40

- **Heme**
  - Anemia: Hgb < 5 / Hct < 15

- **Jaundice**: Tbili > 3

- **Bleeding**

- **Renal**
  - Impairment: Creat > 3 / BUN > 20

- **ID**
  - Hyperparasitemia: Pfalciparum > 10%
Definitions

• **Neuro**
  - ALOC: GCS < 11 (adults) / BCS < 3 (children)
  - Prostration
  - Seizures: >2 in 24h

• **Resp**
  - Pulmonary edema: CXR / O2sat < 92% with RR > 30

• **CVS**
  - Shock: CRT > 3 sec / SBP < 70 (decomp)

• **Metabolic**
  - Acidosis: BD > 8 / HCO₃ < 15 / Lactate > 5
  - Hypoglycemia: <40

• **Heme**
  - Anemia: Hgb < 5 / Hct < 15

• **Renal**
  - Renal impairment: Creat > 3 / BUN > 20

• **ID**
  - Hyperparasitemia: *P falciparum* > 10%
Definitions

- **Neuro**
  - ALOC: GCS < 11 (adults) / BCS < 3 (children)
  - Prostration
  - Seizures: >2 in 24h

- **Resp**
  - Pulmonary edema: CXR / O2sat < 92% with RR > 30

- **CVS**
  - Shock: CRT > 3 sec / SBP < 70 (decomp)

- **Metabolic**
  - Acidosis: BD > 8 / HCO3 < 15 / Lactate > 5
  - Hypoglycemia: <40

- **Heme**

- **Renal**

- **ID**

Definitions

- **Neuro**
  - ALOC: GCS < 11 (adults) / BCS < 3 (children)
  - Prostration
  - Seizures: >2 in 24h

- **Resp**
  - Pulmonary edema: CXR / O2sat < 92% with RR > 30

- **CVS**
  - Shock: CRT > 3 sec / SBP < 70 (decomp)

- **Metabolic**
  - Acidosis: BD > 8 / HCO3 < 15 / Lactate > 5
  - Hypoglycemia: <40

- **Heme**
  - Anemia: Hgb < 5 / Hct < 15
  - Jaundice: Tbili > 3
  - Bleeding

- **Renal**

- **ID**
Definitions

• Neuro
  • ALOC: GCS < 11 (adults) / BCS < 3 (children)
  • Prostration
  • Seizures: >2 in 24h

• Resp
  • Pulmonary edema: CXR / O2sat < 92% with RR > 30

• CVS
  • Shock: CRT > 3 sec / SBP < 70 (decomp)

• Metabolic
  • Acidosis: BD > 8 / HCO3 < 15 / Lactate > 5
  • Hypoglycemia: <40

• Heme
  • Anemia: Hgb < 5 / Hct < 15
  • Jaundice: Tbili > 3
  • Bleeding

• Renal
  • Renal impairment: Creat > 3 / BUN > 20

• ID
  • Hyperparasitemia: P falciparum > 10%
ALOC

<table>
<thead>
<tr>
<th>Blantyre Coma Scale</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tracking (&quot;eyes&quot;)</td>
<td></td>
</tr>
<tr>
<td>Watches/follows</td>
<td>1</td>
</tr>
<tr>
<td>Fails to watch/follow</td>
<td>0</td>
</tr>
<tr>
<td>Verbal (&quot;mouth&quot;)</td>
<td></td>
</tr>
<tr>
<td>Cries appropriately/speaks</td>
<td>2</td>
</tr>
<tr>
<td>Abnormal cry/moans</td>
<td>1</td>
</tr>
<tr>
<td>No vocal response to pain</td>
<td>0</td>
</tr>
<tr>
<td>Withdrawal (&quot;motor&quot;)</td>
<td></td>
</tr>
<tr>
<td>Localizes pain</td>
<td>2</td>
</tr>
<tr>
<td>Withdraws from pain</td>
<td>1</td>
</tr>
<tr>
<td>No response</td>
<td>0</td>
</tr>
</tbody>
</table>

The patient’s smear is positive for malaria. What is your next step?

A. Obtain rapid diagnostic test to confirm smear results
B. Give normal saline bolus 20 mL/kg
C. Obtain lumbar puncture
D. Start parenteral antimalarial
E. Intubate
The patient’s smear is positive for malaria. What is your next step?

A. Obtain rapid diagnostic test to confirm smear results
B. Give normal saline bolus 20 mL/kg
C. Obtain lumbar puncture
D. **Start parenteral antimalarial**
E. Intubate
Work-up

- CBC
- Blood culture
- Chem panel
- Type and cross
- Smear
- LP

Work-up

- CBC √
- Blood culture?
- Chem-panel
- Type and cross √
- Smear √
- LP???
Cerebral Malaria

- Clinical dx considerably improved by ophthalmoscopy
  - retinal whitening
  - vessel changes
  - retinal hemorrhages
  - papilledema
Objectives of Tx

- **Primary:** prevent death (❗)
  - Mortality 100% without treatment, 10-20% with
- **Secondary:**
  - Prevent disability
  - Prevent recrudescent infection
  - Prevent spread of infection

First steps

- **A**
  - Control airway in unconscious patient
- **B**
  - Supplemental oxygen
  - Respiratory support
- **C**
  - IV access
- **D**
  - Coma score
  - Glucose level
Anti-malarials

- Initial - Parenteral
  - Artesunate IV/IM/PR
  - Artemether IM
  - Quinine IV/IM
- Follow-on – PO
  - ACT

Additional aspects

- Fluid Therapy
  - Boluses are contraindicated (!)
- Blood transfusion
- Antibiotics
  - Indicated in areas of moderate/high transmission
- Anticonvulsants
  - Respiratory support is essential
Outcomes

• 2 clinical features, impaired consciousness (defined as coma or prostration) and respiratory distress (a clinical sign of metabolic acidosis), identified 84% of fatal cases [Marsh, NEJM 1995]

• 4 parameters (out of 20 indicators of severity) independently associated with fatality [von Seidlein, Clin Inf Dis 2012]:
  • base deficit (>8 mmol/L)
  • coma
  • elevated blood urea nitrogen (BUN, >20 mg/dL)
  • underlying chronic illness

von Seidlein, Clin Inf Dis 2012
Outcomes (2)

- Outcomes for cerebral malaria remain poor, with high in-hospital mortality and neurological sequelae in survivors
- Greatest mortality were children with coma (19.6%) [Dondorp, Lancet 2010]
- Sequelae occurred in approximately 11% [Newton, Pharm Ther 1998]
  - ataxia (43%)
  - hemiplegia (39%)
  - speech disorders (39%)
  - blindness (30%)
  - cognitive and behavioral abnormalities
Mechanisms of drug resistance

New hope
Take home points

1. For diagnosis, thick smear is gold standard ... but RDT less dependent on technique, and can diagnose pre-treated cases

2. Seizures in children with malaria may be multifactorial ... maintain a broad differential to detect all possible causes
Take home points

1. For diagnosis, thick smear is gold standard ... but RDT less dependent on technique, and can diagnose pre-treated cases
2. Seizures in children with malaria may be multifactorial ... maintain a broad differential to detect all possible causes
3. In a child with coma in RLS, treat empirically with parenteral antimalarials ... without waiting for diagnostic results

4. Familiarize yourself with local resistance patterns AND guidelines ... as local healthcare providers may not have access to similar information
Thank you