Clinical Update in Tropical Medicine

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Faculty/Presenter Disclosure

• Faculty: Isaac Bogoch

• Relationships with commercial interests:
  – Nil
Disclosure of Commercial Support

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• Potential for conflict(s) of interest:
  – NIL
Objectives

- Review new therapeutic options for select Tropical Infectious Diseases
- Understand new diagnostic approaches for Tropical Infectious Diseases
- Describe new insights into Tropical Disease epidemiology and relate this to disease transmission
• We are aiming for breadth, not depth

Cover a lot of ground, not diving too deep
Part 1: Hooray... we are (sort of) out of the stone age!
Pt is 200 kg, needs 12 months of Rx
Malaria – Theme 1: failure

• 50’s yr Male
• Travels regularly to West Africa
• Business traveler – non-immune
• Self tested and treated for malaria in Nigeria
• Felt better after PO Artemether/Lumefantrine
• Returns to Toronto, 3 weeks later has fevers
• 0.3% parasitemia (P. falciparum)
What is going on here?

1. Malaria reinfection
2. Resistant strain malaria
3. Counterfeit medications and only partial treatment (recrudescence)
4. These are gametocytes in his blood
5. Something else
High Rate of Treatment Failures in Nonimmune Travelers Treated With Artemether-Lumefantrine for Uncomplicated *Plasmodium falciparum* Malaria in Sweden: Retrospective Comparative Analysis of Effectiveness and Case Series

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Treatment Failures with AL

• 397 *P. falciparum* cases in Sweden (2000-2015)
• 95 of these treated with AL
  – Mefloquine 162; atovaquone-proguanil 36; other
• 5 treatment failures in those who took AL regimen (24 tabs over 3 days)
  – Genotyping: no resistant strains
  – All were European males >65 kg
  – Lumefantrine concentrations sub-therapeutic in several individuals
In 61 patients where weight was measured, AL was 100% effective in those \( \leq 65 \) kg and 90.4% effective in those \( >65 \) kg.
Artemether-Lumefantrine

• We are seeing more of this drug – self Rx
• In those >65 kg, consider extending the duration of treatment? Or increasing the dose? Other agents?
• Follow up smears in those using AL

“CATMAT recommends standby self-treatment for selected travellers who are unable to access medical assistance within 24 hours…..CATMAT recommends standby malaria treatment with atovaquone-proguanil or quinine and doxycycline, since artemether-lumefantrine is not available in Canada.”
Malaria – theme 2: New Drug

The NEW ENGLAND JOURNAL of MEDICINE

Single-Dose Tafenoquine to Prevent Relapse of Plasmodium vivax Malaria

Tafenoquine versus Primaquine to Prevent Relapse of Plasmodium vivax Malaria

NEJM, 2019
Plasmodium vivax and P. ovale

- Hypnozoites in liver
- Cause recurrent infection
  - Weeks to months after treatment
- Primaquine can kill hypnozoites
- Primaquine causes significant hemolysis with lower G6PD activity
- Must confirm G6PD function prior to giving primaquine
Tafenoquine

• Previously, primaquine was the only drug that could treat hypnozoites
  – 14 day course

• Tafenoquine
  – Single treatment (300 mg) to be taken with chloroquine
  – >70% of normal G6PD activity
  – Need a quantitative assessment of G6PD activity
Figure 3. Patient-Level Meta-Analysis of the Primary Efficacy Outcome of Freedom from Recurrence of *P. vivax* Parasitemia at 6 Months (Per-Protocol Population). Panel A shows the Kaplan–Meier analysis of freedom from recurrence of *P. vivax* parasitemia at 6 months in the tafenoquine group, as compared with the primaquine group, across the phase 3 Dose and Efficacy Trial Evaluating Chloroquine and Tafenoquine in Vivax Elimination (DETECTIVE) trial and the GATHER trial.
• “In the meta-analysis, the majority of patients remained free from recurrence of P. vivax parasitemia at 6 months — 69.1% (226 of 327 patients) in the tafenoquine group and 73.2% (134 of 183 patients) in the primaquine group. The noninferiority of tafenoquine to primaquine could not be shown”

• Largely driven by SE Asia population
Tafenoquine

• FDA approved July, 2018
• Still need G6PD testing
• May help with adherence
• Also can be used for malaria prophylaxis

"Not as good as primaquine, but pretty F#@...ing good"

-anonymous trop med expert
Acetaminophen as a Renoprotective Adjunctive Treatment in Patients With Severe and Moderately Severe Falciparum Malaria: A Randomized, Controlled, Open-Label Trial

Katherine Plewes,1,2,3 Hugh W. F. Kingston,1,4 Aniruddha Ghose,5 Thanaporn Wattanakul,1 Md. Mahtab Uddin Hassan,5 Md. Shafiu Haider,6 Prodip K. Dutta,6 Md. Akhterul Islam,7 Shamsul Alam,8 Selim Md. Jahangir,9 A. S. M. Zahed,5 Md. Abdus Sattar,9 M. A. Hassan Chowdhury,5 M. Trent Herdman,1 Stije J. Leopold,1,12 Haruhiko Ishioka,1,10 Kim A. Piera,6 Prakaykaew Charunwatthana,1,10 Kamolrat Silamut,1 Tsin W. Yeo,4,11 Sue J. Lee,1,12 Mavuto Mukaka,1,12 Richard J. Maude,1,2,12 Gareth D. H. Turner,12 Md. Abul Faiz,13 Joel Tarning,12 John A. Oates,14 Nicholas M. Anstey,4 Nicholas J. White,1,12 Nicholas P. J. Day,1,12 Md. Amir Hossain,5 L. Jackson Roberts II,14 and Arjen M. Dondorp1,2
Malaria theme 3: Kidneys

• Phase 2, open label, randomized study in Bangladesh
• Biological plausibility for renal-protection
• 62 people randomized to acetaminophen or not
  – All > 12 years, treated with IV artesunate
  – Severe and moderately severe *P. falciparum*
  – Received acetaminophen 1g q 6 hrs x 72 hrs vs. no acetaminophen
  – No hepatotoxicity reported
“...larger reduction in serum creatinine and a lower risk of developing AKI compared to control patients not receiving acetaminophen.”

- We do this anyway

Acetaminophen: low risk, low cost intervention with potential high impact?

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CID, 2018
Part 3: Yellow Fever Vaccine
Yellow Fever

• Outbreaks of YF in Africa and South America over past 3 years

• Vaccine provides lifelong immunity

Is this immunogenic? Will this work?

• Global stockpile of vaccine depleted so fractional doses were given
  – Usually $\frac{1}{5}$th of the dose, or 0.1 mL
Immunogenicity of Fractional-Dose Vaccine during a Yellow Fever Outbreak — Preliminary Report

Yellow Fever – Fractional Dose

- Prospective study at 6 YF vaccine sites in Kinshasa
- Neutralizing antibody titers for YF virus prior to and 28-35 days after receiving a fractional dose

**Fractional YF vaccination works. But for how long?**

- Of 493 participants were seronegative at baseline, 482 (98%; 95% CI, 96 to 99) seroconverted
“arbitrary” and “erratic” practices at border regions
Human African trypanosomiasis

- Sleeping sickness
- Transmitted by tsetse fly bite
- *Trypanosoma brucei rhodesiense*
  - East Africa, more acute
- *Trypanosoma brucei gambiense*
  - West and Central Africa, more chronic
- Both species can invade CNS and will cause death without treatment
T. b. gambiense CNS Disease

- Stage II (CNS disease) requires Nifurtimox Eflornithine Combination Therapy (NECT)
  - Nifurtimox: PO TID x 10 days, PLUS
  - Eflornithine IV BID x 7 days

- NECT on WHO’s Essential Medicine List
- Requires hospitalization for IV
  - Very challenging to deliver in low-resource settings
Oral fexinidazole for late-stage African Trypanosoma brucei gambiense trypanosomiasis: a pivotal multicentre, randomised, non-inferiority trial


Summary

Background Few therapeutic options are available to treat the late-stage of human African trypanosomiasis, a neglected tropical disease, caused by Trypanosoma brucei gambiense (g-HAT). The frontline treatment is a combination therapy of oral nifurtimox and intravenous eflornithine that needs to be administered in a hospital setting by trained personnel, which is not optimal given that patients often live in remote areas with few health resources. Therefore, we aimed to assess the safety and efficacy of an oral regimen of fexinidazole (a 2-substituted 5-nitroimidazole with proven trypanocidal activity) versus nifurtimox eflornithine combination therapy in patients with late-stage g-HAT.

Fexinidazole – oral medication x 10 days
1800 mg PO daily on days 1 – 4, then 1200 mg PO daily on days 5 - 10
T. b. gambiense CNS Disease

- Randomized, open label, non-inferiority trial of 394 people with CNS disease in CAR and DRC
- 2:1 randomization to fexinidazole vs. NECT
**T. b. gambiense CNS Disease**

- Successful treatment: alive, symptoms, CSF analysis
- Success rates at 18 months higher than expected

- Fexinidazole will likely be a valuable tool and perhaps a first line treatment for CNS *T. b. gambiense* disease
- Precludes the need for IV therapy and hospitalization
- ...potential for scale in hard-to-reach places
- Paves the way toward *T. b. gambiense* elimination within the margin of acceptable difference...
Part 5: Zika
Zika virus

• Large epidemic in 2015-2016, mostly in Latin America and Caribbean
• Cause of microcephaly and neuropathology
  – Likely from a mutation in the virus (prM protein)
• Guidelines over safe sexual practices and conception have evolved with emerging data
• So... what’s new?
Persistence of Zika Virus in Body Fluids — Final Report

Semen
48/94 pos (51%) in at least one specimen

Serum
251/284 pos (88%) in at least one specimen

Urine
136/231 pos (59%) in at least one specimen

Figure 1. Time until the Clearance of Zika Virus RNA in Serum, Urine, and Semen. Shown are models of the time until the loss of Zika virus (ZIKV) RNA detection after the onset of symptoms as estimated with the use of Weibull regression. NEJM, 2019
Data driving policy

Update: Interim Guidance for Preconception Counseling and Prevention of Sexual Transmission of Zika Virus for Men with Possible Zika Virus Exposure — United States, August 2018

Kara D. Polo, MPH; Suzanne M. Gilboa, PhD; Susan Hills, MBBS; Titilayo Olajuyin, MD; Karin S. Kohl, MD; PhD; John T. Brooks, MD; Alya Adamiuk, PhD; Regina M. Simeone, MPH; Allison T. Walker, PhD; Dmitriy M. Kisin, MD; Lyle R. Petersen, MD; Margaret A. Honokio, PhD; Dana Mancini-Delbanco, MD

On August 7, this report was posted as an MMWR Early Release on the MMWR website (https://www.cdc.gov/mmwr).

Zika virus infection can occur as a result of mosquito borne or sexual transmission of the virus. Infection during pregnancy is a cause of fetal brain abnormalities and other serious birth defects (1,2). CDC has updated the interim guidance for men with possible Zika virus exposure who 1) are planning to conceive with their partner, or 2) want to prevent sexual transmission of Zika virus at any time (3). CDC now recommends that men

CDC, August 2018

Mortality and Mortality Weekly Report

Zika Virus Prevention and Treatment Recommendations

An Advisory Committee Statement (ACS)
Committee to Advise on Tropical Medicine and Travel (CATMAT)

February 5, 2019

The Public Health Agency of Canada has updated the recommendation for prevention of sexual transmission of the Zika virus. Previously, male travellers were advised to wait 6 months before trying for a pregnancy. They also were advised to always use condoms correctly with their sexual partner for 6 months. This recommendation has been revised to 3 months based on new scientific evidence regarding the persistence of infectious Zika virus in semen. It is still advised that male travellers with a pregnant partner should continue to refrain from unprotected sex for the duration of the pregnancy.

CATMAT is currently updating its Zika Virus Prevention and Treatment Recommendations to align with the ones posted on the Zika virus: For health professionals page. The new recommendations will be posted in the near future.

PHAC, Feb 2019

Men should wait 3 months and women should wait 2 months prior to conception if returning from a ZIKV affected country
Part 6: Ebola
Ebola virus

• Largest outbreak in history 2014-2015 in West Africa

• About 28,600 infected with 11,300 deaths

• Awful epidemic, however it expanded our knowledge of the disease
  – Better ways to treat and prevent infection
    • Vaccine
    • Sexual transmission
    • Long-term sequelae
Ebola virus

• PREVAIL III
• Followed EVD survivors and controls in Liberia
• Started evaluating survivors ~ 1 year after onset of Ebola virus infection
• 1145 survivors and 2785 controls
  – Several different cohorts:
    • Uveitis, semen, general medical issues
People have morbidity after infection

The prevalence symptoms decreased at 6 and 12 month follow up

Except for uveitis – 25% at baseline, 33% at 12 months
• 267 survivors provided 2416 samples over time
• EBOV RNA detected in 30% of men who provided semen samples
• 40 month maximum time from illness to detection
WHO Recommends

• Counselling to ensure safe sexual practices or abstain
• Survivors provided with condoms
• Condoms until semen has tested negative x 2 by RT-PCR
• Semen testing at 3 months after onset of disease
  – If positive, test monthly until their semen tests negative for virus twice with an interval of one week between tests.

www.who.int/csr/disease/ebola/faq-ebola/en/
Continue to implement prevention strategies in survivors (e.g. condoms)

Capacity to detect and respond to sporadic cases in sites of past epidemics

- What sites can Ebola persist in? For how long? How do we protect close contacts? How do we manage stigma among survivors?
Update in Tropical Medicine

• Incredible **advances** in our understanding of tropical diseases, many of which are NTD

• This paves the way for better
  – **Clinical** care
  – **Surveillance**
  – Public health and **prevention**

• *There is a lot to look forward to in the year ahead*
References


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