Emerging Infections & Update in STIs

Judy Streit, MD
Infectious Disease
Carver College of Medicine

Figure 1: Mosquito vectors of chikungunya virus
(A) Blood-gorged A albopictus female feeding on a human host. A albopictus is the primary chikungunya virus vector in the current Indian Ocean outbreak. (B) A aegypti mosquito. A aegypti is the primary chikungunya virus vector in Asian chikungunya outbreaks. Images from United States Department of Agriculture.
Objectives

- Know the evolving epidemiology and risk of chikungunya & *Babesia* infection
- Recognize features of chikungunya infection and babesiosis and methods of diagnosis
- Review evolving diagnostic and treatment strategies for certain STDs

Disclosures: None
Chikungunya Virus

Family Togaviridae

-Alphavirus (29 SS RNA viruses)

Old World: 6 cause human joint dz

• O’nyong-nyong virus
• Ross River virus
• Mayaro virus

New World: Encephalitis Viruses (EEEV, VEEV)

Reportable illness
Chikungunya Life Cycle
Evolving Profile of Outbreaks
(Simon Curr inf Dis Rep 2011;13:218)

Current global profile

African profile
- Sporadic cases
- Focal urban outbreaks
- Wild primates
- Forest-dwelling mosquitoes: Ae. fusciger, Ae. taylori
- Humans

Asian profile
- Focal urban outbreaks
- Humans
- Peridomestic mosquitoes: Ae. aegypti, Ae. albopictus

Timeline:
- 1954
- 2004
- 2006
- 2011
Imported Chikungunya: France 2014
(Paty Euro Surveill 2014;19(28):20856)
U.S. Cases of Chikungunya 2015 (CDC)
43 cases (FL, NY > TX, PA, etc); 45 cases in territories
Aedes vectors in U.S.
Chikungunya: Clinical Illness

- Chikungunya = “that which bends up”
  Makonde (Tanzania)
- High rates of illness if infected (~95%)
- Incubation: 3-7 days
- Acute phase: abrupt fever, severe arthralgia & myalgias, prostration > rash
  
  High viral load  [10(9) - 10(12) copies/ml]
- Chronic phase: Polyarthritis, enthesitis, soft tissue pain & fatigue x weeks to years
Chikungunya: Time Course
(Pialoux Lancet Inf Dis 2007 7:319)

Figure 6: Biological diagnosis of chikungunya
Acute Chikungunya
(Pialoux Lancet Inf Dis 2007;7:319)

<table>
<thead>
<tr>
<th></th>
<th>Malaysia 1998 (%)</th>
<th>Réunion 2005–Feb 2006 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin rash</td>
<td>50</td>
<td>39</td>
</tr>
<tr>
<td>Myalgia</td>
<td>50</td>
<td>60</td>
</tr>
<tr>
<td>Headache, spinal pain</td>
<td>50, 50</td>
<td>70, NR</td>
</tr>
<tr>
<td>Arthralgia (all types)</td>
<td>78</td>
<td>100</td>
</tr>
<tr>
<td>Large joints</td>
<td>18</td>
<td>NR</td>
</tr>
<tr>
<td>Fever</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Number of reported cases</td>
<td>51</td>
<td>504</td>
</tr>
</tbody>
</table>

NR=not reported. Data for Malaysia from Lam and colleagues (2001) and data for Réunion from http://www.invs.sante.fr.

*Table:* Frequency of clinical manifestations during the 1998 Malaysian epidemic and the 2005 Réunion epidemic
Adult Skin Manifestations: Return from Reunion Island

(Simon Medicine 2007; 86(3):123)
Rash of Chikungunya in Children
Laboratory Findings: Acute Dz

- Elevated LDH, AST, ALT, GGT
- Elevated CK
- Mild thrombocytopenia
- No or mild leukopenia
- Elevated ESR and CRP in majority

Rare: marked cytopenias
Chikungunya vs Dengue

Epidemiology overlaps
Identical vectors
Dengue: differentiating features
• Lymphadenopathy
• Retro-orbital/ocular pain
• Diaphoresis
• Prominent back pain >> peripheral joint pain
• Absent arthritis/tenosynovitis
• Bleeding more common
Rare/Uncommon Complications

- Severe cytopenias
- Myocarditis
- Meningoencephalitis, GBS, flaccid paralysis
- Mild hemorrhage
- Neonatal infection (if mom viremic near parturition)
- Incidence of severe dz: < 0.02%

more common w/ older age/co-morbidities

(Reunion Island: mortality rate est 0.3-1%)
Acute Chikungunya

**Diagnosis**

- **Serology (ELISA)**
  - IgM (usually present by Day 5-7 of illness) or
  - IgG (us by 2 wk; 4x rise b/t acute/convalesc.)
    (caveats: x-reactive Ab, FN w/ cryoglob’s, persistent IgM x mos)

- **Viral PCR of blood** (or vesicle fluid)
  - Through Day 7 of illness

- **Viral culture**: not routinely used (BSL 3)

**Treatment**: pain medications/NSAIDs; avoid ASA
  - steroids effective but w/ rebound effect
Second Stage of Chikungunya (>10 days)

- Persistent/relapsing arthralgias and stiff joints
- Exacerbation of prior rheumatic conditions
- Tenosynovitis: usually > 2 sites (hypertrophic) wrists/hands and ankles
- Transitory vascular disorders (Raynaud syndrome) possibly 2nd to mixed cryoglobulins
- Decreased strength
- Ocular: ant uveitis, retinitis, episcleritis, optic neuritis
- Chronic sx’s associated with:
  - Age > 60 yrs
  - High viral load
  - High [TNF-a] and [IL12] (Hoaru)
Joint Manifestations: Return from Reunion Island; > 10 d illness

(Simon Medicine 2007; 86(3):123)
MSK DZ of chronic CHIK (Simon Curr Inf Dis Resp 2011;13:218)
Babesiosis

- Emerging Infection, nationally reportable ’11
  Incr recog/# immunocompr; Changing ecology
- Apicomplexan (malaria, toxo); > 100 spp infect animals
  2nd most-common blood parasite in mammals (<tryps)
- Human infx: U.S.—*B. microti*

*Ixodes scapularis* vector; Mice/deer reservoir
  Rare: *B. duncani* (WA/CA) or *B. divergens*-like (KY/MI/WA)
Risk: Transfusion transmission
nejm babesia

Figure 1. Geographic Areas Where Human Babesiosis and Ixodes Tick Vectors Are Endemic.
Life Cycle of Babesia
(Hunfeld Int J Parsit 2008 38:1219)
Babesia: Pathogenesis and Burden in U.S.

(Lobo Curr Opin Hematol 2012 12:170)(CDC--graph)
Wide spectrum of clinical severity

**Sx’s:** 1-4 wks after bite; 1-9 wks after PRBCs
- Gradual malaise, then fever/chills/sweat
- Myalgia, cough, arthralgia, nausea > abd pain, photophobia, depression, conjunctivitis,

**Exam:** splenomegaly, OP erythema, jaundice

**Labs:** low hgb/hapto & plt’s; incr retic/LDH
Immune Competence & Babesiosis

**Immunocompetent**: 25% no sx’s
- If sx’s: 1-2 wks F/C, fatigue x mos
- A’sx parasitemia x months w/ tx; > 1 yr w/o tx

**Immunodeficient**: can see fulminant dz
- Splenect, CA, SOT, HIV, SC, a-TNF, X-age
- ARDS, DIC, CHF, coma, liver failure, AKI
- Fatality rate: up to 20% w/ immunosuppression
Diagnosis of Babesiosis

- Consider: any pt w/ febrile illness & residence in/travel to endemic area < 2 mos or blood transfusion < 6 mos
- Strong clinical suspicion required since no classic signs
- Automated blood counter will not detect
- Suspect co-infx w/ Lyme/Anaplasma if more severe disease/poor response to tx
Thin Smears w/ Babesia microti
Diagnostic Algorithm
(Vannier nejm 2012;366(25):2397)

- Patient at risk for *Babesia microti* infection
  - Lives or travels where babesiosis is endemic
  - Blood transfusion within 6 mo
  - Strong suspicion of babesiosis

- Giemsa or Wright staining of thin blood smear

- Negative
  - If symptoms persist
  - Repeat blood smear
    - Negative: Repeat testing if illness is severe
    - Positive: Antimicrobial therapy

- Positive
  - Antimicrobial therapy
  - PCR or antibody assay
    - Negative: Repeat testing if illness is severe
    - Positive: Consider antimicrobial therapy
Transfusion-transmitted Babesia

- Most common & potentially morbid microbiologic threat of transfusion (Katz ‘14 Transfus)

• CDC compiled cases transfused 1979-2009
• Assume under-reporting and missed dx’s
• 162 cases; donors implicated for 86%
• PRBCs >>> plts; 18% all-cause mortality
• All seasons; Many pts at risk of severe dz
• 19 states, 87% in 7 main endemic states
- Tonnetti (‘09 Transfusion): 5/18 fatal cases
Transfusion-Transmitted Babesia Timeline

(Herwaldt Annals Int Med 2011 155(8):509)
Transfusion-Transmitted Babesia
(Herwaldt Annals Int Med 2011 155(8):509)

Figure 3. Box-and-whisker plots of the distributions of time from transfusion to various events for U.S. transfusion-associated Babesia microti index cases, 1979–2009.
Blood Supply & Babesia

• No FDA-approved screening test
• Regional risk: broad policy more challenging
• Current query of hx of babesiosis
• Assessed Serology or PCR:
• Unfavorable cost/benefit ratio in safety budgets
Treatment of Babesiosis  *(Table: Vannier nejm)*

### Table 1. Antimicrobial Treatment of Human Babesiosis.*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atovaquone and azithromycin†</td>
<td>Adult, 750 mg; pediatric, 20 mg/kg (maximum, 750 mg/dose) every 12 hr</td>
</tr>
<tr>
<td>Atovaquone</td>
<td>Adult, 500 mg on day 1 and 250 mg on subsequent days; pediatric, 10 mg/kg (maximum, 500 mg/dose) on day 1 and 5 mg/kg (maximum, 250 mg/dose) on subsequent days</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>Adult, 600 mg every 8 hr; pediatric, 7–10 mg/kg (maximum, 600 mg/dose) every 6–8 hr</td>
</tr>
<tr>
<td>Clindamycin and quinine</td>
<td>Adult, 300–600 mg every 6 hr; pediatric, 7–10 mg/kg (maximum, 600 mg/dose) every 6–8 hr</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>Adult, 650 mg every 6–8 hr; pediatric, 8 mg/kg (maximum, 650 mg/dose) every 8 hr</td>
</tr>
</tbody>
</table>

No sx’s & immunocompetent: Tx if continued infx @ 3 months
Wks of tx depends on immunocompetence/relapse (1-2 wks vs 4+ wks)
High parasitemia: adjunctive RBC exchange
Poor tolerance w/ quinine regimen (cinchonism, N/V)
Monitor parasitemia load if severely ill until < 5%
Part 3: Update of STIs

- Recommended screening tests for populations
- Evolving aspects of NGU
- Evolving aspects of Tx of Chlamydia, Gonorrhea
Sexually Active MSM: Annual Screening Tests & Other Care

- HIV if pt/partner w/ > 1 partner
- Syphilis serology
- Urethral** Chlamydia/Gonorrhea (urine NAAT)
- Rectal** Chlamydia/Gonorrhea (rectal swab for NAAT)
- Pharyngeal** Gonorrhea (NAAT preferred)
  (STI screen q 3-6 months if ongoing multiple partners)
- Hep B sAg
- If HIV (+): Hep C Ab (Viral load if CD4<200 & incr ALT)
  (HPV vaccine if ≤ 26 yrs; Hep A/B vaccines if nonimmune)
  (**based on sexual practices/sites of exposure)
  (NAAT=nucleic acid amplification test)
Extragenital GC/CT Infection in MSM
MSM @ STD Clinic (Patton Clin Inf Dis 2014;58:1564)

GC: 8% pharyngeal, 10% rectal (at recent visit or prior year)
CT: 32% pharyngeal, 46% rectal

Graph: proportion of positive GC/CT tests w/ neg urethral tests
CT Screening and Women

(Gratrix Clin Inf Dis 2015;60:398) STI clinic: women screened rectally & GU

3055 women screened

Prevalence rectal CT: 12-13%

Rectal scrn: incr detection 44%

25% of rectal-only reported AI

Table 1. Prevalence of Chlamydia Among Women Who Underwent Rectal Screening by Sexually Transmitted Infection Clinic, 20 July–31 December 2012 (N = 3055)

| Anatomical Site          | Calgary |  |
|--------------------------|---------|--|---|
|                          | No. Tested | No. Positive | No. Tested | No. Positive |
| Any site                 | 1570     | 204 (13.0)   | 1485       | 256 (17.2)   |
| Rectal                   | 1570     | 183 (11.7)   | 1485       | 201 (13.5)   |
| Cervix                   | 1500     | 106 (7.1)    | 1278       | 169 (13.2)   |
| Urine                    | 43       | 4 (9.3)      | 125        | 8 (6.4)      |

Chlamydia cases

<table>
<thead>
<tr>
<th></th>
<th>Calgary (n = 191), No. (%)</th>
<th>Edmonton (n = 241), No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectal only</td>
<td>89 (46.6)</td>
<td>43 (17.8)</td>
</tr>
<tr>
<td>Genitourinary and rectal</td>
<td>81 (42.4)</td>
<td>143 (59.3)</td>
</tr>
<tr>
<td>Genitourinary only</td>
<td>21 (11.0)</td>
<td>55 (22.8)</td>
</tr>
</tbody>
</table>
N. gonorrhoea: Whom to Screen

Sexually active women < 25 yrs

Other women:
• New or multiple partners
• Prior gonorrhea or other STIs
• Commercial sex workers, illicit drug use
• Living in communities w/ high prevalence

MSM at high risk
(Not MSW)
Possible Causes Recurrent/Persistent NGU

*Mycoplasma genitalium:* azithro if objective urethritis

? TCN-resistant *Ureaplasma* (inconsistent data)

*Trichomonas vaginalis:* MSW

- Some ref labs: urine-based *T. vaginalis* NAAT
- NAAT more sensitive than culture
- In high-prevalence areas: presumptive metronidazole 2 g or tinidazole 2 g x 1 after failed 1st-line tx for MSW

HSV
Mycoplasma genitalium in STIs

Cause of male urethritis (sole or co-infx)
• ~20% NGU; ~25% Non-CTU; 30% persistent urethritis

Less definitive cause of female STI
• Found in lower, upper genital tract, often a’sx
• Possible role in cervicitis, PID, pre-term delivery

Diagnosis: no FDA-approved test available
• Suspect: persistent/recurrent urethritis/cerv/PID

Tx: Doxy cure 31%; Azithro cure :85→40%
    Moxi 7-14D if failure w/ azithro
Chlamydia: Evolving Tx

- **Doxycycline more effective than azithro**
  (NGU per: Sena et al. J Inf Dis 2012;206:357)
  (CDC maintains Azithro or Doxy as 1\textsuperscript{st} line for CT tx)

- **Anorectal disease**: azithro better than doxy

- **Pregnancy**: Amoxicillin moved to alternate list
  (b/c persistent organisms in vitro)
Gonorrhea—Percentage of Reported Cases by Sex and Selected Reporting Sources, United States, 2012

*HMO=health maintenance organization; HD=health department

NOTE: Of all cases, 11.7% had a missing or unknown reporting source. Among cases with a known reporting source, the categories presented represent 66.2% of cases; 33.8% were reported from sources other than those shown.
GISP: Percent of *Neisseria gonorrhoeae* isolates with resistance or intermediate resistance to ciprofloxacin, 1990–2005

Note: Resistant isolates have ciprofloxacin MICs ≥ 1 μg/ml. Isolates with intermediate resistance have ciprofloxacin MICs of 0.125 - 0.5 μg/ml. Susceptibility to ciprofloxacin was first measured in GISP in 1990.
Percentage of *Neisseria gonorrhoeae* Isolates with Elevated Cefixime Minimum Inhibitory Concentrations (MICs) ($\geq 0.25 \mu g/ml$), Gonococcal Isolate Surveillance Project (GISP), 2005 – 2012

*NOTE:* Isolates were not tested for cefixime susceptibility in 2007 and 2008.
Percentage of *Neisseria gonorrhoeae* Isolates with Elevated Azithromycin Minimum Inhibitory Concentrations (MICs) (≥2.0 μg/ml), Gonococcal Isolate Surveillance Project (GISP), 2005 – 2012
Penicillin, Tetracycline, and Ciprofloxacin Resistance Among Neisseria gonorrhoeae Isolates, Gonococcal Isolate Surveillance Project (GISP), 2012

NOTE: PenR = penicillinase producing Neisseria gonorrhoeae and chromosomally mediated penicillin-resistant N. gonorrhoeae; TetR = chromosomally and plasmid mediated tetracycline-resistant N. gonorrhoeae; and QRNG = quinolone-resistant N. gonorrhoeae.
Gonorrhea Treatment per Revised CDC Guidelines (2013 update of 2010 pub.)

- Ceftriaxone **250 mg** IM  plus
  - Azithro (1 gm) or Doxy** (bid x 7 days)
- Cefixime: no longer 1st-line tx
  - If used: perform test-of-cure from site @ 1 wk
- Persistent infection: **culture w/ susceptibilities**
- 2nd line approaches:
  - If no ceftriaxone: Cefixime 400 mg + Azithro/Doxy
  - Severe cephalosporin allergy: Azithro 2 gm**
  - Perform **test-of-cure** 1 week (?) after treatment!
- Tx partner w/o office eval: cefixime/azithro
- Stay vigilant for cephalosporin tx failure (cx w/ suscept)
  **see proposed 2014 changes**
Antibiotics for *N. gonorrhea* in U.S.
(Kirkcaldy Sex Transm Inf 2013;89:iv5-iv10)
2014 CDC Proposals for *N. gonorrhoea* Tx
(document seeking public comment)

Ceftriaxone 250 mg IM + azithro 1 gm (std)

If cephalosporin allergy:
- Gent 240 mg IM/azithro 2 gm  **or**
- Gemifloxacin 320 mg/azithro 2 gm  (~8% vomited)

Doxycycline no longer a 2\textsuperscript{nd} agent to ceph’s

Azithro: mono-tx no longer recommended

If dual tx used: test-of-cure if w/ pharyngeal dz only

Cefixime and azithro for partner tx
Take-home points

• Int’l travelers have risk of chikungunya; potential for wider US transmission
• We have conditions for endemic babesiosis
• Transfusion recipients have risk of babesiosis
• Recommendations for screening populations for STIs are changing
• Tx rec’s for common STI organisms are changing; causative organisms expanding