WHAT’S NEW IN INFECTIOUS DISEASES?

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Objectives:

review 3 areas of current interest in Infectious Diseases:

- A review on Zika virus infection and present knowledge on epidemiology, transmission, and clinical presentation
- A look at the rise in syphilis cases in Saskatoon and area, and its diagnosis and management
- A brief overview of increasing antibiotic resistance, with a focus on MRSA and ESBL’s
ZIKA VIRUS
ZIKA VIRUS

- Single stranded RNA virus of family *Flaviviridae*
- Closely related to dengue, yellow fever, Japanese encephalitis, and West Nile viruses
- Transmission through infected *Aedes* species mosquito (*Ae. aegypti* and *Ae. Albopictus*)
Zika virus

- Discovered in Zika Forest of Uganda, 1947
- Sporadic cases (14) until outbreak in 2007 Micronesia (Island of Yap), 185 cases
- 2008 - isolated case of sexual transmission
- 2013-14, outbreaks French Polynesia, Easter Island, Cook Islands
- Possible links to Guillain-Barre, congenital malformation
- In utero transmission
2015 Zika Outbreak

- Feb 2015- late April 2015, 7000 cases of rash
- All mild, no fever, no deaths or hospitalizations
- 13% dengue, rest negative (but no Zika done)
- Apr 29, 2015 – 1st confirmed Zika in Bahai, Brazil
- July 2015 – 49 cases of GB syndrome, all but 2 have history of arbovirus infection (Zika, Dengue, Chikungunya)
2015 Zika Outbreak

- 30 Oct 2015 - 54 cases of microcephaly in Brazil
- 11 Nov 2015 - 141 more cases microcephaly
- 21 Nov 2015 - 739 cases under investigation
- Dec-Jan 2016 - Panama, Honduras, Puerto Rico, Guyana, Barbados, Hawaii, Dominican Republic, Haiti,
Figure 2. Global spread of Zika virus, 2013-2016

2015 Zika Outbreak
2015 Zika Outbreak

- 72 countries to date with mosquito-borne Zika transmission
- 55/72 reported since 2015
- 11 countries with person-to-person transmission
- 20 countries with congenital CNS malformations
- 18 countries with increased incidence of Guillian-Barre
Zika transmission

- Modes of transmission:
  - mosquito bite
  - maternal-fetal
  - sexual transmission
  - laboratory exposure
  - Theoretical: blood transfusion, breastfeeding, organ transplant
Zika: Clinical presentation

- 73% infectivity rate
- 18% symptomatic attack rate
- 3-14 day incubation period, viremia for up to 1 wk
- Survival in semen up to 93 days
- Vaginal fluids positive 3 days, cervical mucus 11 days
- Maculopapular rash, +/- fever, conjunctivitis, arthralgias, myalgias, headaches
Clinical presentation (cont’d)

Photo: Dr Peter J Hotez, US National School Tropical Medicine

Photo: Dr. Amit Garg, JAMA Dermatology
Clinical features: Zika virus compared to dengue and chikungunya

<table>
<thead>
<tr>
<th>Features</th>
<th>Zika</th>
<th>Dengue</th>
<th>Chikungunya</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>++</td>
<td>+++</td>
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<tr>
<td>Rash</td>
<td>+++</td>
<td>+</td>
<td>++</td>
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<tr>
<td>Conjunctivitis</td>
<td>++</td>
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<tr>
<td>Arthralgia</td>
<td>++</td>
<td>+</td>
<td>+++</td>
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<tr>
<td>Myalgia</td>
<td>+</td>
<td>++</td>
<td>+</td>
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<tr>
<td>Headache</td>
<td>+</td>
<td>++</td>
<td>++</td>
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<tr>
<td>Hemorrhage</td>
<td>-</td>
<td>++</td>
<td>-</td>
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<tr>
<td>Shock</td>
<td>-</td>
<td>+</td>
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</table>

Zika: Testing

Testing (CDC, NML):

- rRT-PCR within 14 days of symptom onset
- Asymptomatic pregnant women with travel to areas of active ZIKV transmission, urine and serum rRT-PCR within 2 wks of last exposure*, PLUS serology 30 days later
- If neg, Zika IgM-ELISA assay 2-12 weeks after travel or after contact with man confirmed with Zika
- Asymptomatic and pregnant, follow with serial U/S q3-4 wks

Zika: Planning pregnancy

Non-pregnant couples with recent travel to Zika affected areas:

- For women and asymptomatic men, wait 8 weeks
- For men with symptoms or confirmed Zika, wait 6 months prior to pregnancy

SY PHILIS

- Spirochete *Treponema pallidum*
- “the Great Imitator”
- Gram negative, aerobic or anaerobic
- Identified 1905, reportable 1944 in US
- Peak 1990, nadir 2000
- Steady rise 2005 to 2014
• Epidemic early 1990’s
• Nadir 2000
• Increase from 2.9 to 6.3 per 100
Syphilis in Saskatoon...

Infectious syphilis rates, Saskatoon Health Region, Saskatchewan & Canada, 2006-2015

Source: PHAC, iPHIS, Saskatchewan Ministry of Health
Infectious syphilis cases, Saskatoon Health Region, 2008 to 2016*
Infectious syphilis has increased in our Region.

9 in 10 cases of syphilis have been among men in our Region.

Top risks for infectious syphilis in our Region since 2009.

MSM has been the primary risk for five years. Anonymous MSM through Internet partnering was reported by 64% of individuals.

One in three contacts to infectious syphilis in 2016 were not tested or treated.

19% of cases and at least 5% of contacts in 2016 were HIV positive.
82 cases since 2011-2016, 42 from Jan 2014 onward

98% male (85% caucasian)

Identified risks:
- Men who have sex with men (75%)
- Anonymous and internet partners (53-60%)
- Group sex (60%)
- New partner in last 3 months (67%)
- Previous STI (46%)
- Drug use with sex (51%)
Stages of Syphilis

- **Early**
  - primary
  - secondary
  - early latent

- **Late**
  - cardiovascular
  - gummatous
  - neurosyphilis
  - late latent

Exposure: 3-4 weeks
Primary: 2-6 weeks
Secondary: 3-8 weeks
Latent: 2-20 years
Tertiary
Primary

- Painless chancre (10-90 day incubation)
- Spontaneous resolution 3-6 weeks
- Highly contagious, 30% efficiency

Photos from http://www.cdc.gov/std/syphilis/images.htm
Secondary

- Rash appears as chancre heals or a few weeks later
- Maculopapular, pustular, or mucosal
- Contagious if lesions open
- Spontaneous resolution in 2-6 weeks (up to 12)
Secondary (cont’d)

- Rash (75-90%) Palm/Soles (60%)
- Generalized lymphadenopathy (70-90%)
- Constitutional symptoms (50-80%)
- Mucous patches, condyloma lata (5-30%)
- “moth-eaten” alopecia (10-15%)
- Lues maligna (HIV)

Photo: Gregory Melcher, UC; Davis Susan Philip, SF DPH & UCSF
Late Syphilis

- In 25-40% of early cases that go untreated
- From 1-30 years after primary infection
  - Confirmed: clinical symptoms and DF +
  - Probable: clinical symptoms and serology +
- Cardiovascular - ascending aortitis
- Gummatous - rare, skin/bone/visceral granulomas
- Neurosyphilis – general paresis, tabes dorsalis
Who should be tested?

- Have a low threshold!
- If you think it, test it!
- Pregnant women, regardless of risk
Diagnosing Syphilis

- Not cultured
- Dark Field Microscopy
- No commercial PCR
- Serological diagnosis and clinical presentation
What does the serology mean?

- Non-treponemal tests (cardiolipin-cholesterol-lecithin antigen):
  - Rapid plasma reagin (RPR)
  - Venereal Disease Research Laboratory (VDRL)

- Treponemal tests:
  - Fluorescent treponemal antibody absorption (FTA-ABS)
  - Microhemagglutination for antibodies to *T. pallidum* (MHA-TP)
  - *T. pallidum* particle agglutination assay (TPPA)
  - *T. pallidum* enzyme immunoassay (TP-EIA)
  - Chemiluminescence immunoassay (CIA)
Diagnostic algorithm:

- EIA treponemal test
  - RPR
    - Old or new syphilis, treat if 4-fold increase
    - TPPA
      - Treat unless history of therapy
      - Unlikely syphilis
    - No syphilis, but repeat serology in 4 weeks
# Treatment of syphilis

<table>
<thead>
<tr>
<th>Stage</th>
<th>Drug of choice</th>
<th>alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>Benzathine Pen G 2.4 mU i.m. x 1</td>
<td>Doxycycline 100 mg BID for 14d</td>
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<tr>
<td>Secondary</td>
<td>Ceftriaxone 1g iv/im 10-14d</td>
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<tr>
<td>Early latent (&lt;12 months)</td>
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<tr>
<td>Teritary</td>
<td>Benzathine Pen G 2.4 mU i.m.</td>
<td>Doxycycline 100 mg BID for 4 wks</td>
</tr>
<tr>
<td>Late latent (&gt;12 months)</td>
<td>Weekly x 3 weeks</td>
<td>Ceftriaxone 2g iv/im OD 10-14d</td>
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<tr>
<td>Neurosyphilis</td>
<td>Aqueous Pen G 4mU q4h iv 10-14d</td>
<td>Ceftriaxone 2g iv q24h 10-14d</td>
</tr>
</tbody>
</table>
Public Health

- Notification
- Contact tracing
- Ordering medication
ANTIMICROBIAL RESISTANCE

BACTERIA vs. ANTIBIOTICS
Antibiotic resistance

- Growing resistance to antibiotics in both gram positives and negatives
- Global problem! National and international surveillance
- Gram pos: MRSA, VRE
- Gram neg: ESBL, KPC, CPE, MCR-1

- Oral antibiotics
- Higher generation oral agents
- Intravenous antibiotics
MRSA

- US 2005: 60% staph infections in ICU from MRSA
- PBP-2a, penicillin binding protein
- MecA gene on Staphylococcus Chromosomal Cassette
- TRANSFERABLE
- HA-MRSA within 12 months of healthcare exposure
- CA-MRSA no history of hospital contact
- CA-MRSA virulence enhanced by cytotoxin Panton-Valentine Leukocidin (PVL)
MRSA clinical presentation:

Wide spectrum of disease

- Skin/soft tissue – Impetigo, folliculitis, furuncles, abscess, hydradenitis suppurativa, cellulitis, mastitis
- Necrotizing invasive infections – necrotizing cellulitis, fasciitis, pyomyositis, pneumonia
- Deep tissues/systemic – osteomyelitis, endocarditis, line sepsis, meningitis, septic arthritis, septic shock
## Saskatoon Health Region ANTIBIOGRAM 2014

### ADULT OUTPATIENTS - All Isolates

January 1, 2014 - December 31, 2014

<table>
<thead>
<tr>
<th>GRAM-POSITIVE BACTERIA</th>
<th># Isolates tested</th>
<th>Penicillin PC/IV</th>
<th>Ampicillin/Amoxicillin</th>
<th>Aminoglycoside-Cephalothin</th>
<th>Amoxicillin/Clavulanic Acid</th>
<th>Piperacillin/Tazobactam</th>
<th>Cefaclor</th>
<th>Cefactin</th>
<th>Cefprozil</th>
<th>Cefuroxime</th>
<th>Ceftriaxone</th>
<th>Cefoxitin</th>
<th>Cefoperazone</th>
<th>Cefotaxime</th>
<th>Methenamine</th>
<th>Gentamicin</th>
<th>Erythromycin</th>
<th>Tetracycline/Doxycycline</th>
<th>Ciprofloxacin</th>
<th>Marfloxacin</th>
<th>Norfloxacin</th>
<th>Trimethoprim-Sulfamethoxazole</th>
<th>Nitrofurantoin (urine only)</th>
<th>Gentamicin</th>
<th>Tobramycin</th>
<th>Vancomycin</th>
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<tbody>
<tr>
<td>Staphylococcus aureus, all</td>
<td>- methicillin-susceptible (MSSA) - 766</td>
<td>100</td>
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<td>- methicillin-resistant (MRSA) - 307</td>
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<tr>
<td>Staphylococcus epidermidis</td>
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<td>Streptococcus pneumoniae</td>
<td>40</td>
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<td>Enterococcus faecalis, all</td>
<td>1407</td>
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<td>R R R R R R</td>
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<tr>
<td>Enterococcus faecium, all</td>
<td>86</td>
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</table>

R - intrinsically resistant or less than 15% susceptibility

1 These organisms are capable of producing extended spectrum beta-lactamases - 4.79% of all gram negatives were ESBL +ve in 2014
2 These organisms may produce inducible beta-lactamase (AmpC) enzymes. Use of beta-lactams can result in clinical failure despite in vitro susceptibility
3 Susceptibility to gentamicin in gram positive organisms refers to combination synergy treatment only
MRSA - antibiotic choice?

- **Oral:** Clindamycin, Trimethoprim-Sulfamethoxazole, Doxycycline, Linezolid, Moxifloxacin, Ciprofloxacin

- **Intravenous:** Vancomycin, Daptomycin, Tigecycline, Ceftaroline, Oritavancin, Telavancin
### ESBL

#### Chromosomally mediated

<table>
<thead>
<tr>
<th>Intrinsic resistance</th>
<th>Plasmid mediated</th>
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</thead>
<tbody>
<tr>
<td>Gram negatives:</td>
<td>acquired resistance</td>
</tr>
<tr>
<td>Klebsiella – penicillinase</td>
<td>E coli, Klebsiella, Citrobacter, Enterobacter, Pseudomonas, Proteus, Serratia, Salmonella</td>
</tr>
<tr>
<td>Enterobacter – cephalosporinase</td>
<td>Enterobacter, Citrobacter, Serratia - broad β-lactamase</td>
</tr>
<tr>
<td>Citrobacter, Serratia - broad β-lactamase</td>
<td></td>
</tr>
<tr>
<td>Resistance induced depends on the organism</td>
<td>Ineffective: penicillins, cephalosporins ± fluoroquinolones (cipro, moxifloxacin) ± pen-βlactamase inhibitor combos</td>
</tr>
</tbody>
</table>

### Drug of choice:

- **Chromosomally mediated**
  - Carbapenems (Ertapenem, Meropenem, Imipenem)
  - Piperacillin-tazobactam

- **Plasmid mediated**
  - Carbapenems (Ertapenem, Meropenem, Imipenem)
  - Maybe Cefamycins (Cefoxitin, cefotetan)
The next evolution…Carbapenem resistance!

- Metallo-β-lactamase initially in *Klebsiella pneumoniae* called carbapenemase or KPC

- Plasmid mediated, transferable resistance

- Differs from inducible carbapenemases (CPO)

- Reported in *E. coli, Enterobacter, Citrobacter, Morganella Acinetobacter, Salmonella, Proteus, Pseudomonas*

GNR resistance in Canada

Figure A: Carbapenemase-producing Enterobacteriaceae (CPE) in Canada: the Canadian Public Health Laboratory Network (CPHLN) data, 2008 to 2014

Canadian Antimicrobial Resistance Surveillance System,
Public Health Agency of Canada
So now what??

- polymyxins, tigecycline, and less frequently aminoglycoside antibiotics.
- Increasing colistin (polymixin) resistance – MCR-1 from China Nov 2015 to USA April 2016
- 3 isolates of MCR-1 *E. coli* in Canada, one human (Egypt), 2 food source
- New agents ?? Metallo-β-inhibitors, tricyclic carbapenem inhibitor, 5th gen cephalosporins (ceftobiprole, ceftaroline)
I think I need antibiotics for my col...

IT'S A VIRUS!

Pssst! Hey kid! Wanna be a Superbug...? Stick some of this into your genome... Even penicillin won't be able to harm you...!

“It was on a short-cut through the hospital kitchens that Albert was first approached by a member of the Antibiotic Resistance.”

