My Top 3 Picks for What’s Hot in ID & Microbiology

Sumon Chakrabarti MD FRCPC DTM&H
Infectious Diseases & Tropical Medicine
Trillium Health Partners – Mississauga
University of Toronto
Disclosures

-I have no financial or academic conflicts to disclose

-I however have a personal disclosure
Objectives

- Review of my 3 picks for interesting ID/Micro topics from 2016
- Honorable mention of a 4th item
- Speak to potential impact on future practice
- Tell some nerdy science jokes…starting now
Luke, use the mass times the acceleration
Candida auris
**Candida auris**

- First described in Japan 2009
- Isolated in multiple countries since
- First case in N. America 2013

*J Infect 2016;73:369–74*
What’s so hot about C. auris?

- Antifungal resistance
- Difficulties w/ identification & Afx sensis
- Potential for serious infection
- Possible pt to pt transmission
Identification
Identification

- No distinguishing features in microscopy
- Budding yeast cells, single, pairs
- No Pseudohyphae

MMWR Morb Mortal Wkly Rep 2016;65:1234–1237
Misidentification

- VITEK-2
- API20-AUX

- C. haemulonii,
- C. famata,
- Rhodotorula glutinii
Some studies show 90% isolates inaccurately IDed

MMWR Morb Mortal Wkly Rep 2016;65:1234–1237
MALDI-TOF / Molecular Methods more accurate
Antifungal Resistance
Antifungal Resistance

- Resistance not new in Candida (esp. azoles)
- C. auris resistance to multiple agents / classes
C. auris Resistance

- Uniformly high MIC to fluconazole
- Reduced susceptibility seen
  - Voriconazole
  - Caspofungin
  - Flucytosine
  - Ampho B
When something is resistant to Ampho B or Amikacin, this is what I picture...
Beware Pseudoresistance!

- Falsely elevated MIC seen Ampho B
- Seen with VITEK-2
- CLSI-BDM + Etest better

MMWR Morb Mortal Wkly Rep 2016;65:1234–1237
Clinical Features
Clinical Features

- Mainly candidemia in reports
- Majority sig. chronic Med conditions
- Concurrent MDR bacterial colonization

MMWR Morb Mortal Wkly Rep 2016;65:1234–1237
<table>
<thead>
<tr>
<th>Patient</th>
<th>Site of Infection</th>
<th>Co-Morbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Candidemia</td>
<td>High dose steroids</td>
</tr>
<tr>
<td>2</td>
<td>Candidemia</td>
<td>CNS Malignancy</td>
</tr>
<tr>
<td>3</td>
<td>Candidemia</td>
<td>Leukemia</td>
</tr>
<tr>
<td>4</td>
<td>Candidemia</td>
<td>Bone Marrow Tx</td>
</tr>
<tr>
<td>5</td>
<td>Candidemia</td>
<td>Short Gut - TPN</td>
</tr>
<tr>
<td>6</td>
<td>Candiduria</td>
<td>Paraplegia</td>
</tr>
<tr>
<td>7</td>
<td>Cutaneous</td>
<td>Severe PAD / Skull Osteomyelitis</td>
</tr>
</tbody>
</table>

MMWR Morb Mortal Wkly Rep 2016;65:1234–1237
Infection Control Issues

- C. auris looks to have patient to patient transmission
- US patients persistently colonized post Afx
- Terminal clean (bleach + UV) could eradicate

MMWR Morb Mortal Wkly Rep 2016;65:1234–1237
Summary of What’s Hot

1. C. auris is a newly recognized spp of Candida with potential person to person spread

2. Usually resistant to fluconazole, reduced susceptibility seen with all other fungal classes
Summary of What’s Hot

3. Has mainly been seen in those with multiple health conditions

4. Has the potential of causing significant morbidity in chronically / critically ill patients
Fever is not a sign of ceftriaxone deficiency.
Zika & Microcephaly

Baby with Typical Head Size

Baby with Moderate Microcephaly

Baby with Severe Microcephaly

Zika Virus and Birth Defects — Reviewing the Evidence for Causality

Sonja A. Rasmussen, M.D., Denise J. Jamieson, M.D., M.P.H.,
Margaret A. Honein, Ph.D., M.P.H., and Lyle R. Petersen, M.D., M.P.H.

SUMMARY
The Zika virus has spread rapidly in the Americas since its first identification in Brazil in early 2015. Prenatal Zika virus infection has been linked to adverse pregnancy and birth outcomes, most notably microcephaly and other neurodevelopmental sequelae.

POTENTIAL RELATIONSHIP BETWEEN ZIKA VIRUS INFECTION AND BIRTH DEFECTS
Since the identification of the Zika virus in Brazil in early 2015, the virus has spread rapidly throughout the Americas, fueling increased interest in the potential relationship between Zika virus infection and birth defects.
Zika Virus Associated with Microcephaly

Jernej Mlakar, M.D., Misa Korva, Ph.D., Nataša Tul, M.D., Ph.D., Mara Popović, M.D., Ph.D., Mateja Poljšak-Prijatelj, Ph.D., Jerica Mraz, M.Sc., Marko Kolenc, M.Sc., Katarina Resman Rus, M.Sc., Tina Vesnaaver Vipotnik, M.D., Vesna Fabjan Vodušek, M.D., Alenka Vizjak, Ph.D., Jože Pižem, M.D., Ph.D., Miroslav Petrovec, M.D., Ph.D., and Tatjana Avšič Županc, Ph.D.
Yet another in a series of epidemic spread arboviruses

Highly suspected to be teratogenic, but not proven

This article gives strong evidence of teratogenicity
Why is it Important?

- Conspiracy theories abound on social media
- Social media primary news source for many in today’s world
- Misinformation can hamper recommendations
THE ZIKA VIRUS EXISTED FOR 60 YEARS, BUT THE MEDIA INSIST IT'S CAUSING AN EPIDEMIC OF BIRTH DEFECTS IN BRAZIL.

SAME AREAS OF BRAZIL HAVE HISTORY OF MOSQUITO SPOTTING WITH A MONSANTO PRODUCT THEY KNOW TO CAUSE BIRTH DEFECTS. THAT IS NONE OF MY BUSINESS.

Conspiracy Theory!!!!
What is Zika Virus?

• Originally described Uganda 1947, found in rhesus monkey

• Sporadic infections over Africa, Asia next several decades
Where did it come from?

1st major outbreak Yap Islands 2007 (~8000 affected)

2nd major outbreak Polynesia 2013-2014 (~32,000 affected)

First case in Western Hemisphere Easter Island 2014

Where did it come from?

8000km
West Nile, Chikungunya, Influenza, now Zika

Epidemics may now be the rule
Congenital Effects
These have been collectively termed “Congenital Zika Syndrome”

http://jamanetwork.com/journals/jamapediatrics/fullarticle/2579543
Congenital Zika Syndrome

1. severe microcephaly collapsed skull
2. thin cerebral cortices, subcort calci
3. macular scars & focal retinal mottling
4. Congen contractures
5. marked early hypertonia, extrapyr Sx.

Congenital Zika Syndrome

Suggests early disruption in CNS formation sequence

More than 2300 congenital cases have been confirmed in Brazil since beginning of outbreak

How was a causal link established?
To prove causality, need to satisfy:

Criteria #1, 2 & 3 (Epi approach)

Criteria #1, 3 & 4 (Rare Exposure / Rare Defect Approach)
Shepard's Criteria

Criterion 1

Satisfied?

Seen in multiple studies. Risk appears highest 1st & early 2nd trimester

Shepard’s Criteria

Criterion 2

Satisfied?

Only partially met. Studies are ongoing.

Done! Multiple studies pointing towards “Congenital Zika Syndrome”
Shepard’s Criteria

<table>
<thead>
<tr>
<th>Criterion 4</th>
<th>Satisfied?</th>
</tr>
</thead>
</table>

Zika + Microcephaly rare. Unlikely to occur together by chance alone.
Shepard’s Criteria

Criterion 6 Satisfied?

- Zika known to be neurotropic
- Zika RNA/culture in CZS brain tissue
- CNS & Eye abnormalities seen in affected
Zika is Teratogenic

- Shepard’s postulates of causation are met!
- Rare Exposure / Rare Defect Approach
- Causation met Bradford-Hill criteria
1. Zika is an arbovirus with recent epidemic spread in Western Hemisphere

2. Current Epidemic coincidental with sharp rise in microcephaly

3. Shepard criteria of teratogenicity shows causal link w/ Zika & Congenital Zika Syndrome
Safety first
MCR-1
Emergence of a microbial mechanism for the control of HIV in China:

Yi-Yun Liu*, Yang Wang*, Lin-Feng Yu, Danxia Gu, Haining Hong, Xianhui Huang, Xuanzhe Sun, and Shanzhong Shen
Why it’s hot...

First description of cell to cell transfer of polymyxin resistance

Potential of pan-resistant Gram negative pathogens
Some Background (Polymyxins)

- Originally made 1950s
- Nephrotoxic, fell out of favour
- Used recently for MDR G- bacteria

Some Background (Polymyxins)

“Last line therapy”

Some Background (Polymyxins)

- Polymyxin cationic polypeptide
- Disruption of cell membrane binding LPS (lipid A)

Some Background (Polymyxins)

- Broad spectrum activity G-
- ESBLs
- Pseudomonas
- Carbapenem R gram negatives

In Clinical Use..

- Polymyxin B (Polysporin)
- Polymyxin E (colistin)

MCR-1: What does it do?
Changing of Antibiotic Target

MCR-1 codes for enzyme that alters membrane LPS

Decrease binding of Colistin

Resistance!
Mobile Strike!

What’s driving its spread?
Antibiotic use in Agriculture
It’s all about the Environment

Colistin use on the Rise

- Colistin use heavy in agriculture
- Largest producers of livestock largest users of colistin
- Cultivation of resistant bacteria

MCR-1 Slowly Spreading

Seen in...

- E. coli
- Klebsiella
- Salmonella
- Pseudomonas

MCR-1 Slowly Spreading

- Ongoing plasmid mediated transmission
- Eventually pan-resistant strain will emerge

It’s not a matter of if….it’s when

Is there any hope?
A new antibiotic kills pathogens without detectable resistance

Losee L. Ling¹*, Tanja Schneider²,³*, Aaron J. Peoples¹, Amy L. Spoering¹, Ina Engels²,³, Brian P. Conlon⁴, Anna Mueller²,³, Till F. Schäberle³,⁵, Dallas E. Hughes¹, Slava Epstein⁶, Michael Jones⁷, Linos Lazarides⁷, Victoria A. Steadman⁷, Douglas R. Cohen¹, Cintia R. Felix¹, K. Ashley Fetterman¹, William P. Millett¹, Anthony G. Nitti¹, Ashley M. Zullo¹, Chao Chen⁴ & Kim Lewis⁴
Teixobactin

- Soil contains +++ uncultured bacteria
- Potential production of antimicrobials
- *Eleftheria terrae* produces teixobactin

Teixobactin

- Active vs. cell wall
- Gram positive bacteria mainly (including resistant strains)
- Resistance not seen (yet) in vitro

Perhaps other antibiotics await ...
“What did you take away from the meeting?”
Summary of What’s hot

1. mcr-1 gene confers resistance to polymyxins, a “last resort” class

2. Described for 1st time to have plasmid mediated transmission

3. Discovered in humans & animals multiple countries around the world

Summary of What’s hot

4. Has the potential to spread between unrelated bacteria

5. Pan-resistant Gram negative a real possibility

6. Uncultured soil bacteria potential source for new Abx
YOUR DAD’S BEEN UNDER A LOT OF PRESSURE LATELY.
Audience Question #1

To which of the following antifungals has *Candida auris* demonstrated reduced susceptibility or resistance?

1. Amphotericin B
2. Fluconazole
3. Caspofungin
4. Voriconazole
5. All of the above
To which of the following antifungals has *Candida auris* demonstrated reduced susceptibility or resistance?

- Amphotericin B: 3%
- Fluconazole: 6%
- Caspofungin: 0%
- Voriconazole: 2%
- All of the above: 89%
Where did the first recorded epidemic of Zika virus take place?

1. French Polynesia
2. India
3. Brazil
4. Yap Islands
5. Papua New Guinea
Where did the first recorded epidemic of Zika virus take place?

- French Polynesia: 7%
- India: 0%
- Brazil: 0%
- Yap Islands: 91%
- Papua New Guinea: 2%
What is the mechanism of colistin resistance conferred by mcr-1?

1. Efflux pump
2. Enzymatic destruction
3. Changing of antibiotic target
4. Cell wall thickening
5. Direct methylation
What is the mechanism of colistin resistance conferred by mcr-1?

- Efflux pump: 3%
- Enzymatic destruction: 4%
- Changing of antibiotic target: 83%
- Cell wall thickening: 6%
- Direct methylation: 4%
Thank you!
References

- Nature 517, 455–459 (22 January 2015)
- https://www.cdc.gov/mmwr/volumes/65/wr/mm6544e1.htm?s_cid=mm6544e1_w
- https://wwwnc.cdc.gov/eid/article/22/9/16-0464_article