# 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



# 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

### Identification

Misidentification
 VITEK-2
 API20-AUX

C. haemulonii,
C. famata,
Rhodotorula glutinii

# VITEK

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



# Some studies show 90% isolates inaccurately IDed

MMWR Morb Mortal Wkly Rep 2016;65:1234-1237



#### MALDI-TOF / Molecular Methods more accurate

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

ONS DN-

### Antifungal Resistance

### Antifungal Resistance

#### Resistance not new in Candida (esp. azoles)

C. auris resistance to multiple agents / classes

#### C. auris Resistance

FLZ 150

Uniformly high MIC to fluconazole

Reduced susceptibility seen
 Voriconazole
 Caspofungin
 Flucytosine
 Ampho B

#### - big - claws - sharp teeth

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

### Cases from the US

Patient	Site of Infection	Co-Morbidities
1	Candidemia	High dose steroids
2	Candidemia	CNS Malignancy
3	Candidemia	Leukemia
4	Candidemia	Bone Marrow Tx
5	Candidemia	Short Gut - TPN
6	Candiduria	Paraplegia
7	Cutaneous	Severe PAD / Skull Osteomyelitis

MMWR Morb Mortal Wkly Rep 2016;65:1234-1237

# Infection Control

### 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

 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



# Zika & Microcephaly



Baby with Typical Head Size Baby with Moderate Microcephaly Baby with Severe Microcephaly

#### N Engl J Med 2016;374:951-8. N Engl J Med 2016; 374:1981-1987



The NEW ENGLAND JOURNAL of MEDICINE

#### SPECIAL REPORT

#### 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 no-

#### ZIKA VIRUS INFECTION AND BIRTH DEFECTS

Since the identification of the Zika virus in Brazil in early 2015, the virus has spread rapidly

> N Engl J Med 2016;374:951-8. I Engl J Med 2016; 374:1981-1987



The NEW ENGLAND JOURNAL of MEDICINE

#### BRIEF REPORT

#### 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 Vesnaver 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.

N Engl J Med 2016;374:951-8. N Engl J Med 2016; 374:1981-1987

# What's so hot about Zika?

 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





Instagram

THE ZIKA VIRUS EXISTED FOR 60 YEARS, BUT THE MEDIA INSIST IT'S CAUSING AN EPIDEMIC OF BIRTH DEFECTS IN BRAT

consp

A KAYED WITH A MONSANTO KNOW TO CAUSE BIRTH DEFECTS. HAT IS NONE OF MY BUSINESS

# 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?

#### 1<sup>st</sup> major outbreak Yap Islands 2007 (~8000 affected)

#### 2<sup>nd</sup> major outbreak Polynesia 2013-2014 (~32,000 affected)



First case in Western Hemisphere Easter Island 2014

N Engl J Med 2009, 360:253

# Where did it come from?



#### Beyond Geographic Constraints!

# West Nile, Chikungunya Influenza, now Zika



T

#### Epidemics may now be the rule
## **Congenital Effects**

### Complications



N Engl J Med 2016;374:951-8. N Engl J Med 2016; 374:1981-1987

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.

JAMA Pediatr. 2017;171(3):288-295.

# **Congenital Zika Syndrome**



Suggests early disruption in CNS formation sequence

JAMA Pediatr. 2017;171(3):288-295.

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



http://www.paho.org/hq/index.php?option=com\_content&id=11599&Itemid=41691

# How was a causal link established?

### Shepard's Criteria of Teratogenicity

Table 1. Shepard's Criteria for Proof of Teratogenicity in Humans as Applied to the Relationship between Zika Virus Infection and Microcephaly and Other Brain Anomalies.\*

### prove causality, need to satisfy:



trol of confounding factors, sufficient numbers, exclusion of positive and negative bias factors, prospective studies if possible, and relative risk ≥6

Two epidemiologic studies have been published. In a study in Brazil<sup>14</sup> that used a prospective cohort design, 29% of women with Zika virus infection at any time during pregnancy had abnormalities on prenatal ultrasonography, some of which have not been confirmed postnatally, In a study in French Polynesia,<sup>2</sup> retrospective identification of eight



N Engl J Med 2016; 374:1981-1987

ARR ALB PA

NA

### Criteria #1, 2 & 3 (Epi approach)

The phenotype in some infants appears to be consistent with the fetal

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

Proof in an experimental system that the agent acts in an unaltered state

munonistochemical staining and identification of Zika virus Kiva This criterion applies to a medication or chemical exposure. not to infectious agents.

live virus,16,17,19 provides strong biologic plausibility.

#### **Criterion 1**

#### Satisfied?

# Seen in multiple studies. Risk appears highest 1<sup>st</sup> & early 2<sup>nd</sup> trimester

#### **Criterion 2**

#### Satisfied?

# Only partially met. Studies are ongoing.

#### **Criterion 3**

#### Satisfied?

# Done! Multiple studies pointing towards "Congenital Zika Syndrome"

**Criterion 4** 

Satisfied?

# Zika + Microcephaly rare. Unlikely to occur together by chance alone.

Criterion 6

Satisfied?

Zika known to be neurotropic

Zika RNA/culture in CZS brain tissue

CNS & Eye abnormalities seen in affected

N Engl J Med 2016; 374:1981-1987 N Engl J Med 2016;374:951-8.

# Zika is Teratogenic

#### Shepard's postulates of causation are met!

#### Rare Exposure / Rare Defect Approach

 Causation met Bradford-Hill criteria



## Summary of What's Hot

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



# MCR-1

#### Emergence mechanisr a microbio

Yi-Yun Liu\*, Yang Wang\* Lin-Feng Yu, Danxia Gu, I



Scary sharp teeth

#### e 1 China:

ng, Xianhui Huang, nzhong Shen



# Why it's hot...

# First description of cell to cell transfer of polymyxin resistance

## Potential of pan-resistant Gram negative pathogens

#### Originally made 1950s

#### Nephrotoxic, fell out of favour



Used recently for MDR Gbacteria

### "Last line therapy"



#### Polymyxin cationic polypeptide

#### Disruption of cell membrane binding LPS (lipid A)



### Broad spectrum activity G-See 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

Lancet Infect Dis. 2016;16:161-8

www.nature.com/news/spread-of-antibiotic-resistance-aene-does-not-spell-bacterial-apocalypse-vet-1,19037

### 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**

### Ongong plasmid mediated transmission

### Eventually pan-resistant strain will emerge

### It's not a matter of if....it's when

### Is there any hope?
#### It's all about the environment again!

### ARTICLE

doi:10.1038/nature14098

# A new antibiotic kills pathogens without detectable resistance

Losee L. Ling<sup>1</sup>\*, Tanja Schneider<sup>2,3</sup>\*, Aaron J. Peoples<sup>1</sup>, Amy L. Spoering<sup>1</sup>, Ina Engels<sup>2,3</sup>, Brian P. Conlon<sup>4</sup>, Anna Mueller<sup>2,3</sup>, Till F. Schäberle<sup>3,5</sup>, Dallas E. Hughes<sup>1</sup>, Slava Epstein<sup>6</sup>, Michael Jones<sup>7</sup>, Linos Lazarides<sup>7</sup>, Victoria A. Steadman<sup>7</sup>, Douglas R. Cohen<sup>1</sup>, Cintia R. Felix<sup>1</sup>, K. Ashley Fetterman<sup>1</sup>, William P. Millett<sup>1</sup>, Anthony G. Nitti<sup>1</sup>, Ashley M. Zullo<sup>1</sup>, Chao Chen<sup>4</sup> & Kim Lewis<sup>4</sup>

Nature 517, 455–459 (2015)

## Teixobactin

Soil contains +++ uncultured bacteria

Potential production of antimicrobials

Eleftheria terrae produces teixobactin

Nature 517, 455–459 (2015)

### Teixobactin

#### Active vs. cell wall

Gram positive bacteria mainly (including resistant strains)

resistance not seen (yet) in vitro

Nature 517, 455–459 (2015)

#### 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 1<sup>st</sup> time to have plasmid mediated transmission

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

Lancet Infect Dis. 2016;16:161-8

# 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?



# **Audience Question #2**

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?



# Audience Question #3

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?



# Thank you!



### References

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