What’s Hot in Infectious Diseases - Clinical Science?

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No Disclosures
A Perfect Storm: Convergence of MDR and Hypervirulence in *Klebsiella pneumoniae* – Hangzhou, China

- 5 critically ill mechanically ventilated trauma patients with severe pneumonia
- Carbapenem-resistant *K. pneumoniae* (ST11) recovered from blood/respiratory
- All died with severe pneumonia, multiorgan system failure, septic shock
- Isolates were hypervirulent: + string test, multiple virulence factors, survived within neutrophils, highly lethal in wax moth larvae model; lethal to patients

Gu et al. Lancet Infect Dis 2017; published online Aug 29.
K. Pneumoniae ST11

KPC Acquired a Virulence Plasmid

170 kbp pLVPK-like virulence plasmid
A Perfect Storm: Convergence of MDR and Hypervirulence in *K. pneumoniae*  
China National Study

- 387 clinical ST11 carbapenem-resistant *K. pneumoniae* in 2015 from 25 provinces & municipalities
- **11/387 (3%)** from 3 different provinces carried the 170 kbp pLVPK-like virulence plasmid
- All 11 carried *bla*<sub>KPC-2</sub>
- All 11 from blood or respiratory secretions
- **5/11 patients died**

Gu et al. Lancet Infect Dis 2017; published online Aug 29.
Virulent Carbapenem-Resistant *K. pneumoniae*
Wenzhou Medical University, Wenzhou, China

- 140 (7.6%) of 1838 clinical *K. pneumoniae (KP)* isolated in 2013-15 were carbapenem resistant.
- 21/140 (15%) had a + string test & carried other virulence genes.
- All 21 carried *bla*$_{KPC-2}$, 20 also harbored *bla*$_{SHV-11}$, and 15 had *bla*$_{CTXM-65}$
- All 21 isolated were in 2014-15 (many during possible ICU outbreak) – none in 2013
- 12/21 (61.9%) patients had previously received a carbapenem
- 11/21 (52%) died, - with septic shock & MOSF, 10 “giving up treatment”,
Immediate Need:

Potent new antibiotics active against MDR GNR!
Expediting FDA Approval of Antibiotics

• **Fast Track** designation – serious illness with unmet need

• **Breakthrough Therapy** – serious unmet need; may use surrogate endpoints

• **Accelerated Approval** – can be based on preliminary approval

• **Priority Review** - ≤6 months

• **Generating Antibiotic Incentives Now (GAIN) provisions of the Food and Drug Administration Safety and Innovation Act of 2012** -
  • **qualified infectious disease product (QIPD)** designation - eligible for several incentives, including fast track designation, priority review designation and an additional five years of market exclusivity
Ceftazidime/Avibactam: The 505(b)(2) Pathway

• 505(b)(2) established in 1984 to facilitate approvals that involve changes to previously approved drugs

• Ceftazidime/avibactam approved in 2015 on the basis of previous data re ceftazidime alone, Phase II clinical data on the combination (total N=160) and PK/PD data, as well as some preliminary information from uncompleted trials

• Label initially indicated its use should be confined to patients with limited or no alternative treatment options – warning removed after additional data when phase III cUTI and cIAI data became available (June 2016)
TANGO-2: Meropenem/Vaborbactam vs. Best Available Rx

- Serious Infection: Bacteremia, Pneumonia, cUTI, IAI
- 72 patients (43 CRE, 20 with bacteremia; 86% KP)
- Study stopped by DSMB:
  - “risk-benefit analysis of available no longer supported randomization of additional patients to the best available therapy comparator arm”

<table>
<thead>
<tr>
<th></th>
<th>CLINICAL CURE</th>
<th>CRE POPULATION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mero/Vab N (%)</td>
<td>Best Avail. N (%)</td>
</tr>
<tr>
<td># Pts</td>
<td>28</td>
<td>15</td>
</tr>
<tr>
<td>EOT</td>
<td>18 (64.3%)</td>
<td>6 (40.0%)</td>
</tr>
<tr>
<td>TOC</td>
<td>16 (57.1%)</td>
<td>4 (26.7%)</td>
</tr>
</tbody>
</table>

Kaye et al. IDWeek 2017. Abst 1826
Some Antibiotics Active Against MDR GNR with Expected/Possible 2018-2019 Approval Dates

- Eravacycline (Tetraphase)
- Plazomicin (Achaogen)
- Fosfomycin IV (Zavante)
- Cefiderocol (Shinogi)
Cefiderocol

- Siderophore cephalosporin
- Panel (N=315) of carbapenemase-producing MDR GNR – MIC ≤4 mcg/ml:
  - Enterobacteriaceae – 87.5%
  - *P. aeruginosa* - 100%
  - *A. baumanii* - 89%
- Activity by carbapenemase type:
  - A – 91.8%    B - 74.8%    D – 98.0%

IDWeek 2017. Abstract 1230
Cefiderocol Vs. Imipenem/Cilastatin in Acute cUTI +/- Pyelonephritis Or Acute Uncomplicated Pyelonephritis APEKS-cUTI

Response at Test of Cure in Microbiological Intent-to-Treat Population

<table>
<thead>
<tr>
<th></th>
<th>Cefiderocol N (%)</th>
<th>Imipenem/Cil N (%)</th>
<th>Adjusted Δ %</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td># Pts</td>
<td>252</td>
<td>119</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical + Micro*</td>
<td>183 (72.6%)</td>
<td>65 (54.6%)</td>
<td>28.9%</td>
<td>8.23%, 28.92%</td>
</tr>
<tr>
<td>Clinical</td>
<td>226 (89.7%)</td>
<td>104 (87.4%)</td>
<td>2.4%</td>
<td>-4.66%, 9.44%</td>
</tr>
</tbody>
</table>

*Primary endpoint

Portsmouth et al. IDWeek 2017. Abstract 1869
More Efforts To Accelerate Antibiotic Development

• **CARB-X**: Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator
  - Created by Executive Order, September 18, 2014
  - **Public-private partnerships focused on preclinical discovery and development of new antibacterial products to help address the threat of antibiotic resistance**

• **ARLG**: Antibacterial Resistance Leadership Group
  - Mission: “prioritize, design and **execute clinical research** that will reduce the public health threat of antibacterial resistance.”
  - Creating clinical research networks.
Sexually transmitted diseases hit record U.S. high, officials say
The **state of STDs** in the United States in 2016:

- **1.59 million** cases of chlamydia, 4.7% increase since 2015.
- **468,514** cases of gonorrhea, 18.5% increase since 2015.
- **27,814** cases of syphilis, 17.6% increase since 2015.

STDs tighten their grip on the nation's health as rates increase for a third year.
Mycoplasma genitalium

- Overall, 2nd most frequent STI after Chlamydia trachomatis
- Approximately 2% of population infected
- Symptoms in men with urethritis of similar severity to C. trachomatis
- Generally asymptomatic in women, but associated with cervicitis, PID
- Diagnosis by nucleic acid amplification (NAA), but there is no FDA-approved test
- Treatment generally syndromic, but anti-Chlamydia Rx often ineffective with continuing emergence of resistance to azithromycin (67% cure rate) and doxycycline (31% cure rate); 7 days moxifloxacin (89% cure rate)

Syphilis in U.S. 2014-2015
Cases per 100,000 Population

https://www-cdc-gov.laneproxy.stanford.edu/std/stats15
“Number of ocular syphilis cases creeps to record high”
Royal Victoria Eye & Ear Hospital (RVEEH)

Posterior placoid chorioretinitis

Disc swelling

Punctate inner retinitis

Perivascular retinitis

Clinical & Experimental Ophthalmology
CEO-17-02-0126.R2, 23 AUG 2017 DOI: 10.1111/ceo.13021
PENICILLIN CURES GONORRHEA IN 4 HOURS
SEE YOUR DOCTOR TODAY
Ceftriaxone + Azithromycin
Failure in a Patient with Gonorrhea, 2014 - UK

- Heterosexual male with gonorrhea (apparently acquired in Japan)
- Urine, pharynx NAA +, urethra culture +
- Rx: 500 mg ceftriaxone, 1 g azithromycin
- Pharyngeal swab remained +
- Re-Rx: (Day 98) 1 g ceftriaxone, 2 g azithromycin
- Pharyngeal swab negative @ Day 112

- Resistant* to ceftriaxone (0.25 mcg/ml), azithromycin (1.0 mcg/ml), cefixime, cefotaxime, penicillin, tetracycline, ciprofloxacin
- Susceptible to spectinomycin

By EUCAST criteria: CTX >0.125, Azithro >0.5

NEJM 2017; 374:2504-5
Meningococcal Serotype B Vaccine Provides Protection Against Gonorrhea

- Retrospective case-control study of:
  - individuals ages 15-30 years born between 1984 and 1998 and
  - who presented to sexual health clinics where a diagnosis of either gonorrhea and/or Chlamydia infection was made and
  - who had been eligible to receive MeZNB in 2004-2006
- MeZNB contains outer membrane vesicles (OMV) of *Neisseria meningitides* serotype B
- MeZNB vaccination in 2004-6 had estimated **protective effect against the development of gonorrhea of 31%** (95% CI, 21 TO 39; P<0.0010).

- Bexsero is a multivalent vaccine that includes OMV of serotype B and will be evaluated for prevention of gonorrhea

Aspergillus - Azole Resistance

Figure 3. Worldwide map of azole resistance in *Aspergillus fumigatus*. The red highlighted countries have reported azole resistance.

Aspergillus – Azole Resistance

- 20%-30% of clinical isolates in Germany, Netherlands are azole resistant
- Demethylase inhibitors used in agriculture, as a biocide in paint and coatings, wallpaper paste, clothing, and wood preservation
- Netherlands exported 2.4 million plant bulbs in 2014
  - 5/6 lots contained azole-resistant A. fumigatus.
- 38/200 (19%) A. fumigatus from peanut crop in Georgia fields with exposure to DMIs were triazole resistant; 20/38 contained TR_{34}/L98H

Clinical cases of *Candida auris* reported by state, United States, as of August 31, 2017

- 1st identified in 2009
- High mortality rates
- Easily misidentified – grows at 40°C, no pseudohyphae
- Nosocomial transmission
- Environmental persistence
- Phylogenetically related to *C. lusitaniae* and *C. krusei*
- Multidrug resistant

[Map showing cases](https://www.cdc.gov/fungal/diseases/candidiasis/tracking-c-auris.html)
### Candida auris – Antifungal Susceptibility – 54 Isolates

<table>
<thead>
<tr>
<th>Antifungal</th>
<th>MIC Range, µg/mL</th>
<th>MIC50, µg/mL</th>
<th>MIC90, µg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluconazole</td>
<td>4–256</td>
<td>128</td>
<td>256</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>0.03–16</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>0.125–2</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>0.06–1</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>0.03–16</td>
<td>0.25</td>
<td>1</td>
</tr>
<tr>
<td>Anidulafungin</td>
<td>0.125–16</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>Micafungin</td>
<td>0.06–4</td>
<td>0.25</td>
<td>2</td>
</tr>
<tr>
<td>Flucytosine</td>
<td>0.125–128</td>
<td>0.125</td>
<td>0.5</td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>0.38–4</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

**Resistance Based on Proposed Breakpoints**

<table>
<thead>
<tr>
<th>Antifungal</th>
<th>% Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluconazole</td>
<td>93%</td>
</tr>
<tr>
<td>Amphotericin</td>
<td>35%</td>
</tr>
<tr>
<td>Echinocandins</td>
<td>7%</td>
</tr>
<tr>
<td>2 Classes</td>
<td>41%</td>
</tr>
<tr>
<td>3 Classes</td>
<td>4%</td>
</tr>
</tbody>
</table>
Candida glabrata – Echinocandin Resistance

- 83/1385 cases non-susceptible – 64 resistant
- Increased from 4.2% → 7.8% from 2008 to 2014 (P < 0.001)
- 59% had no known prior echinocandin exposure
- 32.9% also fluconazole resistant

- Resistance ranged from 0% - 25.8% by hospital
- 3 large academic hospitals accounted for 48%

C. glabrata – haploid, frequent mutator phenotype due to mutations in DNA mismatch repair gene (MSH2)

Why Not: CDC Recommends Adding Vanco & Zosyn to the Water

BY DR. 99

Why Not: CDC Recommends Adding Vanco & Zosyn to the Water

Antimicrobial Stewardship

• Piperacillin/tazobactam nephrotoxicity
• Joint Commission requirement as of Jan 1, 2017
  • Includes affiliated outpatient facilities
• HICPAC: incorporate stewardship principles into IDSA Guidelines
• Dealing with antibiotic overuse resulting from Surviving Sepsis Campaign
• Focus on duration of antibiotic administration
• Surgical prophylaxis – no dose post-OR per CDC
• Diagnostic stewardship, including rapid & point-of-care testing
Stewardship Intervention: The Soup Nazi

No Antibiotic for You!
Maybe Not So Hot
Where Has All the Zika Gone?

United States

- 2016:
  - 4830 travel-related
  - 224 local transmissions – all in Florida & Texas

- 2017 (as of August):
  - 200 travel-related
  - 1 local transmission - Texas

Herd Immunity?
Overestimates due to X-reactivity with dengue?

Problem: Vaccine trials!

Hepatitis A Outbreaks in Homeless, Illicit Drug Users Right Around the Corner

Table. Outbreak Associated Hepatitis A infections by California Jurisdiction

<table>
<thead>
<tr>
<th>Jurisdiction</th>
<th>Cases</th>
<th>Hospitalizations</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>San Diego</td>
<td>461</td>
<td>315</td>
<td>16</td>
</tr>
<tr>
<td>Santa Cruz</td>
<td>68</td>
<td>33</td>
<td>0</td>
</tr>
<tr>
<td>Los Angeles</td>
<td>8</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Others</td>
<td>5</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>542</td>
<td>357</td>
<td>16</td>
</tr>
</tbody>
</table>

Vaccine Doses Distributed by CDPH to Date: 55,740

San Diego largest person to person outbreak since vaccine intro in 1995
Related strains of the IB genotype (uncommon in U.S.; most prevalent in the Mediterranean region, South Africa and Turkey

Also: Utah – 33 outbreak cases (0 deaths) as of 9/25/17; Southeast Michigan – 341 cases, 268 hospitalized, 14 (4.4%) died

https://www.cdph.ca.gov/Programs/CID/DCDC/Pages/Immunization/Hepatitis-A.aspx
http://www.michigan.gov/mdhhs/0,5885,7-339-71550_2955_2976_82305_82310-447907--,00.html
That’s Not All Folks...

• Management of *C. difficile* infection
  • Integrating (& paying for) fidaxomicin, bezlotoxumab, fecal microbiota transplantation

• Hospital Epidemiology
  • Fecal microbiota transplantation for gastrointestinal MDR decolonization
  • Whole genome sequencing
  • Isolation for VRE, MRSA – is it warranted?

• Viral Disease
  • Impending New Antivirals: letermovir, maribavir, brincidofovir, cytotoxic T cells
  • HCV - pangenotype DAA
  • Increasing (?) Powassan virus, autochthonous chikungunya in France, Italy (including Rome)

• Laboratory Diagnostics
  • Unbiased metagenomic next generation sequencing

• Miscellaneous
  • *Plasmodium falciparum* – increasing artemisinin resistance
  • *Borrelia miyamotoi*
  • *Mycobacterium chimaera*

Infections post-disaster, extreme weather events
Syndemic: Opioids & infection
Powassan Virus: An Emerging Arbovirus of Public Health Concern in North America

Meghan E. Hermance¹ and Saravanan Thangamani¹-³
That’s Not All Folks...

• Antimicrobial Stewardship
  • Joint Commision requirement for ASP (1 Jan 2017), including affiliated outpatient sites
  • HICPAC: include stewardship principles in IDSA guidelines
  • Diagnostic stewardship; including rapid, POC testing
  • Focus on duration of antimicrobial therapy
  • Surgical prophylaxis – no doses post-OR

• Hospital Epidemiology
  • Whole genome sequencing
  • Fecal microbiota transplant for gastrointestinal MDR decolonization

• Viral Disease
  • New Antivirals: letermovir, maribavir, brincidofovir, cytotoxic T cells

• Some Miscellaneous Pathogens
  • *Plasmodium falciparum* – increasing artemisinin resistance
  • *Borrelia miyamotoi*
  • *Mycobacterium chimaera*
Meningococcal B Vaccine Prevents Gonorrhea

- Each dose of MeNZBis 0.5 ml and contains: 25 mcg of outer membrane vesicles from the *Neisseria meningitidis* group B strain NZ98/254.
- NM, NG have 80-90% genetic homology
- Bexsero: factor H binding protein (fHbp), neisserial adhesin A (NadA), Neisseria heparin binding antigen (NHBA) and outer membrane vesicles from a New Zealand epidemic strain (which provides PorA)
- is composed of five antigens, GNA1870 (fHbp), GNA1994 (NadA), GNA2132 (NHBA), GNA1030 and 2091 (Table 1). In the vaccine NadA is present as a single recombinant protein, while fHbp and NHBA are expressed as fusions to GNA2091 and GNA1030 respectively, composing a three protein vaccine.