What’s Hot in Infectious Diseases - Clinical Science?

Stan Deresinski MD FACP FIDSA
Clinical Professor of Medicine
Stanford University

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.
KPC Acquired a Virulence Plasmid

K. Pneumoniae ST11
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*$_{KPC-2}$
- 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”,

Dr. Schnabel von Rom

Von Groätls ab einem Tafel, und darüber von anderer Stätte der Epoche des Cæsareum, et aufft einen Sohn, dessen Cadaver sich er auf freien, gleich wie der Corvus auf der Mimmel, als Credula, zuletzt nicht dort bei dem Romst regna des Bovis.

Gnum non debebunt sequefus, 
Sue fœnicis Melos, fruæ 
Quad laguartus als war er summo, und er se suo consilium. 
Wemender Credit obsequent ut, 
Das im terthe von zuverlässem 
Musiquum hat seine Heil, und euerum der gehe lieb.
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** - \( \leq 6 \) 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)

The Inevitable Emergence of Resistance

• Ceftazidime/avibactam - Initial FDA Approval Feb 2015
  • Rx CRE: 3/10 microbiological failures developed resistance
  • Resistance due to mutations in *blaKPC3* (but restored carbapenem susceptibility in some isolates.

• Ceftolozane/tazobactam – Initial FDA Approval Dec 2014
  • Rx MDR PA: 3/21 developed resistance
  • *ampC* overexpression and structural mutations

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”

Kaye et al. IDWeek 2017. Abst 1826

<table>
<thead>
<tr>
<th></th>
<th>Mero/Vab N (%)</th>
<th>Best Avail. Therapy N (%)</th>
<th>Δ %</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td># Pts</td>
<td>28</td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EOT</td>
<td>18 (64.3%)</td>
<td>6 (40.0%)</td>
<td>24.3%</td>
<td>-6.2% to 54.8%</td>
</tr>
<tr>
<td>TOC</td>
<td>16 (57.1%)</td>
<td>4 (26.7%)</td>
<td>30.5%</td>
<td>1.6% to 59.4%</td>
</tr>
</tbody>
</table>
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
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\textsubscript{34}/L98H

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

- 1\textsuperscript{st} 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

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>

Clinical Infectious Diseases, Volume 64, Issue 2, 15 January 2017, Pages 134–140
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)

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

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

BY DR. 99

Antimicrobial Stewardship

• Piperacillin/tazobactam/gentamicin 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!

DOI: [http://dx.doi.org/10.15585/mmwr.mm6631a4](http://dx.doi.org/10.15585/mmwr.mm6631a4)
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

As of 22 Sept 2017; San Diego 12 Oct: 576 cases, 386 hosp, 18 deaths

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 – 397 cases, 320 hospitalized, 15 (4.0%) died as of 10/12/17

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

As of 6 Oct:

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<td>490</td>
<td>342</td>
<td>18</td>
</tr>
<tr>
<td>Santa Cruz</td>
<td>71</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>Other</td>
<td>7</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>576</td>
<td>386</td>
<td>18</td>
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Vaccine Doses Distributed by CDPH to Date: 80,110 doses

San Diego largest person to person outbreak since vaccine intro in 1995
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[Links]
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**Vaccine Doses Distributed by CDPH to Date: 80,110 doses**
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
Antibiotic resistance
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.