What Every HIV Clinician Needs to Know about Infectious Diseases

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Conflicts of Interest: None
• MACRA: US data
• Resistance: Bad bugs, no drugs
• Molecular microbiology
• Readiness: ZIKA etc. & bioterrorism
• Microbiome
MACRA

- **Why**: The US healthcare costs are >2x those of any other country and rank 23d in healthcare outcomes (longevity, infant death, addiction, etc)

- **Plan**: Reimbursement based on volume changed to reimburse based on value ("Value vs Volume")

- **Clout**: CMS- major US healthcare payer & Joint Commission requirement for stewardship

- **Data**: CDC Source: EHR

- **Evaluation**: needed

- **Concern**: EHR/time demands
CDC: ANTIMICROBIAL USE & RESISTANCE (AUR) Module

Goal: Establish risk-adjusted benchmarks for antimicrobial use by antimicrobial agent, route of treatment (PO, IV, IM) & days of therapy (DOT) analyzed by patient units (medical, surgery, ICUs, pediatrics, obstetrics, outpatients, etc):

**JHH: Use of levofloxacin during August 2016**

<table>
<thead>
<tr>
<th>Mo/Yr.</th>
<th>Drug</th>
<th>Total</th>
<th>IV</th>
<th>IM</th>
<th>GI</th>
<th>Resp</th>
</tr>
</thead>
<tbody>
<tr>
<td>8/2016</td>
<td>Cipro</td>
<td>307 Days</td>
<td>234 Days</td>
<td>0</td>
<td>178 Days</td>
<td>0</td>
</tr>
</tbody>
</table>
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Antibiotic Resistance

*Neisseria gonorrhoeae* - azithromycin

*H. pylori* - macrolides; metronidazole; rifampin

*S. pneumoniae* - macrolides, amoxicillin

*Mycoplasma pneumoniae* - macrolides

*M. tuberculosis* - INH, rifampin, PZA, quinolones

Influenza - oseltamivir

*Bacteroides fragilis* - clindamycin, moxifloxacin, metronidazole, carbapenems

*Vibrio cholera* - MDR

*Enterococcus* - vancomycin
## Major Resistant Pathogens

**4,000 US Hospitals, CDC, March 2016**

<table>
<thead>
<tr>
<th>Major Resistant Bacteria</th>
<th>Recent Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESBL <em>Enterobacteriaceae</em></td>
<td>18%</td>
</tr>
<tr>
<td>Enterococcus- VRE</td>
<td>27%</td>
</tr>
<tr>
<td>MDR <em>P. aeruginosa</em></td>
<td>13%</td>
</tr>
<tr>
<td>MDR <em>Acinetobacter</em> sp</td>
<td>45%</td>
</tr>
<tr>
<td><strong>Carbapenemase + GNB</strong></td>
<td>3%</td>
</tr>
</tbody>
</table>

* 8 states in US, esp. SC and Illinois
WHO Priority Pathogen List

**Critical:**  
- *A. baumannii* — carbapenem-resistant  
- *P. aeruginosa* — carbapenem-resistant  
- *Enterobacteriaceae* — carbapenem-resistant & 3d gen. cephalosporin-resistant

**HIGH:**  
- Vanco-resistant enterococcus  
- MRSA — Vanco-resistant  
- *H. pylori* — clarithromycin-resistant  
- Salmonella — FQ-resistant  
- *N. gonorrhoeae* — FQ & 3d-gen ceph resist
Antibiotic Resistance Intervention Bundle

- Short course
- **Procalcitonin** to guide when to start and stop
- Peer comparisons +/- report cards
- Molecular diagnostics use and interpretation
- Automatic stop orders
- “Time-out” at 72 hrs: Review abx, cult, response
- IV ➔ PO switch early
- Gene sequencing to trace transmission paths
- Guidelines from authoritative sources
- Preauthorization required
Assessment: Abx prescribing based on audits of 249 primary care MDs for 214,753 RTI visit

Results: Change in prescribing antibiotics at baseline to intervention 24.1% → 13.1%

Most successful: Accountable justification (-17%) & peer comparison (-18%) P <0.001

Postscript: NY Times 3/28/16: Note in EHR to all providers for top 10% and lowest 10%
Recent Antibiotic Recommendations

**Acute bronchitis**: No abx & no microbiology

**Pharyngitis**: Pos strep test only: beta lactam

**Common cold**: “No, never”

**Sinusitis**: “Watchful waiting” x >7 days

**Asymptomatic UTI**: No abx due to harm-symptomatic UTI & resistance

*ACP 2016; **Am Acad Otolaryngol. 2015; ***IDSA, 2015
Ciprofloxicin
“Just say no”

FDA-approved 1987-
* Wide range of indications: UTI, CAP, sinusitis, EACB, cellulitis, IAS, anthrax
* WHO—Essential drug
* Largest-selling antibiotic in world- $0.04/pill

FDA- New warning (July 26, 2016)
* ADRV—tendonitis, neuropathy, CNS (CDI!!!)

FDA: “Always use alternatives if possible”
Antibacterial Decision Making: Role of Procalcitonin (?CRP-POC)

**Biology:** Marker of bacterial replication

**Utility:** Facilitates decision to start or stop antibacterial agents

**Europe:** Extensive use POC CRP; US – minimal

**Cochrane review:** 7 controlled trials, 1,458 patients: 51% decrease in Abx

(Tang H. Infection 2009;37:497)
Multiple studies show rapid initiation of effective antibiotics for seriously ill patients consistently correlates with improved outcome, including survival.

1. **CAP**: Survival data mandate starting antibiotics within 4-6 hours (Bratzler; UK)

2. New [sepsis guidelines](#) recommend initiation of antibiotics within 1 hr. or penalties
Number of New Antibiotics by Year

Total # New Antibacterial Agents

- '83-'87: 16
- '88-'92: 14
- '93-'97: 10
- '98-'02: 8
- '03-'07: 6
- '08-'12: 4
- '13-'15: 2

The graph shows a decrease in the number of new antibacterial agents from '83-'97, with a sharp decline after '08-'12.
<table>
<thead>
<tr>
<th>New abx</th>
<th>FDA Date</th>
<th>Indication</th>
<th>ESCAPE Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fidaxomycin</td>
<td>2003</td>
<td>CDI</td>
<td>No</td>
</tr>
<tr>
<td>Bedaquiline</td>
<td>2012</td>
<td>TB</td>
<td>No (MDR-TB)</td>
</tr>
<tr>
<td>Dalbavancin</td>
<td>2014</td>
<td>ABSSI</td>
<td>No</td>
</tr>
<tr>
<td>Tedizolid</td>
<td>2014</td>
<td>ABSSI</td>
<td>No</td>
</tr>
<tr>
<td>Oritovancin</td>
<td>2014</td>
<td>ABSSI</td>
<td>No</td>
</tr>
<tr>
<td>Ceftaroline</td>
<td>2010</td>
<td>CAP; ABSSI</td>
<td>Yes</td>
</tr>
<tr>
<td>Ceft/tazobactam</td>
<td>2014</td>
<td>CIAI</td>
<td>Yes</td>
</tr>
<tr>
<td>Ceftaz/avibactam</td>
<td>2015</td>
<td>CIAI; CUTI</td>
<td>Yes</td>
</tr>
</tbody>
</table>

ABSSI-acute skin/STI; IAI-intra-abd Inf; CUTI-complex UTI
Ceftolozane/Tazobactam (CID 2016;63:234)

**Class**: 2\textsuperscript{nd}-gen cephalosporin/beta lactamase inhibitor

**Spectrum**: Active vs most enteric GNB

**Special advantage**: Active vs ESBL and some multiply resistant *P. aeruginosa*

**Dose**: 1.5 gm q 8 hrs infused over 1 hr; renal dosing

**T1/2**: Ceftolozone- 3 hr/tazobactam-1 hr

**Cost**: $240/day; doripenem-$120; imipenem- $50; Cefepime- $16; pip/tazo-$40; cefotaxime- $10

**FDA Approval**: Complicated UTIs & intra-abdom infect
### Ceftazidime-Avibactam: Activity (Sader H. AAC 2014;58:1692)

**In vitro activity clinical isolates: % sensitive**

<table>
<thead>
<tr>
<th>Microbe</th>
<th>N</th>
<th>Ceft</th>
<th>Ceft/Avi</th>
<th>Mero</th>
</tr>
</thead>
<tbody>
<tr>
<td>All coliforms</td>
<td>640</td>
<td>89%</td>
<td>100%</td>
<td>99%</td>
</tr>
<tr>
<td>Klebsiella</td>
<td>1,847</td>
<td>100%</td>
<td>99%</td>
<td>94%</td>
</tr>
<tr>
<td>E. coli</td>
<td>767</td>
<td>92%</td>
<td>100%</td>
<td>99%</td>
</tr>
<tr>
<td>Morganella</td>
<td>295</td>
<td>86%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>P. aeruginosa</td>
<td>1,967</td>
<td>83%</td>
<td>97%</td>
<td>82%</td>
</tr>
<tr>
<td>ESBL +</td>
<td>328</td>
<td>31%</td>
<td>97%</td>
<td>99%</td>
</tr>
</tbody>
</table>
New Antibiotics in Development

* IV minocycline: *Acinetobacter* sp, *Stenotrophomonas*, *Bulkholdaria* sp

* New polymyxins: non-nephrotoxic

* Meropenem/RPX7009: carbapenemase inhibitors - KPC, *A. baumanii*, *P. aeruginosa*

* Plazomicin
• MACRA: US data
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FDA-cleared Nucleic Acid Amplification Tests (NAAT)

- **Viruses**: Measles, mumps, varicella, RTI-rhinovirus, coronavirus, enterovirus, adenovirus, HMV, RSV, paraflu, influenza, encephalitis- WNV, HSV, JCV; Other- EBV, dengue, HPV, BK virus, rabies, CMV


- **Other**: Trichomonas, PCP
## BioFIRE FILM ARRAY- GI Panel
(Buss SN. J Clin Micro 2015;53:379)

**Method:** 4 sites; 1,555 specimens; BioFIRE vs lab standard

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>BioFire</th>
<th>Control</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. jejuni</td>
<td>58</td>
<td>35</td>
<td>97%</td>
</tr>
<tr>
<td>C. difficile</td>
<td>204</td>
<td>165</td>
<td>99%</td>
</tr>
<tr>
<td>Salmonella</td>
<td>37</td>
<td>31</td>
<td>100%</td>
</tr>
<tr>
<td>Shigella</td>
<td>47</td>
<td>49</td>
<td>96%</td>
</tr>
<tr>
<td>ETEC</td>
<td>38</td>
<td>22</td>
<td>99%</td>
</tr>
<tr>
<td>EPEC</td>
<td>348</td>
<td>317</td>
<td>99%</td>
</tr>
<tr>
<td>Cryptosporidium</td>
<td>18</td>
<td>24</td>
<td>100%</td>
</tr>
<tr>
<td>Norovirus</td>
<td>70</td>
<td>55</td>
<td>95%</td>
</tr>
</tbody>
</table>
Plex-ID: The Next-Generation System: T5000

RT-PCR → Electron ionization – mass spec
Detects bacteria, viruses, and fungi
Result: <8 hr (expect 3 hrs)
Quantitative
Cost: $500K, $80/sample
Next-generation Sequencing
Pak TR & Kasarskis A. CID 2015;61:1695

EMR

ID & IC

Management

Specimen

Lab

Current

Future

Sequencing

Pathogen database
**CDI: British Health System**

**NHS:** CDI epidemic throughout the UK

Decrease rate mandate

**Response:**
1) Epidemiology: NAP-1
2) “Stopped” FQ (+ cephalosporins)
3) Gene sequencing - infection control

**Result:** Rates ↓ 80%!
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Issue: Medical leaders never seem ready

Examples: Flu-1918; HIV; SARS

Precedent: War – NATO

Last example of preparing for pandemic: Dark Winter- Smallpox (Inglesby T. CID; 2002;34:972)

Recommended components: 1) Health systems; 2) surveillance; 3) trained respondents; 4) good data; 5) diagnostics, vaccines, drugs
<table>
<thead>
<tr>
<th>Microbial Epidemics That Usually Required Local Engagement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxic shock - <em>S. aureus</em></td>
</tr>
<tr>
<td>AIDS</td>
</tr>
<tr>
<td>West Nile virus</td>
</tr>
<tr>
<td>Lyme disease</td>
</tr>
<tr>
<td><em>H1N1; H5N1 influenza</em></td>
</tr>
<tr>
<td>SARS</td>
</tr>
<tr>
<td>MERS</td>
</tr>
<tr>
<td><em>S. aureus USA-300</em></td>
</tr>
<tr>
<td>Legionella</td>
</tr>
<tr>
<td><em>Hepatitis C</em></td>
</tr>
<tr>
<td><em>C difficile</em> NAP-1 strain</td>
</tr>
<tr>
<td>Measles, mumps</td>
</tr>
<tr>
<td>Anthrax (bioterrorism)</td>
</tr>
<tr>
<td>Iatrogenic fungal meningitis</td>
</tr>
<tr>
<td>Foodborne: salmonella, Listeria, <em>E. coli</em> 0157</td>
</tr>
<tr>
<td><em>Ebola</em></td>
</tr>
<tr>
<td><em>Zika virus</em></td>
</tr>
<tr>
<td>Persistence &amp; STDs</td>
</tr>
</tbody>
</table>
Mosquito-borne Travelers’ Infections

* **Dengue**: (“Bone-break”)
  * S. America 1990s

* **West Nile virus**: US-1999

* **Chikungunya**: “Bent-up”
  Reunion Island at 1 yr
  - 44% still had disabling arthritis
  (Medicine. 2012;91:212)

* **Zika virus**: Uganda; fever, rash, joint pain 2015
  S. America (esp. Brazil), Caribbean; 40 M/yr; then Florida
  New- Neurotrophic; pregnancy complication; STD; persistence

* **Yellow fever**: Now epidemic in Brazil; clinically the most serious with 3.5%-7.5% mortality.

Common to all- *A. aegypti* mosquito vector

Fauci A. NEJM. 2016;374;601.
Bioterrorism

2001: The event using *B anthracis* (anthrax)

Anthrax: spore form; inert & stable for decades in all conditions; vegetative form: highly lethal

Distribution: Mail to politicians and journalists

Final data: 15 cases with 5 deaths and massive panic

**Major bioterrorism agents:** Anthrax and smallpox

**Who:** Russia, Iraq, & N. Korea

**Data source for Russia:** K. Alibek: Responsible for Russian bioterrorism program, then defected to US and authored book on Soviet program- >20 metric tons of weaponized smallpox.

**Planning:** CDC: Smallpox-

New guideline, antibiotic and vaccine

(for the only pathogen “eliminated” from globe)
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Metabolic Syndrome with Fecal Transplant in Rodent Model

**B** WT  |  T5KO

**C** WT  |  T5KO

**E**
Serum Triglycerides [mg/dl]

- WT: 60
- T5KO: 80

**F**
Serum Cholesterol [mg/dl]

- WT: 120
- T5KO: 150

**G**
Blood Pressure [mmHg]

- Systole: WT, T5KO
- Diastole: WT, T5KO

* indicates statistical significance.
Openbiome- Commercial Stool for Transplant for Relapsing CDI: (openbiome.com)

**Donors**: 2.5 hr interview for acceptability- diet, activities, health, GI disease, wt, BMI, abx, etc., CRE, ESBL, MRSA: 2.8% accepted

**Donors**: Stool donated 3X/week

**Product**: Available for $385, shipped to 50 states and 7 countries frozen on dry ice (nonprofit)

**No. shipped**: 17,572;

**Outcome** – **Successful**: 87%

**Wt gain**: <2%; **Plan**: Eradicate mcr-1 gene?

**Plan**: NIH-funded: 5-year changes—wt, DM, lipids
Abx resistance is a crisis that was predicted in 2006
Response is antibiotic stewardship— major role in clinical care is “smart use” of antibiotic.

The CDC/CMS MACRA plan: Expect audits of use by EHR for comparison with benchmarks & ?EHR review by health facility, service, DRG, provider.

Molecular micro will transform the micro lab; need caution

*C. dif*- High CMS/CDC priority to reduce (like UK); stool transplant is “hot” & may have a transformative future

ID always has surprises: 2015-Ebola; 2016- Zika; 2017-?
The END