What’s Hot in Infectious Diseases - Clinical Science?

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No Disclosures
Pakistan: Salmonella enterica serovar typhi
MDR → XDR

- November 2016, Hyderabad Pakistan
- Appearance of a H58 haplotype strain resistant to antibiotics of 5 classes
- Resulted from acquisition of chromosomal and plasmid mediated mechanisms by dominant H58 haplotype
- Plasmid carrying *qnrS*, *bla*\textsubscript{CTX-M-15} acquired from *E. coli*
- Susceptible only to imipenem, azithromycin

Integrated transposon encoding amp, chloro, T/S resistance + gyrA single mutation

IncY plasmid* 

\[\text{bla}_{\text{CTXM-15}} \quad \text{qnrS}\]

MDR – chloramphenicol\textsuperscript{R}, T/S\textsuperscript{R}, ampicillin\textsuperscript{R}
XDR – MDR plus ceftiraxone\textsuperscript{R}, fluoroquinolone\textsuperscript{R}

mBio. January/February 2018 Volume 9 Issue 1 e00105-18
XDR Typhoid – Pakistan & Beyond

- Rapid increase in case numbers with spread to Karachi
- WHO prequalified use of conjugate vaccine (Typbar-TCV®) – single dose, immunogenic in children >6 months of age

- At least 3 travelers returned with infection - one to UK, 2 to US
“Novartis joins the Big Pharma exodus out of antibiotics, dumping research, cutting 140 and out-licensing programs”

https://gizmodo.com/novartis-becomes-the-latest-pharma-company-to-give-up-on-antibiotics-research-1827524081
### Selected Antibacterials Expected to Be Submitted to the FDA for Approval by Mid-2019

<table>
<thead>
<tr>
<th>Investigational drug name</th>
<th>Manufacturer</th>
<th>Class</th>
<th>Proposed indication(s)</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefiderocol</td>
<td>Shinogi</td>
<td>Siderophore-cephalosporin</td>
<td>cUTI, HABP/VABP, CRE</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Eravacycline</td>
<td>Tetraphase</td>
<td>Tetracycline</td>
<td>clAI (failed cUTI study)</td>
<td>PDUFA date Aug 28, 2018</td>
</tr>
<tr>
<td>Fosfomycin (intravenous)</td>
<td>Zavante</td>
<td>Phosphonic acid derivative</td>
<td>cUTI, clAI, HABP/VABP, ABSSSI</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Iclaprim</td>
<td>Motif Bio PLC</td>
<td>Dihydrofolate reductase inhibitor</td>
<td>ABSSSI, HABP</td>
<td>NDA filed Q2 2018</td>
</tr>
<tr>
<td>Lefamulin</td>
<td>Nabriva</td>
<td>Pleuromutilins</td>
<td>CABP, ABSSSI</td>
<td>Estimated NDA filing Q4 2018</td>
</tr>
<tr>
<td>Omadacycline</td>
<td>Paratek</td>
<td>Tetracycline</td>
<td>CABP, ABSSSI</td>
<td>NDA filed Q2 2018 (PDUFA estimated Oct 2018)</td>
</tr>
<tr>
<td>Plazomicin</td>
<td>Achaogen Inc.</td>
<td>Aminoglycoside</td>
<td>cUTI</td>
<td>Approved Jun 25, 2018</td>
</tr>
<tr>
<td>Imipenem-cilastatin/relebactam</td>
<td>Merck</td>
<td>Carbapenem</td>
<td>cUTI, AP, HABP/VABP</td>
<td>Phase 3</td>
</tr>
</tbody>
</table>

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*a Adapted from Pew Charitable Trusts.*

[https://cdn2.hubspot.net/hubfs/498900/Jul2018_DrugPriceForecast_Media_FINAL.pdf](https://cdn2.hubspot.net/hubfs/498900/Jul2018_DrugPriceForecast_Media_FINAL.pdf)
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

Also active against *Stenotrophomonas maltophilia*
Minocycline
Oxytetracycline derivative

Tigecycline
Glycylglycine

Eravacycline
Fluorocycline

Omadacycline
Aminomethylcycline
## Tigecycline, Eravacycline, Omadacycline Tissue-Directed Pharmacokinetics

**Tigecycline**

*Diagn Microbiol Inf Dis 2005; 52:165-71.*

<table>
<thead>
<tr>
<th></th>
<th>Tigecycline</th>
<th>Eravacycline*</th>
<th>Omadacycline**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (µg/mL)</td>
<td>0.82</td>
<td>1.8 – 2.1</td>
<td>1.8</td>
</tr>
<tr>
<td>T1/2 (hours)</td>
<td>36</td>
<td>20</td>
<td>16.8</td>
</tr>
<tr>
<td>Vd (L)</td>
<td>350-500</td>
<td>320</td>
<td>200</td>
</tr>
<tr>
<td>Renal Excretion (%)</td>
<td>33</td>
<td>16</td>
<td>14</td>
</tr>
</tbody>
</table>

*1.0 mg/kg IV

**100 mg IV
# Eravacycline Vs. FDA Breakpoints & Tigecycline

<table>
<thead>
<tr>
<th>Organism</th>
<th>Eravacycline (mcg/ml)</th>
<th>Tigecycline (mcg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MIC90 (µg/ml)</td>
<td>FDA Breakpoint (µg/ml)</td>
</tr>
<tr>
<td>MRSA</td>
<td>0.12</td>
<td>&lt;0.06</td>
</tr>
<tr>
<td>VRE</td>
<td>0.06</td>
<td>&lt;0.06</td>
</tr>
<tr>
<td>K. pneumoniae</td>
<td>1.0</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>E. coli (ESBL)</td>
<td>0.5</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>P. aeruginosa</td>
<td>16</td>
<td>None</td>
</tr>
<tr>
<td>S. maltophilia</td>
<td>0.5</td>
<td>None</td>
</tr>
<tr>
<td>B. fragilis</td>
<td>2.0</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>C. difficile</td>
<td>0.12</td>
<td>&lt;0.5</td>
</tr>
</tbody>
</table>

Drugs 2016; 76:567-88.
Eravacycline (Xerava)

• Failed in two Phase 3 cUTI studies (q24h dosing)  Note: 16% in urine.
  • IGNITE 2: Vs. levofloxacin (both IV -→ oral) – LL of difference (95%CI): -14.2%
  • IGNITE 3: Vs. ertapenem(both IV only) – LL of difference (95%CI): -14.2%

• Non-inferior to carbapenems in 2 Phase 3 cIAI studies (q12h dosing); micro ITT
  • IGNITE 1: 1 mg/kg q12h vs. ertapenem – success in 86.8% Vs. 87.6% [1]
  • IGNITE 4: 1 mg/kg q12h vs. meropenem – success in 90.8% vs. 91.2% [2]

• FDA approval for cIAI August 27, 2018

Efficacy of Eravacycline in Secondary Bacteremia: A Post Hoc Analysis of Two Phase 3 studies of Complicated Intra-Abdominal Infection

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Eravacycline (N=415)</th>
<th>*Comparators (N=431)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Gram-negative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E. coli</td>
<td>5/6 (83.3)</td>
<td>6/7 (85.7)</td>
</tr>
<tr>
<td>Gram-positive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptococcus spp.</td>
<td>8/8 (100)</td>
<td>4/4 (100)</td>
</tr>
<tr>
<td>Enterococcus spp.</td>
<td>2/2 (100)</td>
<td>5/5 (100)</td>
</tr>
<tr>
<td>Anaerobes</td>
<td>9/9 (100)</td>
<td>13/14 (92.9)</td>
</tr>
<tr>
<td>Bacteroides spp.</td>
<td>6/6 (100)</td>
<td>8/8 (100)</td>
</tr>
</tbody>
</table>

* Meropenem and Ertapenem

2018 IDWeek Abstract 1978
Omadacycline

- IV/PO q24h dosing (2 doses 1st d)
- CABP (OPTIC) – non-inferior to moxifloxacin, each IV (≥3 days) → PO
- ABSSI (OASIS I, II) – non-inferior to linezolid (both PO)

- August 29, 2018: FDA Advisory Committee voted approval for ABSSI and CABP
- FDA Approval October 3, 2018

AAC 2018; PMID 28223386  
AAC 2016; 60:7431-5.
Plazomicin (ZEMDRI)

- Sisomicin derivative
- Unaffected by 15/17 aminoglycoside modifying enzymes; Exceptions:
  - AAC(2’)-Ia (only in *P. stuartii*)
  - APH(2’’)-IVa (only in Enterococcus)
- Methyltransferases cause resistance - highly associated with NDM-carrying organisms

97 CRE – MIC90 1.0 mcg/ml (amikacin – 32 mcg/ml)

*P. aeruginosa, Acinetobacter* – MIC90: 16 mcg/ml (72%, 65% inhibited at ≤4 mcg/ml)

64% amikacin-resistant Enterobacteriales inhibited at ≤4 mcg/ml

<table>
<thead>
<tr>
<th>Susceptible</th>
<th>Intermediate</th>
<th>Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2 mcg/ml</td>
<td>4 mcg/ml</td>
<td>&gt;8 mcg/ml</td>
</tr>
</tbody>
</table>


Plazomicin cUTI – FDA approval – June 26, 2018
For “Patients with limited or no options”

**EPIC Trial**

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Response</th>
<th>Plazomicin N=191 N (%)</th>
<th>Meropenem N=197 N(%)</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Day 5</strong></td>
<td>Cure</td>
<td>168 (88.0)</td>
<td>180 (91.4)</td>
<td>-3.4 (-10.0, 3.1)</td>
</tr>
<tr>
<td></td>
<td>Failure</td>
<td>20 (10.5)</td>
<td>15 (7.6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Indeterminate</td>
<td>3 (1.6)</td>
<td>2 (1.0)</td>
<td></td>
</tr>
<tr>
<td><strong>TOC</strong></td>
<td>Cure</td>
<td>156 (81.7)</td>
<td>138 (70.1)</td>
<td>11.6 (2.7, 20.3)</td>
</tr>
<tr>
<td></td>
<td>Failure</td>
<td>29 (15.2)</td>
<td>51 (25.9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Indeterminate</td>
<td>6 (3.1)</td>
<td>8 (4.1)</td>
<td></td>
</tr>
</tbody>
</table>

[https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM607642.pdf](https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM607642.pdf)
Plazomicin Vs. Colistin (Each + Meropenem or Tigecycline) in MDR BSI, HABP/VABP

FDA: Complete Response Letter

Figure 2. Mortality-Based Outcomes

Difference (plazomicin minus colistin) (90% CI)
-39.0 (-65.5 to -9.4)
-32.9 (-60.1 to -4.0)

Patients (%)

<table>
<thead>
<tr>
<th>All-cause mortality at day 28 or significant complications</th>
<th>All-cause mortality at day 28</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plazomicin</td>
<td>Colistin</td>
</tr>
<tr>
<td>2/14</td>
<td>8/15</td>
</tr>
<tr>
<td>14.3</td>
<td>53.3</td>
</tr>
<tr>
<td>7.1</td>
<td>40.0</td>
</tr>
</tbody>
</table>

Figure 3. Survival Through Day 60

Plazomicin: 0.37 (0.15-0.91)

McKinnell JA, et al. IDWeek 2017. Poster 1853

Approximately 2100 pts screened over 2 years; <2% met inclusion criteria CRE. Planned 286 with.
IV Fosfomycin (Contepo) Vs. Pip/Tazo
ZEUS Trial: cUTI and Acute Pyelonephritis

• 465 inpatients randomized to 7d days IV Rx (14 days if bacteremic)
  • Fosfomycin: 6 g q8h over 1 hour
  • Pip/Tazo: 4.5 g q8h over 1 hour

• 1° outcome: Clinical + Micro in MITT @ TOC

• NDA filing expected Q4 2018

• Upcoming problem:
  • Agar dilution Only reliable method of susceptibility testing

Diagn Microbiol Infect Dis. 2018 Jul 31
OFID 2017:4 (Suppl 1) S528, Abstract 1845
MRSA Bacteremia: Open-Label Multicenter Randomized Trial -- Daptomycin +/- Fosfomycin

- Daptomycin 10 mg/kg/d; Fosfomycin 2 g q6h
- Rx duration: Uncomplicated 10-14 days; Complicated 28-42 days

<table>
<thead>
<tr>
<th></th>
<th>Dapto</th>
<th>Dapto + Fosfomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>81</td>
<td>74</td>
</tr>
<tr>
<td>7 days of Rx</td>
<td>62 (76.5%)*</td>
<td>69 (93.2%)*</td>
</tr>
<tr>
<td>Difference</td>
<td></td>
<td>16.7% (5.4% to 27.7%)</td>
</tr>
<tr>
<td>TOC</td>
<td>34 (42%)*</td>
<td>40 (54.1%)*</td>
</tr>
<tr>
<td>Difference</td>
<td></td>
<td>12.1% (0% to 27.0%)</td>
</tr>
<tr>
<td>Micro Failure @ TOC Visit</td>
<td>9</td>
<td>0 (P = 0.009)</td>
</tr>
</tbody>
</table>

- *7 day success: Alive, bacteremia cleared without relapse
- **Test-of-cure success: 6 wks after end of Rx
Lefamulin (Nabriva): First Systemic Antibiotic Representative of a New Class

• A pleuromutilin – binds to peptidyl transferase component of 50S ribosome subunit, inhibiting protein synthesis
  • Retapumulin approved for topical use

• Active against respiratory pathogens (including “atypicals”), STD pathogens (including *M. genitalium* and resistant gonococci) plus MRSA and VRE

• IV and oral formulations

• Non-inferior to moxifloxacin +/- linezolid in CABP

• NDA (CABP) planned 4th quarter 2018

Pharmacotherapy 2018; doi: 10.1002/phar.2166
Iclaprim (Motif Bio PLC)

- Tricyclic diaminopyrimidine
- 20X more potent against *S. aureus* DHFR than trimethoprim (TMP)
- Active against many TMP-resistant *S. aureus* & *S. pneumoniae* DHFR
- Also active against *H. influenzae* & *M. catarrhalis*

- Targeted Infections: ABSSI, HAP/VAP, CF with *S. aureus*
- ABSSI – non-inferior to vanco
- PDUFA (ABSSI): February 13, 2019

https://www.motifbio.com/iclaprim/
Make Antibiotics Great Again
MERINO: Pip/Tazo Vs. Meropenem

- Ceftriaxone-nonsusceptible, pip/tazo susceptible *E. coli* or *K. pneumoniae* bacteremia
- 26 sites in 9 countries; open-label

- Randomized within 72 h of blood culture draw to:
  - Pip/tazo 4.5 g Q 6h (30 minute infusion) OR
  - Meropenem 1 g Q 8h
- Study stopped at 3rd interim analysis for “futility and harm” based on 30-day mortality in mITT population (the primary outcome measurement).

JAMA 2018; 320:984-94.
MERINO: Kaplan-Meier Failure Estimates for Primary Outcome

86.2% *E. coli*

Primary outcome – 30-day mortality

- **23/187 (12.3%)**
- **7/191 (3.7%)**

Δ8.6% (1-sided 97.5% CI, -∞ to 14.5%; P = 0.90 for noninferiority)

# Needed to Harm = 12

JAMA 2018; 320:984-94.
MERINO: Day of Clinical & Micro Resolution (mITT)

- Clinical & micro resolution @ Day 4
  - Pip/Tazo – 68.4%
  - Meropenem – 74.6% (P= 0.19)

- Median day of resolution of signs of infection
  - Pip/Tazo – 3
  - Meropenem – 2 (P = 0.18)

- No significant differences in: micro resolution by Day 4, micro relapse, 2° MDR infection, CDI

JAMA 2018; 320:984-94.
MERINO: Secondary Outcomes

All subgroup and secondary analyses favored meropenem.

Measure of Success

Clinical and microbiological success at day 4
Microbiological success at day 4

Measure of Failure

Microbiological relapse
Secondary infection with multiresistant organism or Clostridium difficile

a. Survival, neg BC, T $\leq$ 38°C, WBC $\leq$ 12K

JAMA 2018; 320:984-94.
No association between MIC and 30-day mortality
Some MERINO Issues

- Is a 30 minute infusion adequate?
  - MIC of 8 → 81% PTA\(^1\) (PTA: >50% T>MIC)
  - 3 h infusion → 100% PTA

- What accounts for the low mortality (7.9% overall)?
  - No significant difference in microbiological, clinical resolution
  - Only 2.6% high-risk – nonurinary and PITT>4
  - Had to survive to randomization at up to 72 hours

- Effect of empiric Rx, including X-overs

- Step-down allowed after 5 days – 20% of each group received ertapenem

- If no significant difference in clinical & microbiological response, what accounts for the 30-day mortality difference?

\(^1\)AAC 2012; 56:4087-94.

### Potential Bias Favors:

<table>
<thead>
<tr>
<th>Factor</th>
<th>Pip/Tazo</th>
<th>Meropenem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pip/Tazo 30 minute infusion</td>
<td></td>
<td>✔</td>
</tr>
<tr>
<td>Mero 30 minute infusion???</td>
<td>✔ ???</td>
<td></td>
</tr>
<tr>
<td>Low mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Empiric Rx; carba in 13.8% PT</td>
<td>✔</td>
<td></td>
</tr>
<tr>
<td>Step-down; carba in 20.2% PT</td>
<td>✔</td>
<td></td>
</tr>
<tr>
<td>AmpC (10%), ESBL+AmpC (2%)</td>
<td></td>
<td>✔</td>
</tr>
</tbody>
</table>
POET: Endocarditis Rx -- IV -> PO Conversion

Entry Criteria

• Age >18 years
• Left-sided infective endocarditis
  Fulfills modified Duke criteria
  Native or prosthetic valve
• Streptococcus, E. faecalis,
  S. aureus, or coagulase-negative staph
• IV antibiotic for >10 days and T <38°C for >2 days, WBC <15K, CRP <2 or decreased to <25% of peak
  >7 days after valve surgery (if performed)
• No abscess or valve dysfunction requiring surgery (by trans-esophageal echo) within 48 hours of randomization

POET: Endocarditis Rx -- IV \(\rightarrow\) PO Conversion

**Enrollment, Population, Management**

- Multiple cardiac centers in Denmark
- 400 of 1954 referred were randomized to all IV or IV \(\rightarrow\) PO
  - 90% power to confirm non-inferiority with 1-sided CI of 97.5%
- Major reasons for exclusion: not meeting criteria, no consent
- Mean age 67 y; 38% with significant comorbidity

- Aortic valve – 54.7%, AV + MV – 10.8%, MV – 34.3%; Prosthetic valve – 27%
- Strep – 40.1%, *E. faecalis* – 24.3%, MSSA – 21.3%, CNS - 5.7%
- 38% had valve surgery prior to randomization at median of 17 days after which IV Rx continued for median 19 days and PO median 17 days
- PO Rx based on PK/PD principles & always included 2 antibiotics from different classes, targets, PK; rifampin frequently used
  - 7 PO patients below target levels for 1 of 2 drugs; no effect on outcome despite no change in Rx

### Table 2. Distribution of the Four Components of the Primary Composite Outcome.*

<table>
<thead>
<tr>
<th>Component</th>
<th>Intravenous Treatment (N=199)</th>
<th>Oral Treatment (N=201)</th>
<th>Difference</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>13 (6.5)</td>
<td>7 (3.5)</td>
<td>3.0 (−1.4 to 7.7)</td>
<td>0.53 (0.21 to 1.32)</td>
</tr>
<tr>
<td>Unplanned cardiac surgery</td>
<td>6 (3.0)</td>
<td>6 (3.0)</td>
<td>0 (−3.3 to 3.4)</td>
<td>0.99 (0.32 to 3.07)</td>
</tr>
<tr>
<td>Embolic event</td>
<td>3 (1.5)</td>
<td>3 (1.5)</td>
<td>0 (−2.4 to 2.4)</td>
<td>0.97 (0.20 to 4.82)</td>
</tr>
<tr>
<td>Relapse of the positive blood culture†</td>
<td>5 (2.5)</td>
<td>5 (2.5)</td>
<td>0 (−3.1 to 3.1)</td>
<td>0.97 (0.28 to 3.33)</td>
</tr>
</tbody>
</table>

* Six patients, three in each group, had two outcomes.

<table>
<thead>
<tr>
<th>1° Outcome N (%)</th>
<th>Risk Diff (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV Only</td>
<td>24 (12.1%)</td>
</tr>
<tr>
<td></td>
<td>3.1% (-3.4% to -9.6%)</td>
</tr>
<tr>
<td>IV -→ PO</td>
<td>18 (9.0%)</td>
</tr>
</tbody>
</table>

Strep
*E. faecalis*
*S. aureus*
*CNS*

POET: Endocarditis Rx -- IV -> PO Conversion
Primary Composite Outcome

IV: 12.1%
IV to PO: 9.0%

Risk Difference (95% CI): 3.1% (-3.4% to 9.6%)
P = 0.40

Conclusion: IV->PO switch in the selected population was non-inferior to all IV Rx.

**Tuberculosis**

- **Preventive Vaccination**
  - Repeat BCG prevent Mtb efficacy in prevention of infection (by sustained QFT conversion).
  - Efficacy 45.4% (P=0.03)¹

- **Latent TB Infection (LTBI) – Prevention of Activation**
  - 12 wks weekly rifapentine + INH *without DOT* is effective²
  - 4 *months daily rifampin* non-inferior to 9 months daily INH in adults & children; rifampin better tolerated, more completions³,⁴
  - 1 *month daily rifapentine/INH* non-inferior to daily INH for 9 months in HIV-infected⁵
  - M72/AS01_e recombinant adjuvanted vaccine in LTBI (most BCG vaccinated in infancy) provided 54% protection⁶

- **Treatment**
  - WHO revised recommendations for Rx of MDR TB (additions, re-prioritization, dropped kanamycin & capreomycin)⁷

---

¹ NEJM 2018; PMID: [29996082](http://www.nejm.org/doi/full/10.1056/NEJMoa1803484)  
² MMWR 2018; 67:723-6  
³ NEJM 2018; 379:440-53  
⁴ NEJM 379: 454-63  
⁵ CROI 2018 #37LB  
⁶ NEJM 2018; DOI: 10.1056/NEJMoa18034840.  
Inhaled Liposomal Amikacin (Arikayce) for Pulmonary MAC

- FDA approval Sept 28, 2018 as part of combination Rx of pulmonary MAC in adults with limited or no treatment options.

Convertors (3 monthly consecutive negative cultures) had significantly improved 6 minute walk test results.

*Figure 5: Cumulative Proportion of Patients Achieving Culture Conversion by Month 6 Shown by the First Month of Conversion in Study 212 (ITT Population)*

Culture Conversion reported as first month of 3 consecutive monthly negative sputum samples. Patients had to have their first of 3 negative sputum cultures by Month 4 at the latest to meet the endpoint by Month 6.

Convertors (3 monthly consecutive negative cultures) had significantly improved 6 minute walk test results.

Malaria

- Tafenoquine\(^1\).
  - July 20, 2018 single 300 mg dose FDA approved for radical cure (relapse prevention) in *P. vivax* malaria in \( \geq 16 \) years receiving appropriate antimalarial therapy.
  - Aug 8, 2018 prophylaxis age \( \geq 18 \) years

- Higher chloroquine dose\(^2\). Increasing dose in \(<5\)y to 30 mg/kg in absence of radical cure significantly reduces recurrences (LID)

- Ivermectin\(^3\). Ivermectin mass drug administration to humans disrupts malaria parasite transmission in Senegalese villages. For at least 2 weeks.

Viral Infections

• Smallpox - tecovirimat\textsuperscript{1}
  • Monkeypox?

• Influenza – Baloxavir\textsuperscript{2} – inhibits CAP-dependent endonuclease
  • Single dose – symptom resolution noninferior to oseltamivir; greater decrease viral load at 24 h; 9.7% emergence of resistance in Phase 3 trial
  • FDA Priority Review granted 28 June 2018

• CAR T-Cell antiviral therapy\textsuperscript{3}

• HAV – continued outbreaks homeless, drug users\textsuperscript{4}

• HPV – rate of oropharyngeal cancers in men > cervical cancers\textsuperscript{5}

5. https://www.cdc.gov/mmwr/volumes/67/wr/mm6733a2.htm
And Even More Hot Topics...

• Opioid abuse – Infectious Disease Syndemic: e.g., HIV, HCV, Endocarditis (incl Candida), pneumococcal infection
• CHEMSEX: STIs
• Microbiome & checkpoint inhibitor response
• Rapid diagnostics
• Unbiased metagenomic next generation sequencing for diagnosis
• Whole genome sequencing for epidemiologic purposes
• Phage therapy
• CDI prophylaxis
• FMT for non-CDI
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