Disclosures

• I have no financial or personal disclosures relevant to this presentation.

• I will be discussing some non-FDA-approved use of antimicrobials as well as un-approved antimicrobials.
Objectives

• Recall resistance patterns for ICU-acquired infections

• Review recently approved antibiotics available for treatment of multi-drug resistant infections
“What’s in a name…”

- **Gram Negative**
  - CRPA
  - CRAB
  - Lactose Non-Fermenters
  - Fermenters (*Enterobacteriaceae*)
  - Wild-Type
  - ESBL (+)
  - CRE
  - KPC (+) *(CPE)*
  - Hybrid
  - MBL (+)
  - Other
    - OXA-48 *(CPE)*

- **Gram Positive**

**CRE** = Carbapenem-Resistant *Enterobacteriaceae* *(CRE ≠ CPE)*

ESBL = extended-spectrum betalactamase, KPC = Klebsiella pneumoniae carbapenemase, MBL = metallobetalactamase, NDM = New Delhi metallobetalactamase, CPE = carbapenemase producing *Enterobacteriaceae*, CRPA = carbapenem R *P. aeruginosa*, CRAB = carbapenem R *Acinetobacter*
Unmet Need: MDR Pseudomonas

- May have utility in CPE(-) CRE infections
  - Debate over BLI’s in ESBL(+) infections
  - MERINO study (poor outcomes for Pip/Tazo)
  - ESBLs were included in Phase-III studies

- Typically gains 2-3 tube dilutions (MIC) better than Cefepime/Ceftazidime

- Remember metronidazole when indicated

- 1.5gm dose = 1gm Ceftolozane/0.5gm Tazobactam

Ceftazidime/Avibactam
(Avycaz™)

Unmet Need: CRE

• Avibactam – novel non-betalactam BLI that regenerates upon hydrolysis (re-usable)
• Inhibits ESBL, KPC, ampC and OXA-48
• FDA – cUTI and cIAI
• Remember metronidazole
• 2-hour infusion
• Resistance is already well characterized (D179Y mutation in the KPC enzyme)

cUTI = complicated urinary tract infection, cIAI = complicated intra-abdominal infection
Unmet Need: CRE

- Vaborbactam = novel cyclic boronic acid BLI
- Inhibits ESBL, KPC, ampC (not OXA-48)
- FDA – cUTI
  - Novel approval path: 1 RCT, 1 pathogen directed trial
    - TANGO-I (cUTI vs. pip/tazo)
    - TANGO-II (CRE, any source vs. BAT – including BSI, HAP/VAP, cIAI, cUTI)
  - TANGO-II included both immunocompromised patients and Ceftaz/Avi treated patients
  - 3-hour infusions & 4-hour stability
  - QIDP status from FDA

TANGO-II - Infect Dis Ther. 2018 Oct 1 (epub), BSI = blood stream infection, QIDP = qualified infectious diseases product (GAIN Act)
Unmet Need: MDR GNRs

- Aminoglycoside ("neoglycoside")
- FDA – GNR cUTI (denied BSI indication)
- Synergistic activity vs. both Gm(-) and Gm(+)
- More potent than current AGs
- ODA dosing (requiring dose-reduction and TDM if CrCl < 90 ml/min)
- Same ADR profile as current AGs
- Formulary approval = a new drug & a new lab
Unmet Need: CRAB, maybe CRE

• “Novel” flurocycline (Similar to Tigecycline)
  – Broad Gm(+), Gm(-) and anaerobe spectrum
  – No activity against Pseudomonas

• FDA – cIAI
  – Failed cUTI vs. Levofloxacin
  – cUTI likely to follow pending additional Phase-III with augmented oral dose and sNDA

• IV (with PO likely to follow post redesigned Phase-III UTI)

• Typical TCN ADEs – photo-, HA, GI (less than Tiga)

• The future... STIs (Gonococcus) and NTM?

STI = sexually transmitted infection, NTM = non-tuberculous mycobacteria
Unmet Need: CRAB, maybe CRE

- **Tetracycline**
  - Empty stomach, no dairy, multi-valent cations
  - Teeth and bones
  - Typical TCN ADEs – photo-, HA, GI (less than Tiga)

- **FDA** – CABP and ABSSSI (maybe UTI to follow)
- IV and PO, once daily dosing
- Despite FDA filing, still with activity against MDR Gm(-)s and Gm(+)s (not Pseudomonas)
- QIDP status
- The future... STIs (Gonococcus) and NTM?

CABP = community-acquired bacterial pneumonia, ABSSSI = acute bacterial skin/soft-tissue infection
Notable Pipeline Agents
Unmet Need: CRPA, CRAB, likely CRE (hybrids)

- Novel siderophore cephalosporin
  - MOA is typical of betalactam
  - Entry into bacterial cell is via iron transporters
  - More potent than current carbapenems

- Stable against ESBL and MBLs, but higher MICs against KPC-2 (breakpoints pending)

- First half of 2019

- QIDP status
Unmet Need: CRE

• Comparable to Mero/Vaobor
• Similar regulatory track to Mero/Vabor (pathogen driven + HAP/VAP)
• QIDP status
• Phase-III, pending NDA submission
• Likely 2019
Unmet Need: CRE, MDR Gram Positive

- Wealth of data from the EU
- Positive experience in the US with MDR UTIs
- Broad Gm(+) and Gm(+) activity (+/- Pseudomonas)
- Phase-III for UTI/Pyelonephritis pending
- NDA filing likely in 2019
Reflections

• Formulary – Ceftaz/Avi vs. Mero/Vabor (vs. Imi/Rel) – either, neither or both?
• New Tetracyclines vs. Tigacycline (vs. Mino)?
• Do you need another Aminoglycoside? (TDM)
• Cefiderocol – Are you a CF and/or Lung SOT center?
• Betalactam sparing strategies?
Resistance in contemporary MDROs is mono-modal (ie, a single novel beta-lactamase)?

a) True
b) False

FALSE - While novel beta-lactamases exist and are epidemiologic threats, multi-modal resistance (beta-lactamase plus efflux/porin) plays a significant role.
Which of the two recently FDA approved novel agents occupy the same functional space in our antimicrobial armamentarium?

a) Ceftolozane/Tazobactam and Meropenem/Vaborbactam
b) Ceftolozane/Tazobactam and Ceftazidime/Avibactam
c) Meropenem/Vaborbactam and Ceftazidime/Avibactam

C) these agents are our two primary tools against KPC-producing CREs.