CRE Treatment Challenges: Part II

Melvin P. Weinstein, MD
Professor of Medicine and Pathology
Robert Wood Johnson Medical School
New Brunswick, NJ

Disclosures

- Research Support
  - BD Diagnostics
  - Siemens
  - JMI Laboratories
- Consultant
  - Accelerate Diagnostics
  - PDL Biopharma
  - Rempex

Topics

- Alternative methods of drug administration
  - Prolonged and continuous infusions
  - Direct administration to site of infection (e.g., aerosolized therapy for pneumonia)
- New agents with activity against CRE

Prolonged or Continuous Infusions

- To take advantage of pharmacokinetic and pharmacodynamic properties
- Several antimicrobials whose efficacy is based upon T > MIC have been evaluated for or administered by prolonged IV infusion
  - Examples:
    - Piperacillin-tazobactam
    - Doripenem
    - Meropenem

Doripenem

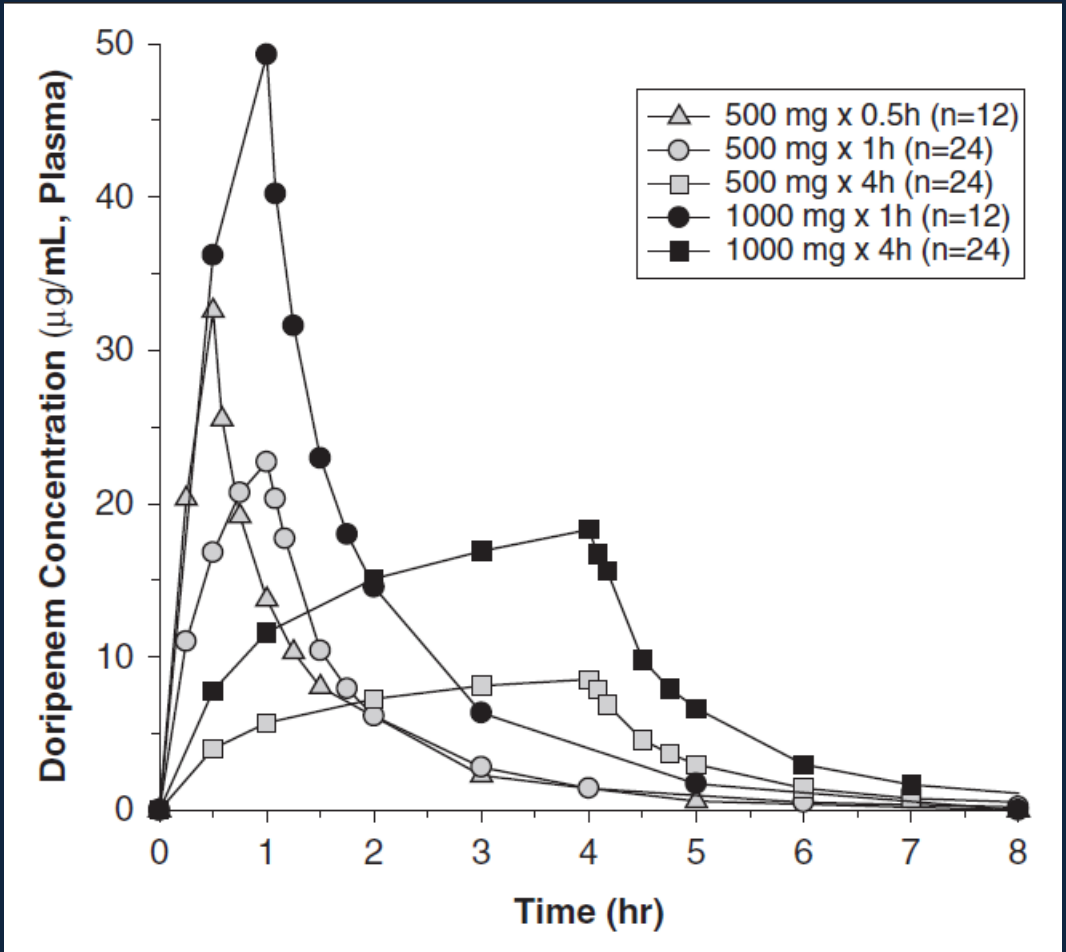

Figure 1. Mean plasma doripenem concentration-time curves following single doses of doripenem administered by intravenous infusion.

Alternative Routes of Drug Administration

- Inhaled antimicrobials for patients with pneumonia
  - Achieves high drug concentrations at site of infection
  - Used primarily for patients with CF
  - Used in desperation for MDR GNR pneumonia
  - Aminoglycosides, polymyxins
  - Cefotaxime, ceftazidime, aztreonam, levofloxacin
  - Requires a nebulizer that is customized for specific agent to optimize drug delivery
- Mean sputum concentrations of inhaled tobramycin in range of 700-1000 mcg/g

New Agents

- Plazomicin – aminoglycoside
  - Derivative of sisomicin
  - Designed to avoid resistance mediated by enzymes that inactivate gentamicin/tobramycin
  - Once daily dosing

Klebsiella spp.	Drug	MIC90 (ug/ml)
N = 1155	Plazomicin	1
32% KPCs	Gentamicin	64
52% ESBLs	Amikacin	32
	Ciprofloxacin	>4
	Imipenem	16

Landman. Poster E2059. ICAAC 2010

New Agents

- Beta-lactamase inhibitor combinations
  - Ceftolozone-tazobactam
    - 2:1 fixed ratio
    - Potent activity (MIC90=2) vs. carbapenem, ceftazidime, cefepime-resistant *P. aeruginosa*
    - Addition of tazobactam potentiates activity vs. ESBL but not KPC-producing *Enterobacteriaceae* at 4 ug/ml
    - Clinical trials underway or planned for cUTI, cIAI, and HAP/VAP

New Agents

- New beta-lactamase inhibitors
  - Avibactam, MK7685
  - Inhibit Class A & C beta-lactamases (ESBLs, KPCs, ampC)
  - Avibactam – being studied with ceftaroline, ceftazidime, aztreonam
    - Avi-Taz and Avi-Tar – decreased MICs for Enterobacteriaceae, incl. KPC-producers
  - MK7685 – being studied with imipenem/cilastin

New Agents

- New carbapenem/beta-lactamase inhibitor combination
  - Biapenem-RPX7009
    - Biapenem used in Japan since 2002
    - RPX7009 – cyclic boronic acid
    - Active vs. KPCs and other serine beta-lactamases
    - ICAAC 2012 – several posters
      - Biapenem 2 mcg plus RPX7009 8 mcg vs. 255 MDR *Enterobacteriaceae* – MIC90 0.5 mcg/ml
      - Biapenem 4 mcg plus RPX7009 8 mcg vs. 167 KPC-producing strains – MIC90 < 1 mcg/ml
    - Clinical studies in humans starting