

The Role of Antibiotic Stewardship Programs in the Utilization of New Antibiotics

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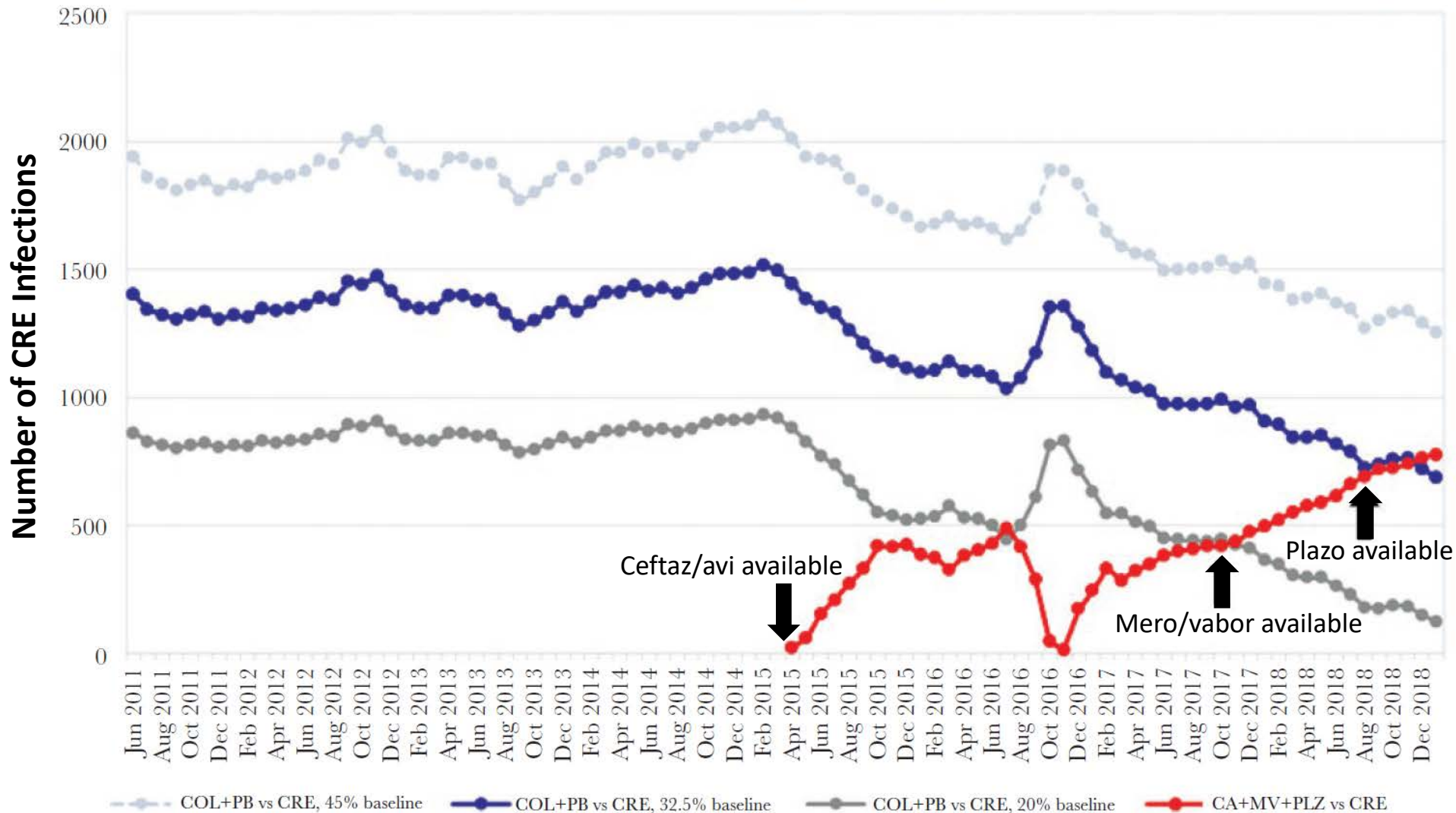
Disclosures

- Theravance: consulting—external infection adjudication committee (past)
- Basilea: consulting—external infection adjudication committee (ongoing)

Objectives

- Discuss real-world challenges with positioning the use of new antibiotics in hospitalized patients
- Discuss the role of antibiotic stewardship programs in implementing use of new antibiotics to improve patient care and minimize emergence of resistance

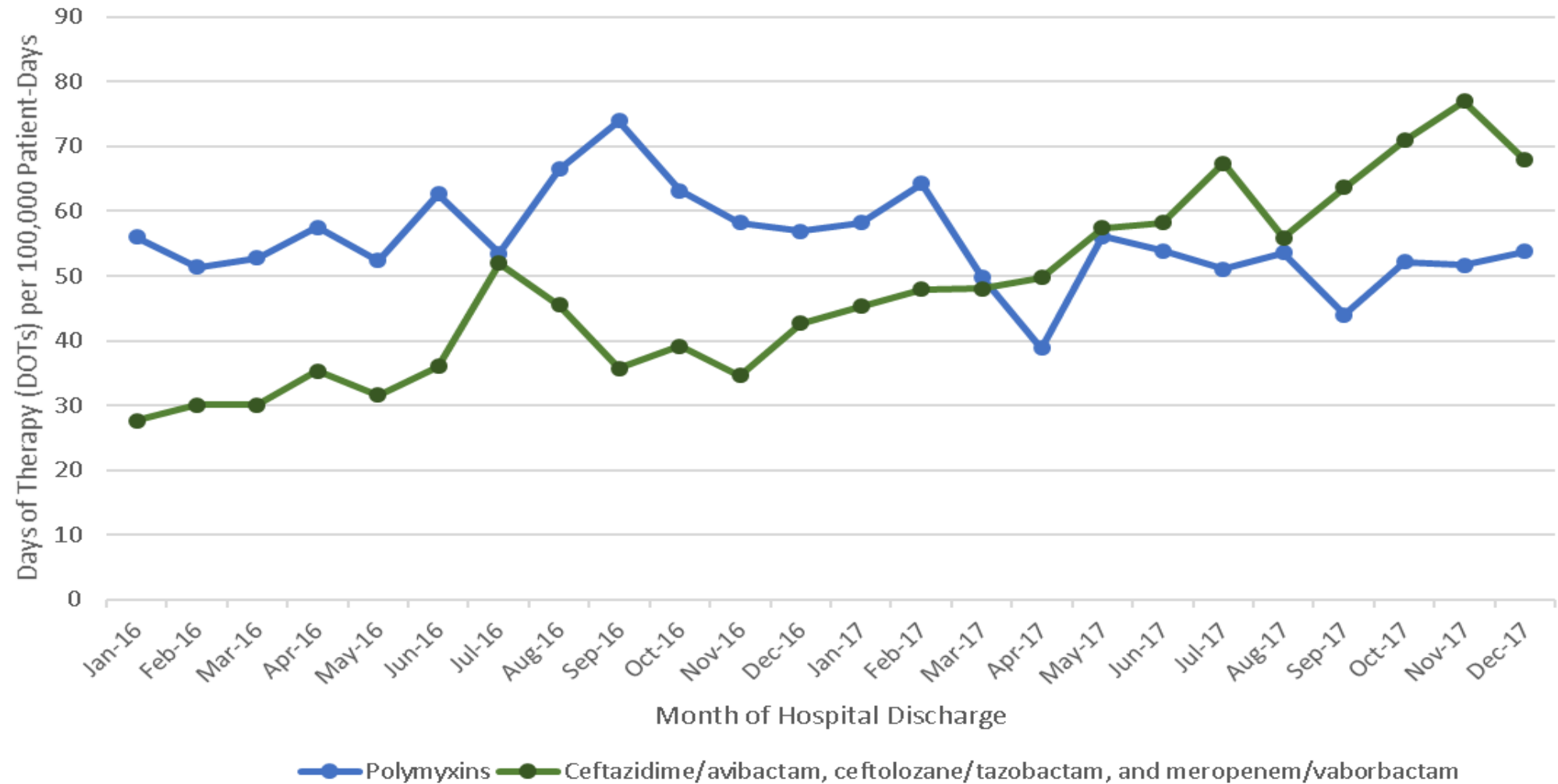
Use of Polymyxins vs New Agents for CRE Infections



- Data from IQVIA
- Data on route not provided → authors estimated 65% of use IV
- 3 estimates of proportion of numbers of CRE infections treated with polymyxins before ceftaz/avi was available (45%, 32.5%, 20%)
- Use of new agents exceeded use of old in December 2018

Use of Polymyxins vs. All New β -Lactam/ β LIs

Usage Rates of Polymyxins and Beta-Lactam/Beta-Lactamase Inhibitors for MDRGNs Across 576 U.S. Hospitals, 2016 - 2017



Survey of Pharmacists on Guidelines for Anti-CRE Agents

- 110 pharmacists in 41 states in 12/2018

	FDA approvals	Type of CRE Infection			
		Pneumonia	Bacteremia	Intra-abdominal	Urinary Tract
Ceftazidime-avibactam	cUTI (2/15) cIAI (2/15) HAP/VAP (2/18)	54%	58%	51%	36%
Meropenem-vaborbactam	cUTI (8/17)	32%	31%	31%	14%
Plazomicin	cUTI (6/18)	2%	1%	1%	5%
Polymyxin		4%	4%	4%	3%
Aminoglycoside		2%	1%	2%	11%
Ceftolozane-tazobactam	cUTI (12/14) cIAI (12/14) HAP/VAP (6/19)	n/a	n/a	n/a	n/a
Eravacycline	cIAI (8/18)	n/a	n/a	n/a	n/a

Why is Uptake Slow?

- Primary studies for FDA approval are non-inferiority studies in patients without resistant organisms
 - Pneumonia indications/dosing late or don't exist
- Low numbers of patients with CRE and MDR Pseudomonas in studies for Fast Track FDA approval
 - Don't actually want to have an abundance of MDR-GNRs to study

	New agent	Best available therapy (BAT)
Meropenem/vaborbactam for CRE all sites	N = 32 (59%)	N = 15 (27%)
Imipenem/relebactam for MDR-PSA and CRE all sites	N = 21 (71%)	N = 10 (40%) (colistin + imi)

- Post-approval studies take time to be done and published
- Agents are expensive
- Difficulties with susceptibility testing
 - Mainly an issue with ceftolozane/tazobactam early on now much improved

ASP Considerations

- ASPs recognize that these are the agents of choice for resistant GNRs
 - ASPs are often the primary driver of formulary addition of new agents
 - ASPs often coordinate micro testing, selection of optimal agent(s), duration
 - ASPs critical in recommending optimal dosing strategies
- ASPs desire to ensure that the agents are used in a way to preserve their utility
 - Concerns about emergence of resistance across the population
 - Concerns about emergence of resistance within a patient
 - Concerns about avoiding treatment of colonization (which leads to resistance)
- ASPs unlikely to support routine empiric use of these agents

Resistance Data

- Large scale data suggest some baseline resistance
 - Ceftolozane/tazobactam: ~7000 PsA isolates → 89-98% susceptible
 - Ceftazidime/avibactam: ~14000 PsA isolates → 91.5% susceptible
 - Ceftazidime/avibactam: ~60000 Enterobacteriaceae → 88% susceptible
 - Meropenem/vaborbactam: ~11500 Enterobacteriaceae → 99% susceptible
 - Plazomicin: ~4700 Enterobacteriaceae → 96% susceptible
- Differences in resistance based on patient population

<i>P. aeruginosa</i> ceftolozane-tazobactam susceptibilities 2017-19	
Cystic fibrosis patients	10/26 (38.5%)
Non-cystic fibrosis patients	54/72 (75%)

Emergence of Resistance During Therapy

- Ceftazidime/avibactam
 - 37 CRE infections (most pneumonia, bacteremia, intra-abdominal)
 - Clinical success in 59%
 - Microbiologic failure in 27%
 - Resistance in 3/10 failures developing at a median of 15 days
- Ceftolozane/tazobactam
 - 35 MDR *P. aeruginosa* infections (most pneumonia and intra-abdominal)
 - Clinical success in 46%
 - Microbiologic failure in 26%
 - Resistance in 6/10 failures developing at a median of 6 days

Shields RK et al. Clin Infect Dis. 2016;63(12):1615.

Trisler M et al. poster #2253 IDWeek, Washington DC 2019

Haider G et al. Clin Infect Dis. 2017;65(1):110.

Why Does Emergence of Resistance Matter?

- Most patients with MDR GNR infections have significant medical complications
 - Issues with source control (particularly intra-abdominal infections)
 - Need for future solid organ transplant, HSCT, chemotherapy
- Often need to consider timing of use of last-resort antibiotics to maximize utility in the window before emergence of resistance

Other Challenges

- Paying for agents after discharge from the hospital
 - Insurance often does not cover outpatient antibiotics, particularly when used off-label
 - Nursing homes often don't have the agents and balk about obtaining them due to cost
- Changes to the Inpatient Prospective Payment System and the Long-Term Care Hospital Prospective Payment System for FY2020 do not address these problems

Agents Not Directed at MDR-GNRs

- FDA approved based on non-inferiority studies for infections that we do not have a big problem with
 - Delafloxacin (CAP, ABSSSI)
 - Omadacycline (CAP, ABSSSI)
 - Lefamulin (CAP)
- Cost 10-25 times more than standard therapy
- Hard to justify preferential use of these agents in the hospital for current indications
- Need a mechanism to investigate these agents for other infections (e.g., omadacycline for *M. abscessus*, *Acinetobacter*)

What Can Be Done?

- Better education of ID specialists and others who care for patients with CRE and MDR PSA, Acinetobacter
 - Guidelines/guidance for these infections that can be modified/updated regularly
- Post-approval data on utility for MDRGNRs from all sites is essential
 - New study designs such as adaptive clinical trials
- Development of approaches to predict what patients may benefit from empiric treatment with these agents to avoid overuse
 - Role of predictive models
 - Role of surveillance cultures
 - Role of rapid diagnostics
- Colistin/polymyxin B breakpoint changes will help
 - Intentional decision by CLSI
 - All isolates are either Intermediate (≤ 2) or Resistant (≥ 4)
- Continue to ensure that methods for susceptibility testing are available when the agent becomes available