The Role of Antibiotic Stewardship in Optimizing the Use of New Antibiotics

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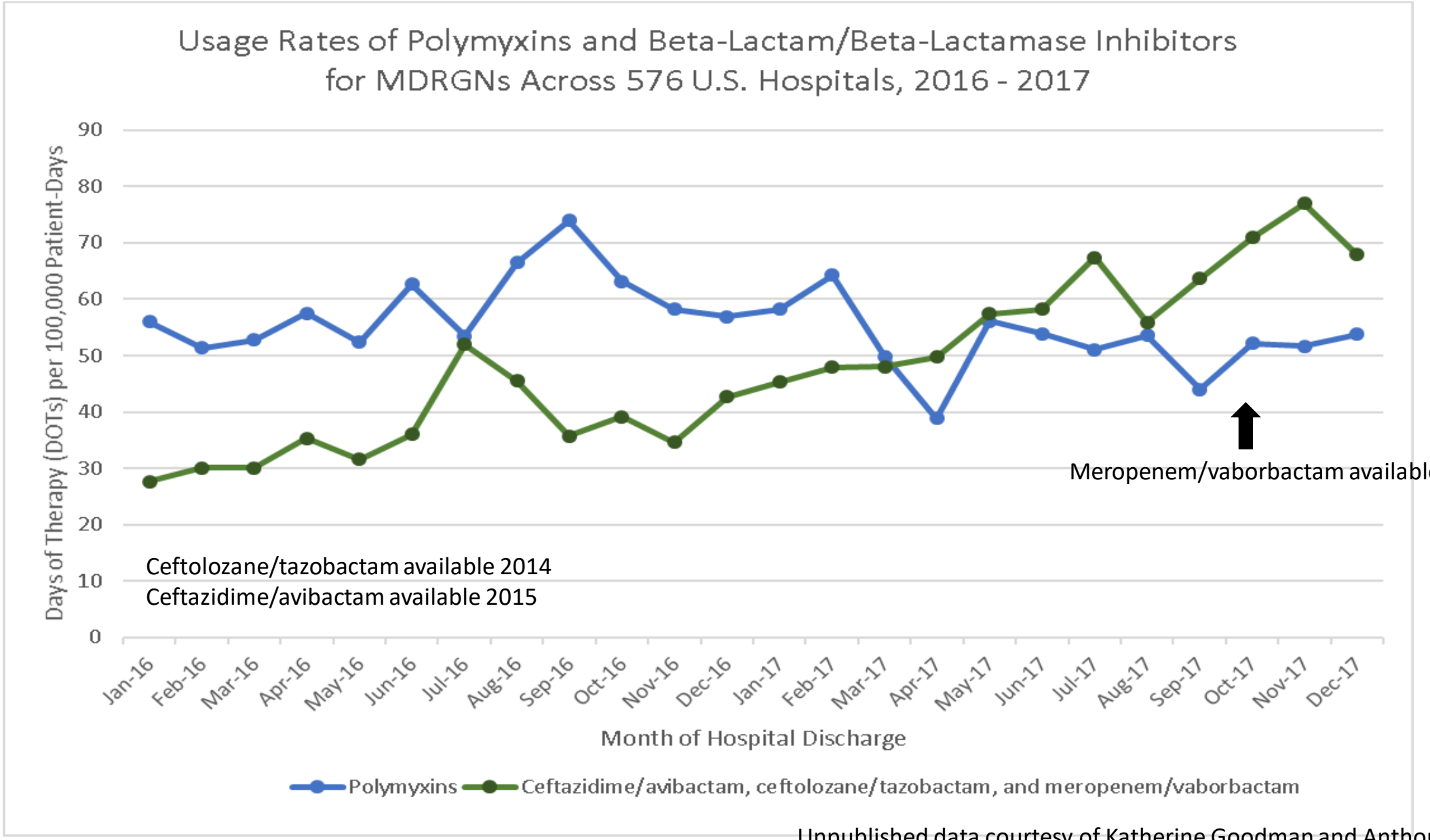
Disclosures

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

Objectives

- Discuss 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. All New β-Lactam/βLIs



Unpublished data courtesy of Katherine Goodman and Anthony Harris

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

Clancy CJ et al. Open Forum Infect Dis. 2019;6(8):ofz344.

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-PSA in studies for FDA approval
  - Don't actually want to have an abundance of MDR-GNRs to study

	New agent (% success)	**Best available therapy (BAT)** (% success)
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 compared to older agents
- Difficulties with susceptibility testing
  - Mainly an issue with ceftolozane/tazobactam early on now much improved

TANGO II: Wunderink RG et al. Infect Dis Ther. 2018;7(4):439; RESTORE-IMI 1: Motsch J et al. Clin Infect Dis. 2019 [Epub ahead of print]
https://clsi.org/media/2277/clsi_astnewsupdate_june2018_final61118.pdf

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 To New Agents

- Some baseline resistance
- Differences in resistance based on patient population

***P. aeruginosa* ceftolozane-tazobactam susceptibilities 2017-19 at Johns Hopkins Hospital**	
Cystic fibrosis patients	10/26 (38.5%)
Non-cystic fibrosis patients	54/72 (75%)

- Emergence of resistance on therapy
  - 37 CRE infections treated with ceftazidime/avibactam
    - Most pneumonia, bacteremia, intra-abdominal
    - Microbiologic failure in 27%
      - Resistance in 3/10 failures developing at a median of 15 days
  - 35 MDR *P. aeruginosa* infections treated with ceftolozane/tazobactam
    - Most pneumonia and intra-abdominal
    - 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
- BUT—these agents may be important for other infections
  - Need a mechanism to keep them available to investigate them further (e.g., omadacycline for *M. abscessus*, Acinetobacter; lefamulin for *M. genitalium*)

What Can Be Done to Ensure Optimal Use of New Agents?

- 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 MDR GNRs 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 using machine learning
  - 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

Lanini S et al. Lancet Infect Dis. 2019: S1473-3099(19)30284-1