Antimicrobial Resistance Solutions

Management. Education. Innovation.

Combating Antimicrobial Resistance with Stewardship

Presented by:

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Learning Objectives

- Understanding how antimicrobial resistance impacts outcomes.
- What you can do today to increase probability of early appropriate therapy in your patients.
- Understand how antimicrobial selection can potentiate resistance.
- Understand how a more refined approach to antimicrobial selection and dosing promote better outcomes while minimizing the risk for the development of resistance.

Antimicrobial Resistance

"Once an antibiotic is proven to be effective and enters widespread human therapeutic use, it's days are numbered."

-C. Walsh, Nature August 17th, 2000

"Antibiotics, the only drug class where use in one patient can deleteriously impact the care of another patient"

Resistance Impact

- Delays effective treatment
- Limits treatment options
- Drives use of expensive and toxic agents
- Increases morbidity, mortality, return to acute care, hospital LOS, costs

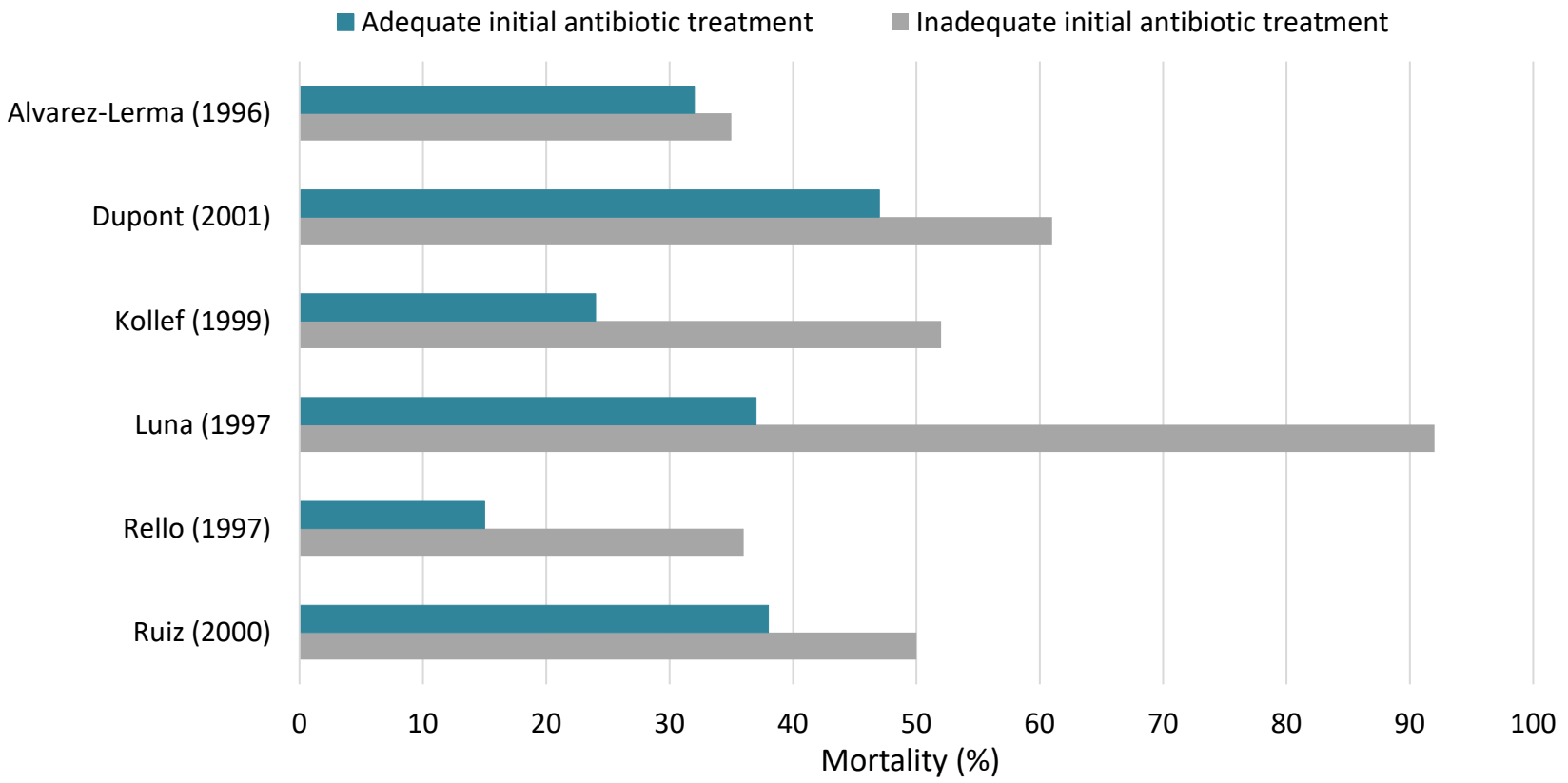
Getting It Right

UTI or *E. coli* Treatment

Antibiotic	MIC	Interpret
Amikacin	<=16	S
Amox/clav	<=8	S
Ampicillin	>16	R
Cefazolin	<=2	S
Cefepime	<=2	S
Cefoxitin	<=8	S
Cefotaxime	<=1	S
Ceftriaxone	<=1	S
Cefuroxime	<=8	S
Ciprofloxacin	<=0.25	S
Gentamicin	<=1	S
Meropenem	<=1	S
Piperacillin/T	<=8	S
Tobramycin	<=1	S
Trimeth/Sulfa	<=2/38	S

Antibiotic	MIC	Interpret
Amikacin	<=16	**S**
Amox/clav	*	**R**
Ampicillin	>16	**R**
Cefazolin	>2	**R**
Cefepime	*	**R**
Cefoxitin	<=8	**S**
Cefotaxime	*	**R**
Ceftriaxone	*	**R**
Cefuroxime	*	**R**
Ciprofloxacin	>2	**R**
Gentamicin	<=2	**S**
Meropenem	<=1	**S**
Piperacillin/T	*	**R**
Tobramycin	<=1	**S**
Trimeth/Sulfa	>2/38	**R**

Importance of Initial Empiric Antibiotic Selection

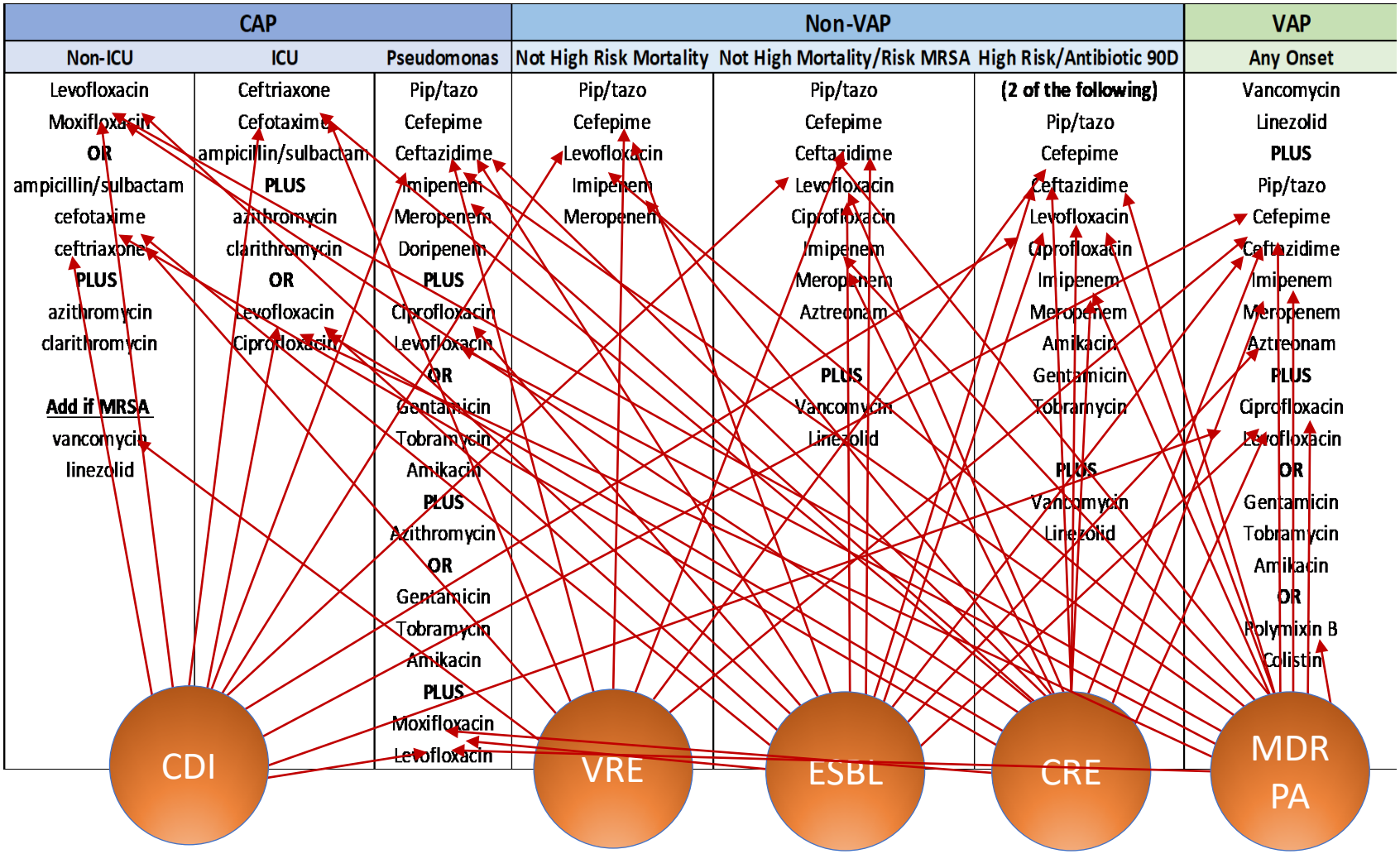


Alvarez-Lerma F. *Intensive Care Med*. 1996;22:387-394.
Dupont H, et al. *Intensive Care Med*. 2001;27:355-362.
Kollef MH, et al. *Chest*. 1999;115:462-474.
Luna CM, et al. *Chest*. 1997;111:676-685.
Rello J, et al. *Am J Respir Crit Care Med*. 1997;156:196-200.
Ruiz M, et al. *Am J Respir Crit Care Med*. 2000;162:119-125.

Increase Probability of Early Appropriate Therapy

- World Health Organization (WHO)
  - Create tools & policy informed by real world data

Guideline Driven Prescribing



Increase Probability of Early Appropriate Therapy

- Assess individual patient risk factors for MDRO

Patient Risks for MDRO's

- **Prior MDRO Infection (3 to 12 months)**
- **Prior hospitalization, Post acute setting**
- **Prior antibiotics <90 days**
  - Colonizing bacteria more likely MDRO (GI tract and skin)
  - Number and spectrum

*High risk disease states:

Chronic lung disease, bladder dysfunction, inflammatory bowel disease, diabetes, immune suppression, chronic wounds

Nursing Home-acquired Pneumonia

- Predictor of nosocomial and resistant bacteria
  - ADL based on 18-point scale (6 major activity areas, scored 1-3)
  - Prior antibiotics (≥3 consecutive days in last 6 months)

- No prior antibiotics
  - **ADL <12.5 0% of patients with resistant bacteria**
  - ADL ≥12.5 17% of patients with resistant bacteria

- Prior antibiotics
  - ADL <12.5 42% of patients with resistant bacteria
  - **ADL ≥12.5 90% of patients with resistant bacteria**

Solh AE, et al. CID 2004;39:474-80.

Increase Probability of Early Appropriate Therapy

- Assess individual patient risk factors for MDRO

- Know & incorporate local resistance patterns

Resistance Trends
Indiana Skilled Nursing / Referral Facilities

		Facility							
		1	2	3	4	5	6	Ref 1	Ref 2
CRE	K. pneumoniae	6%	0%	10%	NR	0%	0%	6%	1%
ESBL	E. coli	44%	13%	20%	18%	17%	16%	8%	9%
	K. pneumoniae	25%	27%	0%	NR	16%	18%	8%	8%
FQ Resistant	E. coli	56%	28%	56%	45%	41%	33%	21%	25%
	P. mirabilis	59%	62%	NR	75%	43%	55%	40%	31%
	P. aeruginosa	10%	NR	NR	18%	25%	NR	40%	20%
MDR	P. aeruginosa	10%	NR	NR	18%	25%	NR	18%	NR

UTI Treatment % Susceptible	Ceftriaxone	51%	68%	83%	80%	68%	64%	NR	NR
	Ciprofloxacin	58%	71%	61%	54%	63%	61%	NR	NR

Resistance Trends

- Antibiogram (cumulative culture results for a specific facility)
  - **Minimum** to care for your patients
  - Rolling 2-year antibiogram (3 year if necessary)
  - Raw data

- NOT Adequate
  - Antibiogram of ALL SNF data together
  - Data from ALL sites lab services
  - Lab system is not set up to give your cumulative facility results

- Supplemental
  - Referral facility antibiograms

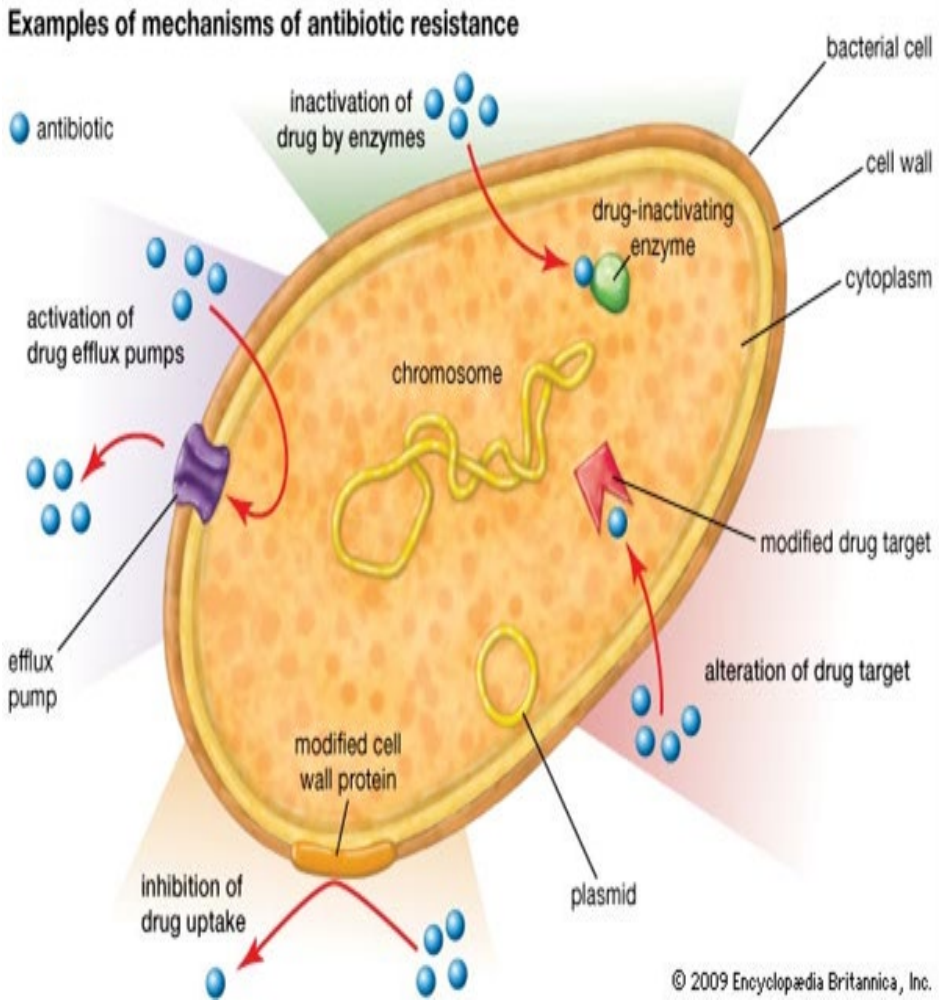
*IDOH website: Antibiogram Presentations - HAI AR webinar series: June 27, 2023
IDOH AAW webinar November 15th, 2023

Increase Probability of Early Appropriate Therapy

- Assess individual patient risk factors for MDRO
- Know & incorporate local resistance patterns
- Minimize antimicrobial resistance
  - Understand antimicrobial resistance and the driving factors

Bacteria Resistance Mechanisms

- Reduction in permeability
- Enzymatic inactivation
- Efflux pumps
- Target site changes



Resistance Types

- AmpC
- Extended Spectrum Beta-Lactamase (ESBL)
- Carbapenem Resistant Enterobacteriaceae (CRE)
- Multi-drug Resistant *Pseudomonas* & *Acinetobacter*

Mechanism of Resistance: AmpC Beta-lactamases

- Major organisms (SPACE)
  - ***S****erratia spp.*
  - ***P****seudomonas spp.*
  - ***A****cinetobacter spp.*
  - ***C****itrobacter spp.*
  - ***E****nterobacter spp.*

- Resistance gene found on chromosomes

- **Resistance can be turned on (induced) with exposure to certain antibiotics and occur within days of exposure, spreading to other patients**

Amp-C in *Serratia* - Resistance Induction

Antibiotic	MIC	Interpret
Amikacin	<=16	S
Amox/clav	<=8	S
Cefazolin	>2	R
Cefepime	<=8	S
Cefoxitin	<=8	S
Ceftriaxone	<=8	S
Cefuroxime	<=8	S
Ciprofloxacin	<=1	S
Gentamicin	<=1	S
Meropenem	<=4	S
Nitrofurantoin	>64	R
Piperacillin/T	<=16	S
Tobramycin	<=2	S
Trimeth/Sulfa	<=2/38	S

CTX

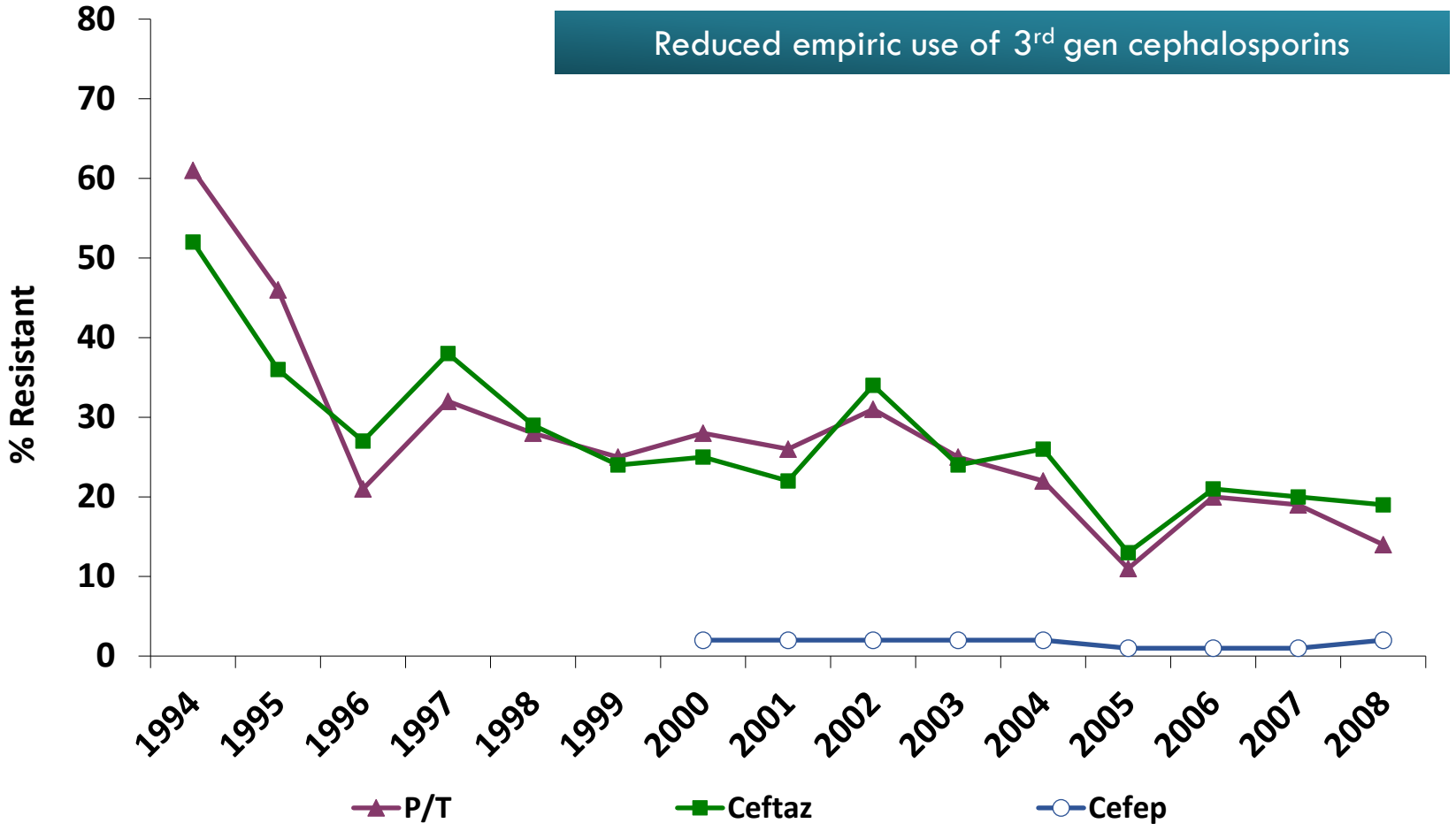
Antibiotic	MIC	Interpret
Amikacin	<=16	S
Amox/clav	>8	R
Cefazolin	>2	R
Cefepime	<=8	S
Cefoxitin	>8	R
Ceftriaxone	>8	R
Cefuroxime	>8	R
Ciprofloxacin	<=1	S
Gentamicin	<=1	S
Meropenem	<=4	S
Nitrofurantoin	>64	R
Piperacillin/T	>16	R
Tobramycin	<=2	S
Trimeth/Sulfa	<=2/38	S

Amp-C Beta-Lactamase
Potential for Induction of Beta-lactamases

Drug Class	Low	Intermediate	High
Penicillins	Ticarcillin Piperacillin	Carbenicillin	
Cephalosporins	Cefoperazone Cefepime	Cefotaxime Ceftriaxone Ceftazidime	Cefazolin Cefoxitin
Carbapenems	Meropenem		Imipenem
B-lactamase Inhibitors	Sulbactam Tazobactam	Clavulanate	

Danziger et al. AJHP. 1995

Amp-C Beta-Lactamase: *Enterobacter* Resistance



ESBL & CP-CRE: Selecting for Resistance

- Major organisms (enterics):
  - ***E. coli***
  - ***Klebsiella spp.***
  - ***Proteus mirabilis***

- Resistance gene is on plasmids
  - Easily passed to other organisms in GI tract
  - Carry multiple resistance mechanisms

- Exposure to certain broad-spectrum antibiotics

ESBL Risk Factors

- **3rd gen cephalosporins**
- **Fluoroquinolones**
- Recent antibiotic use <90 days
- Invasive devices
- Recent ICU or hospital stay
- Nursing home/LTAC resident
- Comorbidities

Rice L. *Chest* 2001;119:391-396.
Patel G, et al. *Infect Control Hosp Epidemiol* 2008;29:1099-1106.
MacDougall C. *J Pediatr Pharmcol Ther* 2011;16(1):23-30.
Rapp RP, et al. *Pharmacother* 2012;32(5):399-407.

Identifying ESBL Resistance
E.coli, Klebsiella, Proteus mirabilis

Antibiotic	MIC	Interpret
Amikacin	<=16	S
Amox/clav	<=8	S
Aztreonam	<=4	S
Cefazolin	>2	R
Cefepime	<=2	S
Cefoxitin	<=8	S
Cefotaxime	>8	R
Ceftriaxone	<=1	S
Cefuroxime	<=8	S
Ciprofloxacin	>2	R
Gentamicin	8	R
Meropenem	<=1	S
Piperacillin/T	<=8	S
Tobramycin	4	S
Trimeth/Sulfa	>2/38	R

ESBL

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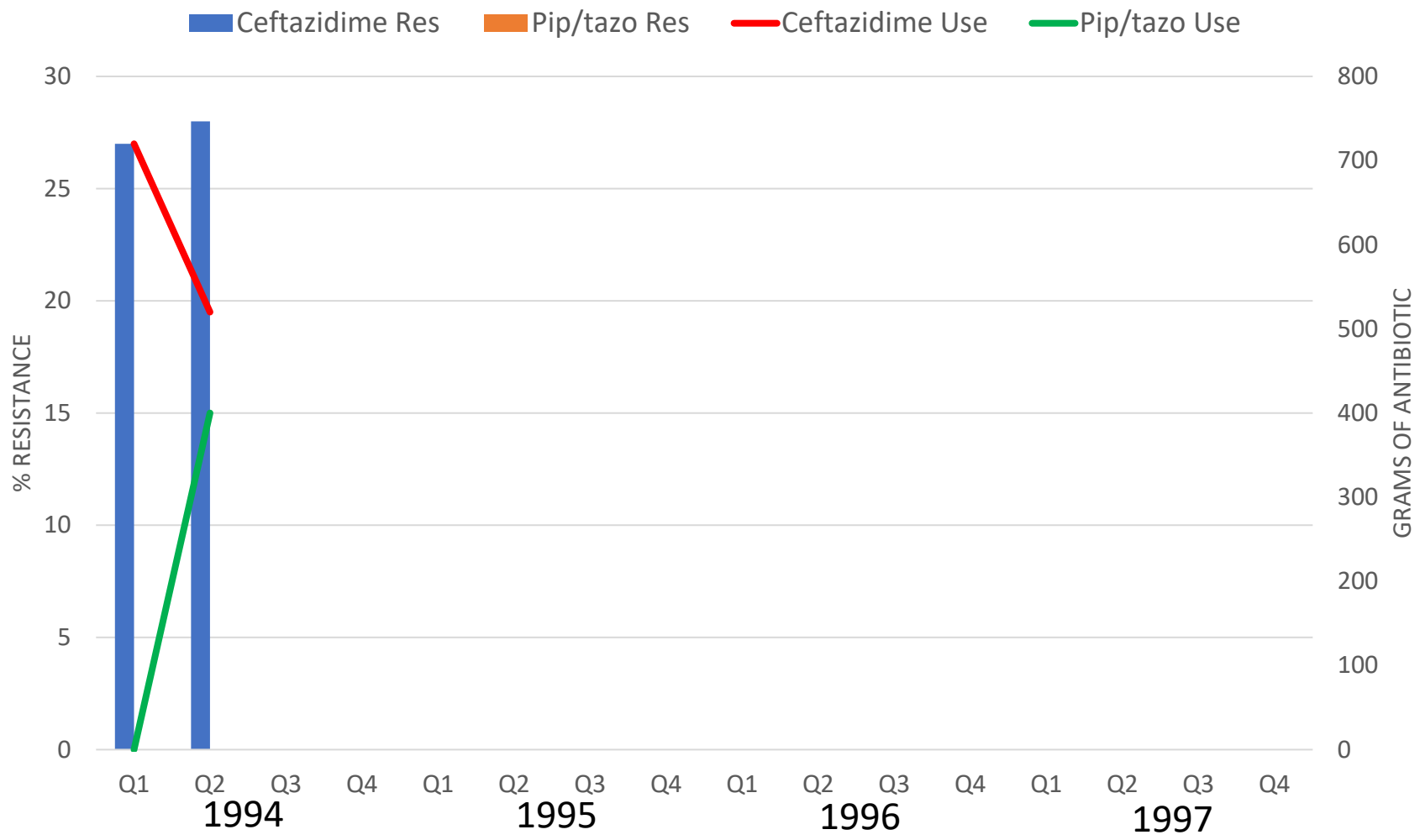
Cefoxitin	<=8	**S**
Cefotaxime	*	**R**
Ceftriaxone	*	**R**
Cefuroxime	*	**R**
Ciprofloxacin	>2	**R**
Gentamicin	8	**R**
Meropenem	<=1	**S**
Piperacillin/T	*	**R**
Tobramycin	4	**S**
Trimeth/Sulfa	>2/38	**R**

Collateral Damage of Antibiotic Use
ESBL Resistance & Use



Rice LB, *Pharmacother* 1999 Aug; 19 (8 Pt2): 120S-128S.

Collateral Damage of Antibiotic Use
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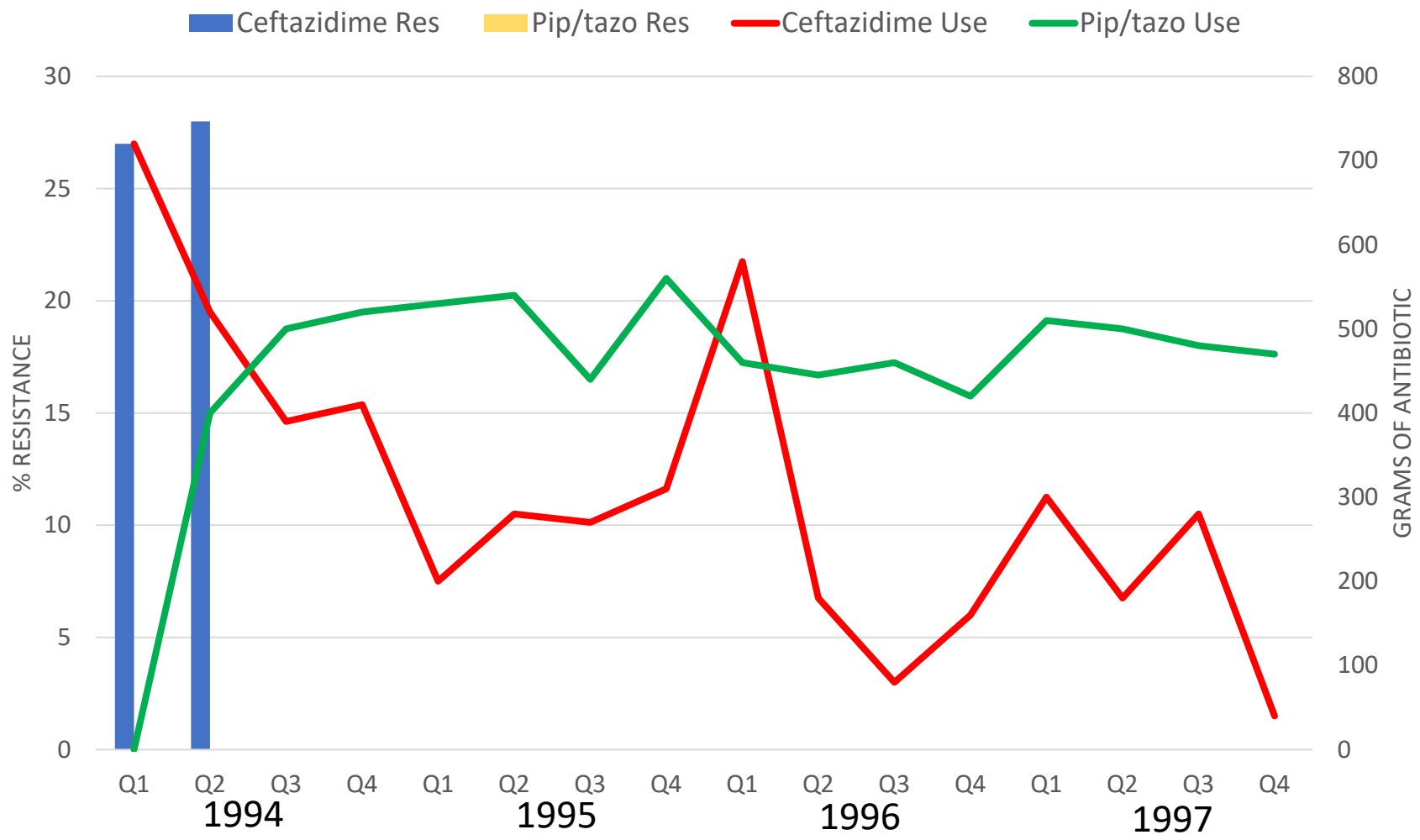

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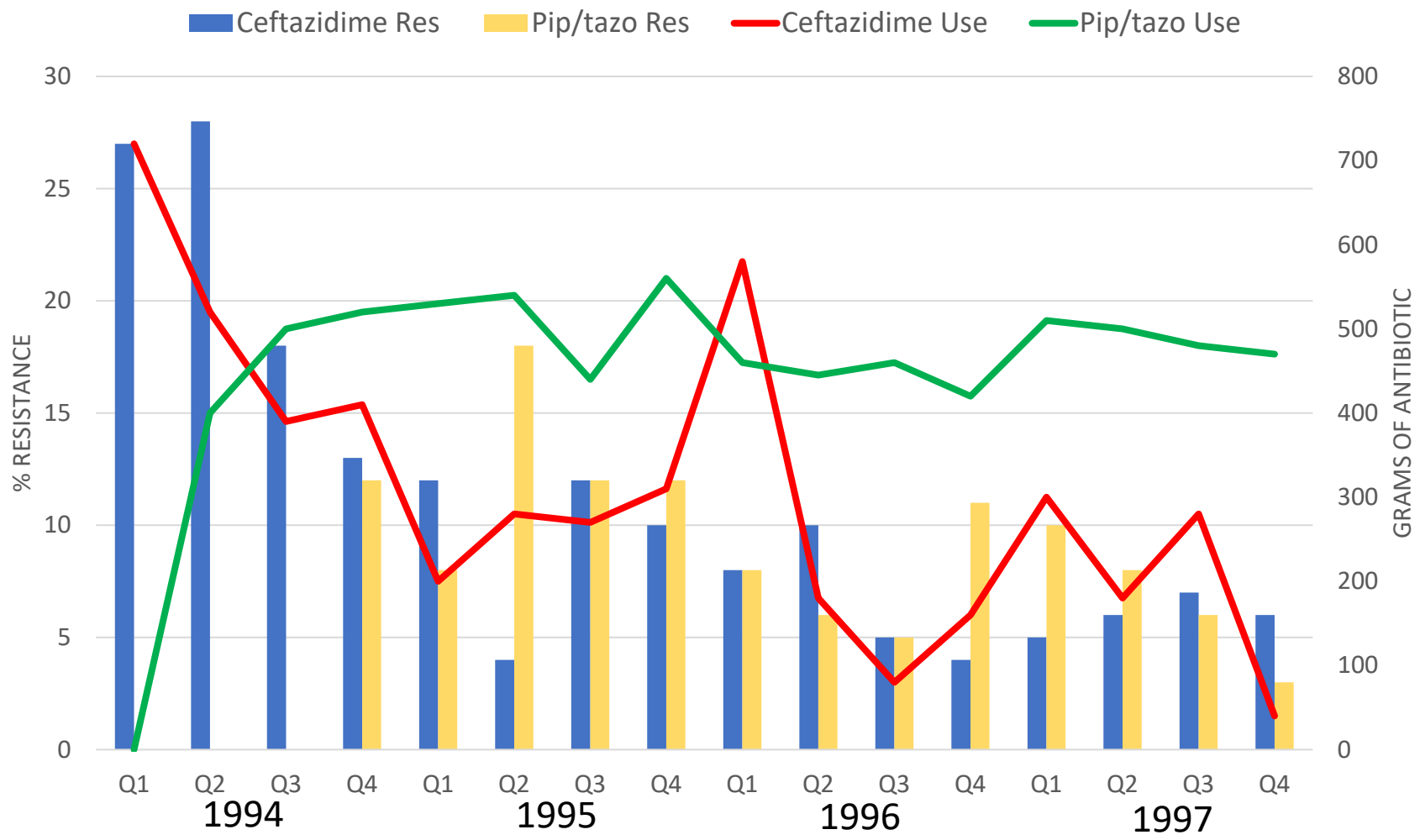

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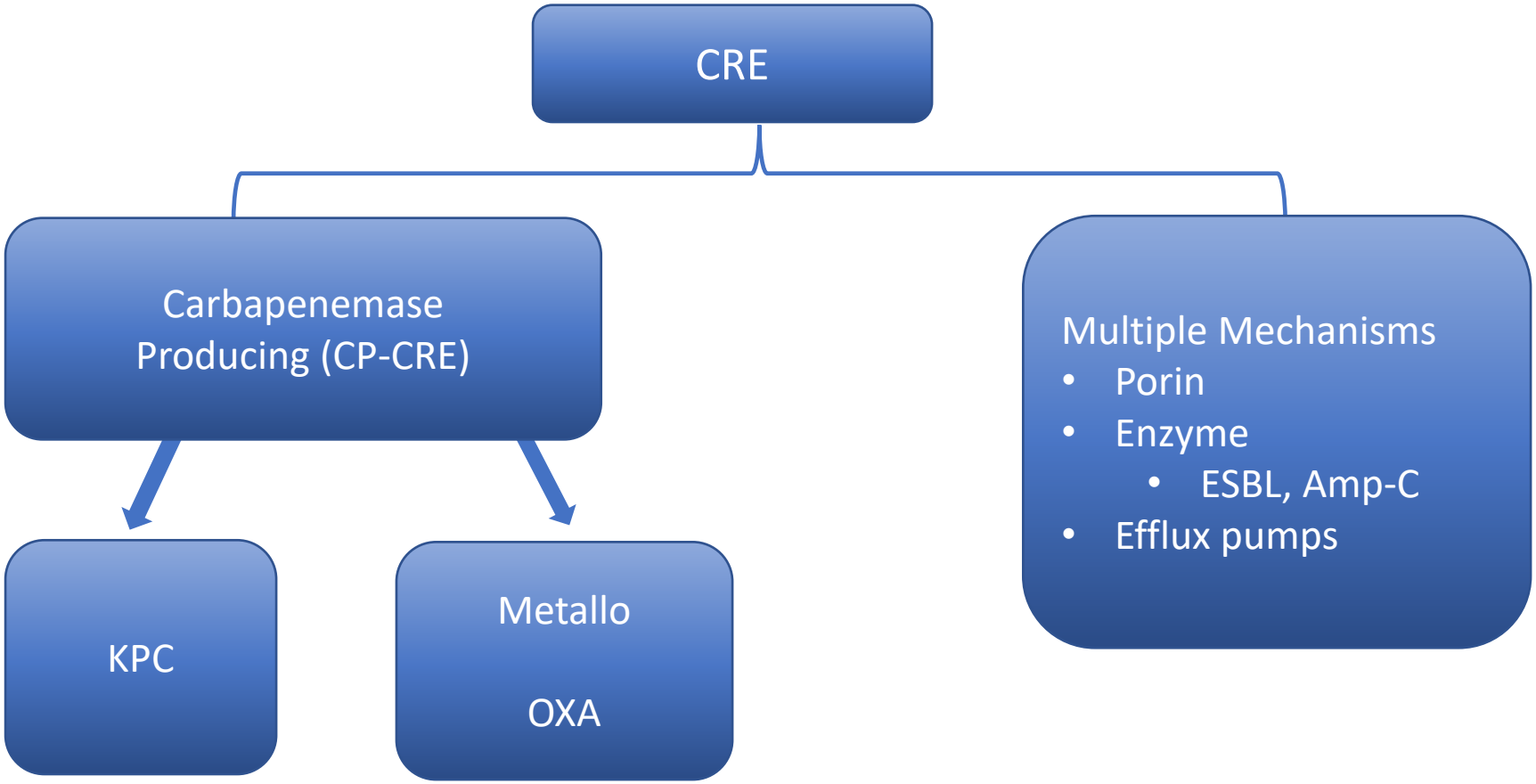
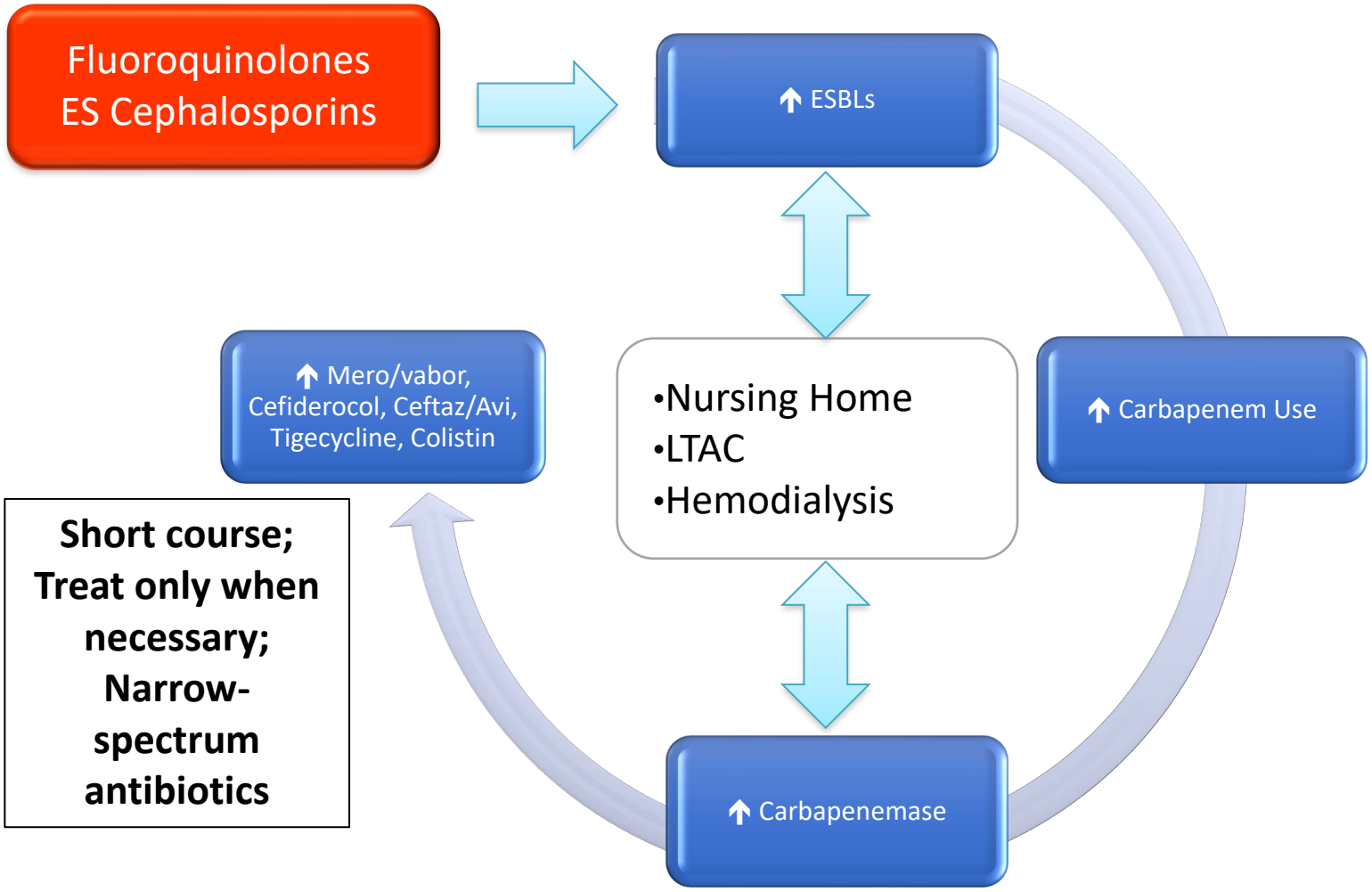
Carbapenem Resistant Enterobacteriaceae (CRE)

Carbapenem Resistant Enterobacteriaceae (CRE)



Vicious Cycle



MDR *Pseudomonas* & *Acinetobacter*

- All four major mechanisms of resistance

- Exposure to certain broad-spectrum antibiotics
  - Fluroquinolones
  - 3rd generation cephalosporins
  - Low potency carbapenems
  - Inadequate dose / concentrations

- Cross resistance to unrelated antibiotics
  - FQ exposure → Carbapenem resistance

- Increased colonization potential

Areas of Impact: Antimicrobial Prescribing

- Decision to treat
- Selection of antimicrobials
  - Avoid use that potentiates selection or induction of resistance
  - Ensure concentration at site of infection (organ, tissue, cells)
  - Recognize potential for collateral damage (colonizing bacteria – gut, mucous membranes)
- Optimal dosing utilizing PK/PD principles
  - Maximize killing and prevent conditions that allow for emergence of resistance
- Limiting length of therapy

Risk for MDRO's
Missing the target: Renal Elimination

Antibiotic	% Unchanged in Urine
Amoxicillin	60-80%
Cefazolin	80-100%
Cefepime	85%
Gentamicin	85-100%
Tobramycin	90-95%
***Ceftriaxone	33-45% (55-67% GI)
***Ciprofloxacin	30-50% (50-70% GI)

Use of antibiotics that do not concentrate at the site of infection, especially those that affect GI flora in patients with chronic conditions, leads to an environment that selects for resistance.

Resistance Summary

	Amp C	ESBL	KPC	MDR PA & AB	VRE
Drivers	**3rd cephs** Clavulanate Cefoxitin Imipenem	**3rd cephs** **FQs**	**3rd Cephs** **FQs** Carbs	**3rd Cephs** **FQs** Low Dose / Potency Carbs	**Cephs** Clinda PO vanc

Summary

- Antimicrobial Resistance increases mortality, morbidity, healthcare costs, return to acute care, and hospital length of stay.
- Assess your patient for risk of antimicrobial resistance.
- Know your local resistance with your facility specific antibiogram.
- Resistance occurs through a variety of mechanisms. Antimicrobials vary in their potential to induce antimicrobial resistance.
- Prescribers must be taught how to select and dose antimicrobials for better outcomes and the prevention of resistance.

Antimicrobial Resistance Solutions

Management. Education. Innovation.

Combating Antimicrobial Resistance with Stewardship

Post Education Survey

https://www.surveymonkey.com/r/ARS_012024

For additional information or questions please contact:
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