



COLUMBIA UNIVERSITY
MEDICAL CENTER
Department of Pediatrics

Division of Infectious Disease

Predicting Successful Combination Therapies for Infections Caused by XDR-GNB

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Outline

Introduction

ARAR Study Overview and Methods

Preliminary Results from Aims 1 & 3

Results from Aim 2

Future Analysis and Related Research

Introduction

Hospital-Associated Infections

- Approximately 1.7 million HAIs occur each year in the U.S.
- Associated with increased mortality, length of stay, and cost
 - 99,000 deaths
 - At least \$6.5 billion in extra costs

Introduction

Antimicrobial Resistance

- More than 70% of bacterial HAIs are resistant to a first-line drug
- Infections with resistant organisms are more difficult and costly to treat
- Reservoirs: hospital environment, colonized patients, healthcare workers, long-term care facilities, community
- The prevalence of multidrug-resistant organisms (MDROs) is increasing

Introduction

Strategies to Reduce Resistance

- Prevent Transmission
- Use Antimicrobials Wisely
- Diagnose and Treat Effectively
- Prevent Infections

Introduction

Multidrug Resistance

- Infections caused by drug-resistant gram-negative bacilli are associated with increased morbidity, mortality, cost, and length of stay among patients hospitalized in intensive care units (ICUs)
- Treatment options have become limited to polymyxin B, tigecycline, and possibly, doripenem

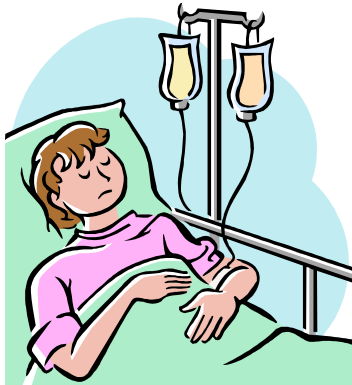
ARAR Study

Applied Research in Antimicrobial Resistance

Studies of Susceptibility Testing & Management of XDR Gram-Negative Pathogens in the ICU

1. To study risk factors and outcomes of infections caused by extremely drug-resistant gram-negative bacilli (XDR-GNB)
2. To study susceptibility testing & management of XDR-GNB infections
3. To measure Knowledge, Attitudes, and Practices (KAP) of ICU physicians regarding susceptibility testing and treatment of XDR-GNB

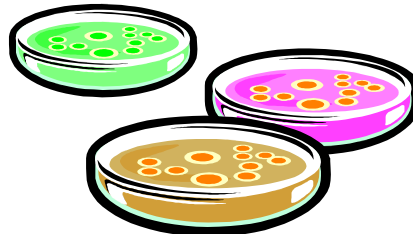
Decisions Affecting Treatment



1



2



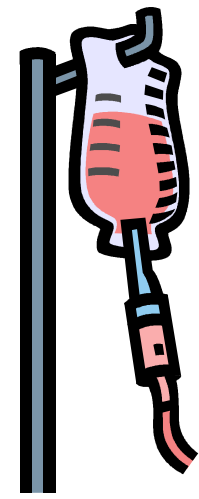
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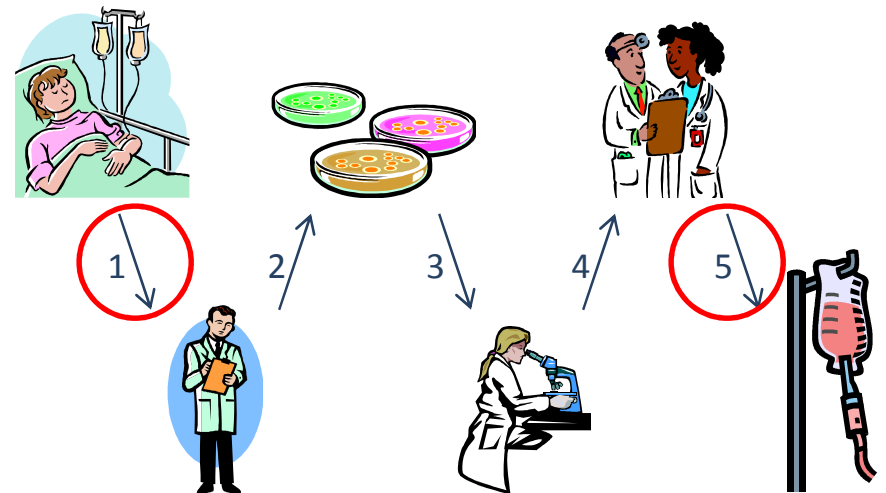
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Aim 1 Approach

Case-Control study

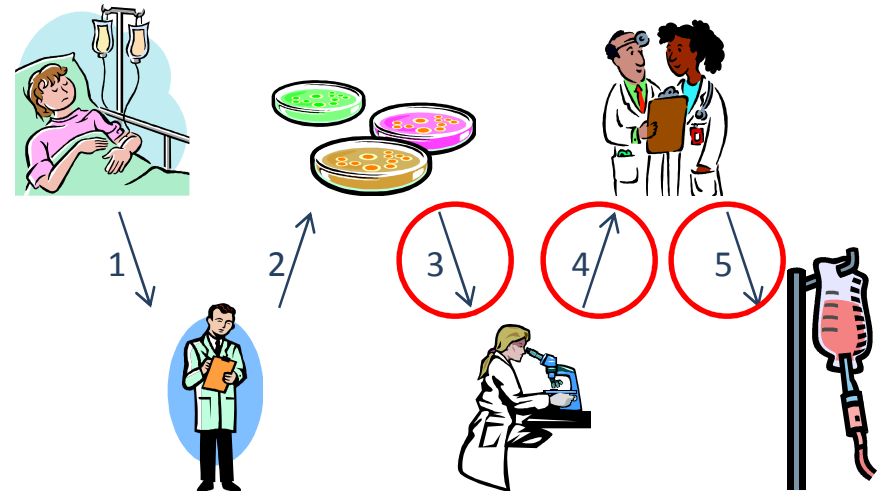
- Enroll Cases with XDR HAIs, Controls with non-XDR HAIs
- Record putative risk factors, co-morbid conditions
- Observe treatment strategies used
- Determine the clinical and microbiologic outcomes associated with selected treatment strategies



Aim 2 Approach

Collect and **test XDR clinical isolates** from Cases

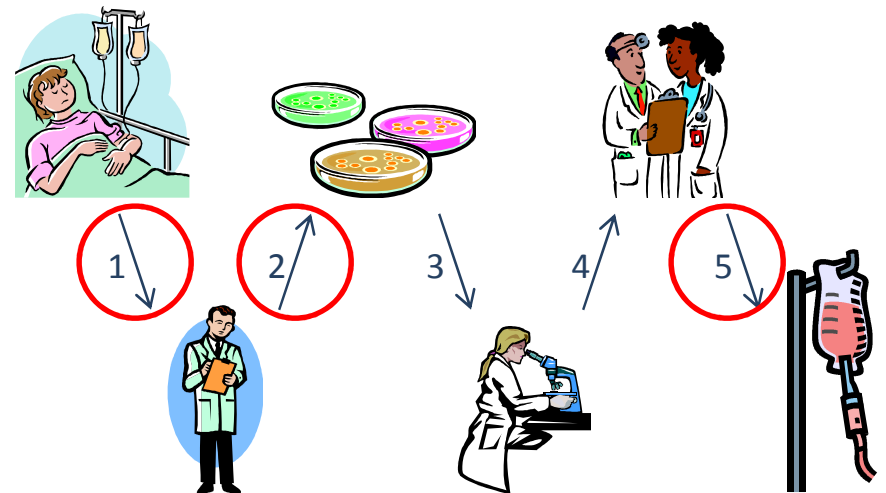
- Determine *in vitro* testing strategies that best predict successful clinical and microbiologic outcomes for XDR-GNB infections



Aim 3 Approach

Conduct anonymous **electronic survey**

- Survey ICU physicians to assess their knowledge, attitudes, and practices regarding antimicrobial susceptibility testing and determine factors associated with the use of test results



Case-Control Study Design

Sites

- Multicenter study, including academic tertiary care centers, community hospital, children's hospital
- 16 ICUs with approx. 14,800 ICU admissions per year
- ICU types include medical, surgical, burn, cardiothoracic, pediatric, and neonatal

Enrollment

- Prospective enrollment of Cases (XDRs), retrospective enrollment of Controls (non-XDRs)
- Approx. 2 year study period
- Approx. 100 Cases, 200 matched Controls

Case Definitions

- Eligible **XDR-GNB**

Acinetobacter baumannii, *Klebsiella pneumoniae*, or *Pseudomonas aeruginosa* susceptible to ≤ 1 agent on conventional antibiogram (Vitek[®] 2), not including polymyxin B or tigecycline

- Eligible **HAIs**

Bloodstream infection (BSI), pneumonia (PNA), or urinary tract infections (UTI) using National Healthcare Safety Network (NHSN) case definitions

- Eligible **Cases**

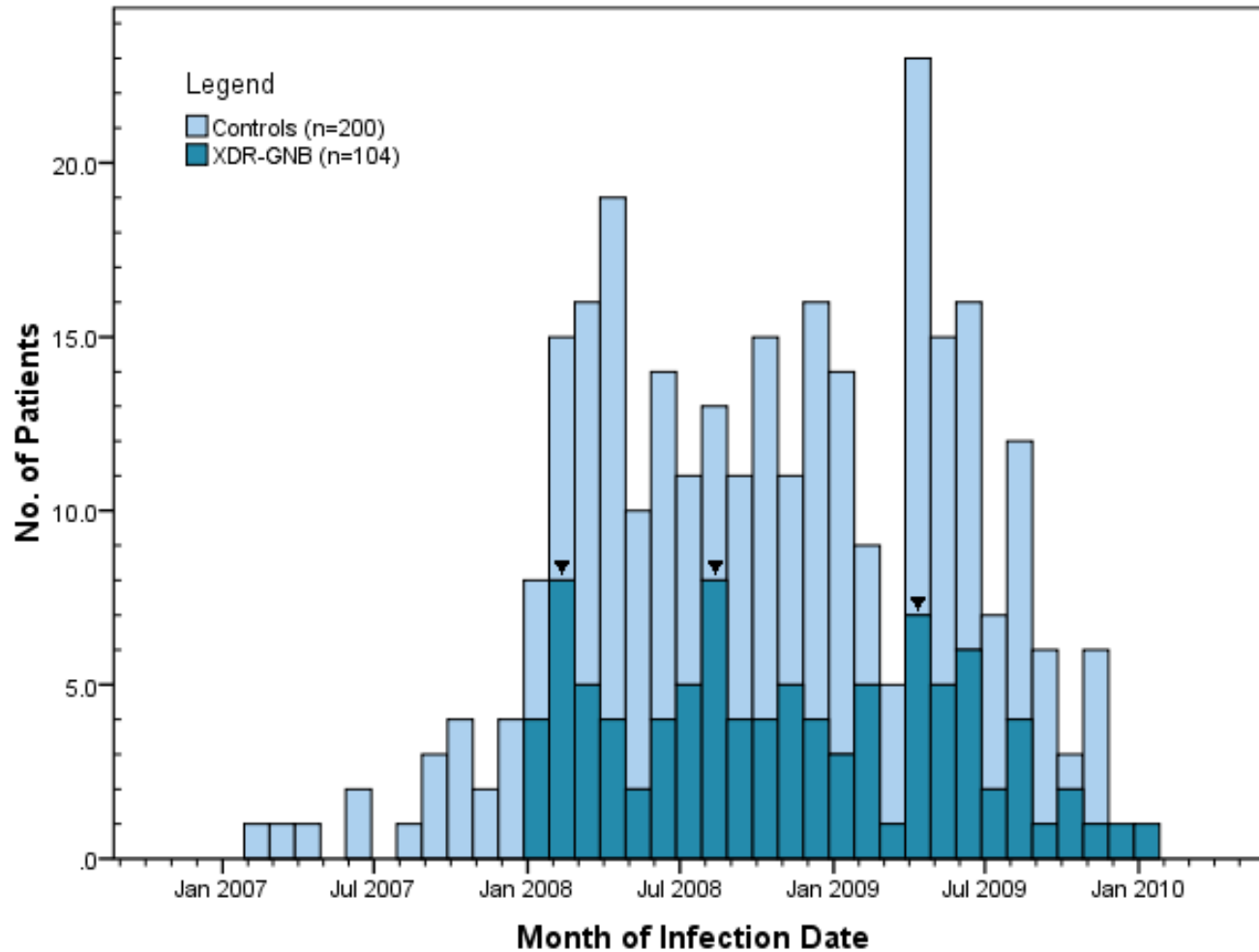
Patients admitted to an ICU from January 2008 to March 2010 and treated for a HAI caused by an XDR-GNB

Surveillance and Validation

EpiPortal, an NYPH-developed automated surveillance tool, is used to identify patients requiring *Transmission Precautions*

- Study team used **EpiPortal** to find ICU patients with XDR *A. baumannii*, *K. pneumoniae*, *P. aeruginosa* cultures from body sites of interest (i.e., blood, respiratory, urine) and reviewed each for Case status
- Study team validated EpiPortal data by manually reviewing antibiograms in **Epidemiology Reports** generated by Clinical Microbiology Laboratories

Distribution of Study Subjects



Clinical Characteristics

- Cases vs. Controls

Characteristic	Case patients (n=104)		Control patients (n=200)		p-value (Pearson's χ^2 test)
	no.	(%)	no.	(%)	
Body site of infection					0.93
HA-BSI	34	(32.7)	68	(34.0)	
HA-Pneumonia	50	(48.1)	97	(48.5)	
HA-UTI	20	(19.2)	35	(17.5)	
Pathogen species					<0.0001
<i>A. baumannii</i>	52	(50.0)	22	(11.0)	
<i>K. pneumoniae</i>	46	(44.2)	102	(51.0)	
<i>P. aeruginosa</i>	6	(5.8)	76	(38.0)	

Crude Mortality

59 %

31 %

$p=0.001$

Survey Results

Respondents: 55 pediatric and 65 adult ICU physicians

- Knowledge deficits

- 44% unaware of MDR-GNB case definition for contact precautions at study site
- 61% did not correctly identify or were unsure of activity of specific antimicrobial agents (e.g., tigecycline, carbapenems)

- Attitudes and Practices

- most were not confident they could interpret *in vitro* susceptibility testing results (59%) or use local resistance patterns (54%) to guide MDR-GNB treatment
- adult ICU physicians were more confident than pediatric ICU physicians ($p < 0.05$)

XDR Strains used for *in vitro* Studies

100 “Case” strains:

Organism	Blood	Respiratory	Urine	Total
<i>A. baumannii</i>	24	15	9	48
<i>K. pneumoniae</i>	13	27	8	48
<i>P. aeruginosa</i>	0	2	2	4
Total	37	44	19	100

In vitro Susceptibility Testing

Susceptibility	
Vitek [®] 2 (MIC)/Etest (MIC)	Clinical labs
Microbroth dilution (MIC)	ARAR study team
Etest (MIC)	ARAR study team
Synergy	
Checkerboard (FIC)	ARAR study team
Etest (FIC)	ARAR study team

Vitek[®] 2



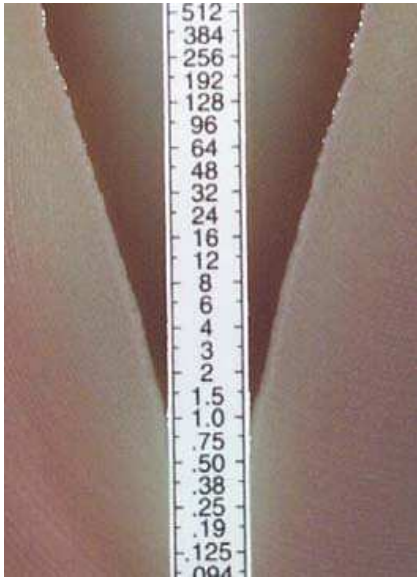
- Automated bacterial identification and antimicrobial susceptibility testing
- Bacteria are inoculated at a fixed CFU/ml and cards are read between 3.3-17.5 hrs by the system
- Not reliable for all agents for all species

Microbroth Dilution Assay



- Commercially prepared frozen panels containing antimicrobial agents over a range of concentrations, in doubling dilutions
- Bacteria are inoculated at a fixed CFU/ml and panels are incubated 16-20 hrs
- Susceptibility is measured by reading the concentration of antimicrobial at which there is no visible growth

Etest Assay



- Plastic strip impregnated with a single antimicrobial agent in an increasing gradient
- Bacteria are plated at a fixed CFU/ml, the strip is applied, and plates are incubated 16-20 hrs
- Susceptibility is measured by reading the concentration at which the intersection of the ellipse of bacterial growth with the strip

Interpretive Criteria

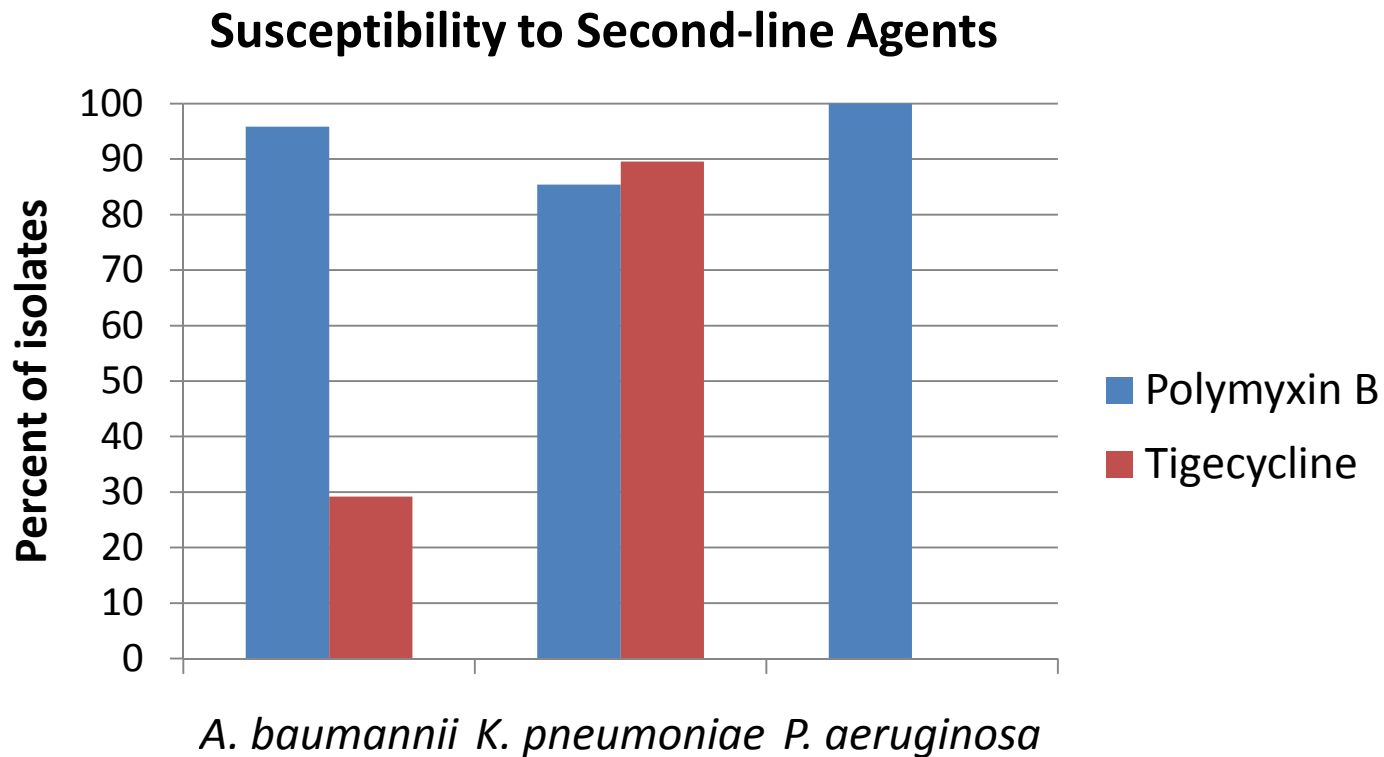
Agent	S	I	R	Panel (µg/ml)	Etest (µg)
Amikacin	≤16	32	≥64	1 -512	256
Aztreonam	≤8	16	≥32	16-1024	256
Ertapenem	≤4	8	≥16	0.5-32	32
Gentamicin	≤4	8	≥16	1-512	256
Meropenem	≤4	8	≥16	0.5-32	32
Cefepime	≤8	16	≥32	2-128	256
Polymyxin B	≤2	4	≥8	0.25-1024	1024
Rifampicin	≤1	2	≥4	0.5-32	32
Tigecycline	≤2	4	≥8	0.5-32	256
	<i>Pa: n/a</i>	<i>Pa: n/a</i>	<i>Pa: n/a</i>		
Tobramycin	≤4	8	≥16	8-1024	256
Trimethoprim-sulfamethoxazole	≤2/38		≥4/76	0.5/9.5-32/608	32
	<i>Pa: n/a</i>		<i>Pa: n/a</i>		
Ampicillin-sulbactam	≤8/4	16/8	≥32/16	--	256
Imipenem	≤4	8	≥16	--	32
Levofloxacin	≤2	4	≥8	--	32
Piperacillin-tazobactam	≤16	32-64	≥128	--	256
	<i>Pa: ≤64</i>		≥128		

Single Agent MICs (MbD)

Agent	<i>A. baumannii</i> (n=48)		<i>K. pneumoniae</i> (n=48)		<i>P. aeruginosa</i> (n=4)	
	MIC ₅₀ /Int.	MIC ₉₀ /Int.	MIC ₅₀ /Int.	MIC ₉₀ /Int.	MIC ₅₀ /Int.	MIC ₉₀ /Int.
Amikacin	32/I	256/R	32/I	64/R	16/S	32/I
Aztreonam	256/R	256/R	>1024/R	>1024/R	256/R	256/R
Ertapenem	>32/R	>32/R	>32/R	>32/R	>32/R	>32/R
Gentamicin	512/R	>512/R	16/R	128/R	16/R	>512/R
Meropenem	>32/R	>32/R	32/R	>32/R	8/I	>32/R
Cefepime	>128/R	>128/R	>128/R	>128/R	16/S	128/R
Polymyxin B	<0.25/S	1/S	<0.25/S	16/R	<0.25/S	1/S
Rifampicin	4/R	>32/R	32/R	>32/R	(I/R)	(I/R)
Tigecycline	4/I	16/R	1/S	4/I	<i>Pa</i> : n/a	<i>Pa</i> : n/a
Tobramycin	32/R	32/R	32/R	32/R	32/R	32/R
Trimethoprim-sulfamethoxazole	64/1216/R	64/1216/R	64/1216/R	64/1216/R	<i>Pa</i> : n/a	<i>Pa</i> : n/a

First-line agent resistance

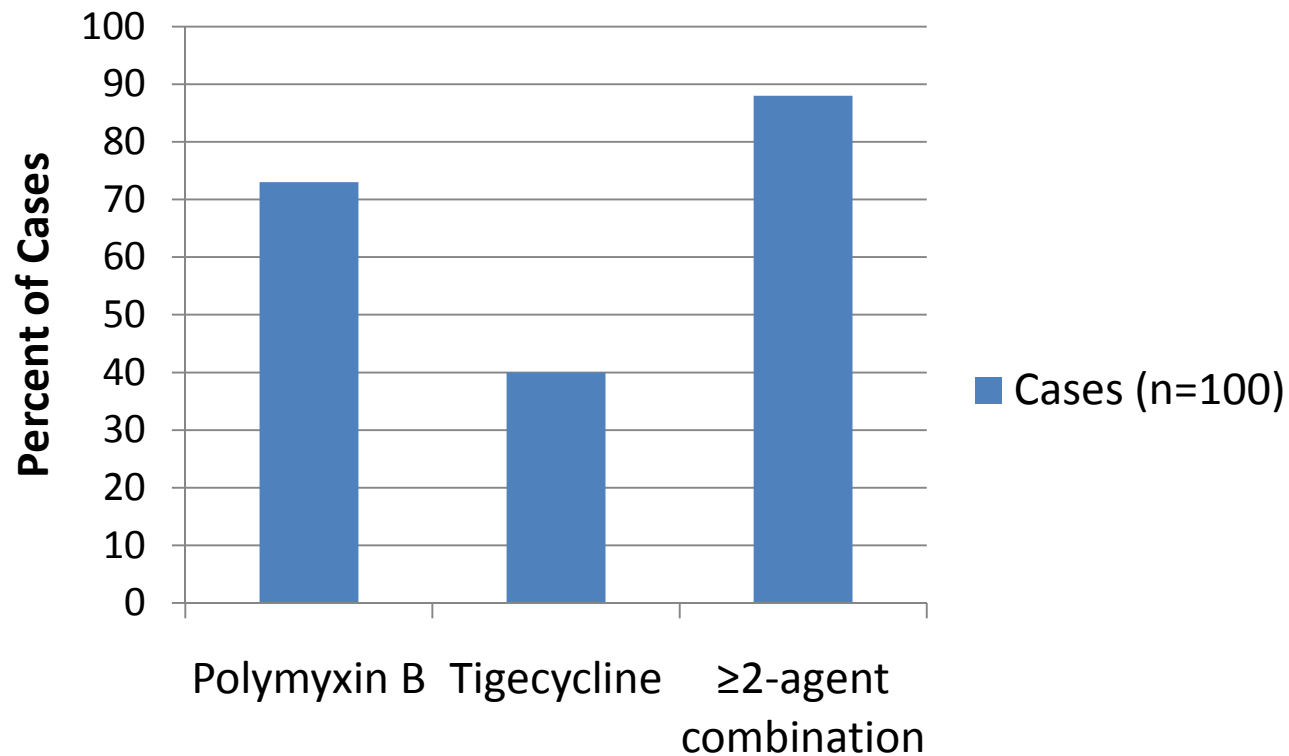
- Overall, 83% of strains were resistant to all tested first-line agents



- But 91% and 59% overall remain susceptible to polymyxin B and tigecycline, respectively

Treatment of XDR-GNB

Antimicrobial Exposure of Case Patients



KPC-producing *K. pneumoniae*

- PCR for bla_{KPC} confirmed all 48 XDR-*Kp* have ≥ 1 KPC
- Comparison of Vitek[®] 2, MbD, and Etest methodologies

Polymyxin B

Etest vs. MbD: categorical agreement = 75%

Etest had higher MICs

Tigecycline

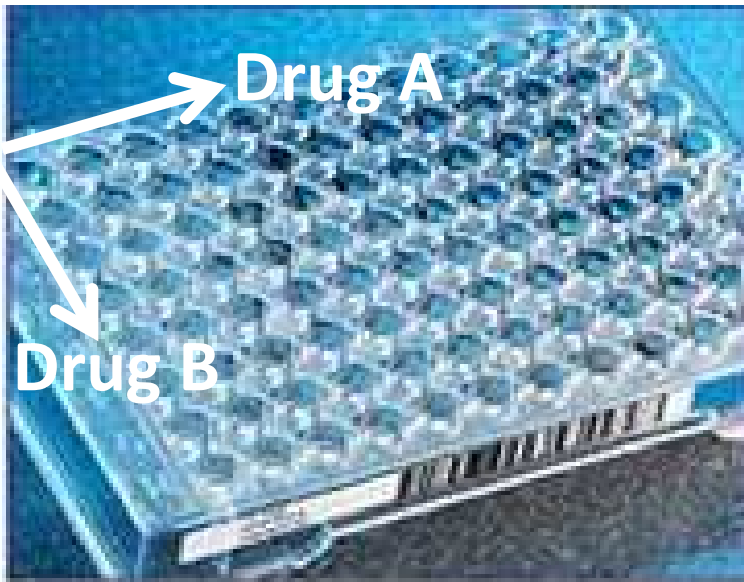
Etest vs. MbD: categorical agreement = 75%

Vitek vs. MbD: categorical agreement = 63%

Cefepime & Meropenem

Etest had better agreement with MbD than Vitek

Checkerboard Synergy



- Commercially prepared frozen panels containing antimicrobial agents in pairs
- Bacteria are inoculated at a fixed CFU/ml and panels are incubated 16-20 hrs
- Susceptibility to pair is measured by reading the concentrations of the antimicrobials at which there is no visible growth

Checkerboard Combinations

2- or 3-drug Combinations	Species Tested
Polymyxin B & Amikacin	<i>Ab, Kp, Pa</i>
Polymyxin B & Cefepime	<i>Ab, Kp, Pa</i>
Polymyxin B & Meropenem	<i>Ab, Kp, Pa</i>
Polymyxin B & Tigecycline	<i>Ab, Kp</i>
Polymyxin B & Trimethoprim-Sulfmethoxazole	<i>Ab, Kp</i>
Amikacin & Cefepime	<i>Ab, Kp, Pa</i>
Amikacin & Tigecycline	<i>Ab, Kp</i>
Tigecycline & Meropenem	<i>Ab, Kp</i>
Polymyxin B & Tigecycline & Cefepime	<i>Ab, Kp</i>
Polymyxin B & Tigecycline & Meropenem	<i>Ab, Kp</i>

Interpretive Criteria

FICs

2-agent combinations

$$\text{FIC} = \frac{\text{MIC A}_{\text{comb A/B}}}{\text{MIC}_{\text{agent A}}} + \frac{\text{MIC B}_{\text{comb A/B}}}{\text{MIC}_{\text{agent B}}}$$

FIC VALUE	Interpretation	Abbreviation Used in Report
<=0.5	Synergistic	SY
>0.5 - 1.0	Additive	AD
>1.0 - <=4.0	Indifferent	IN
>4	Antagonistic	AN
	Not clinically achievable	**

Interpretive Criteria

FICs

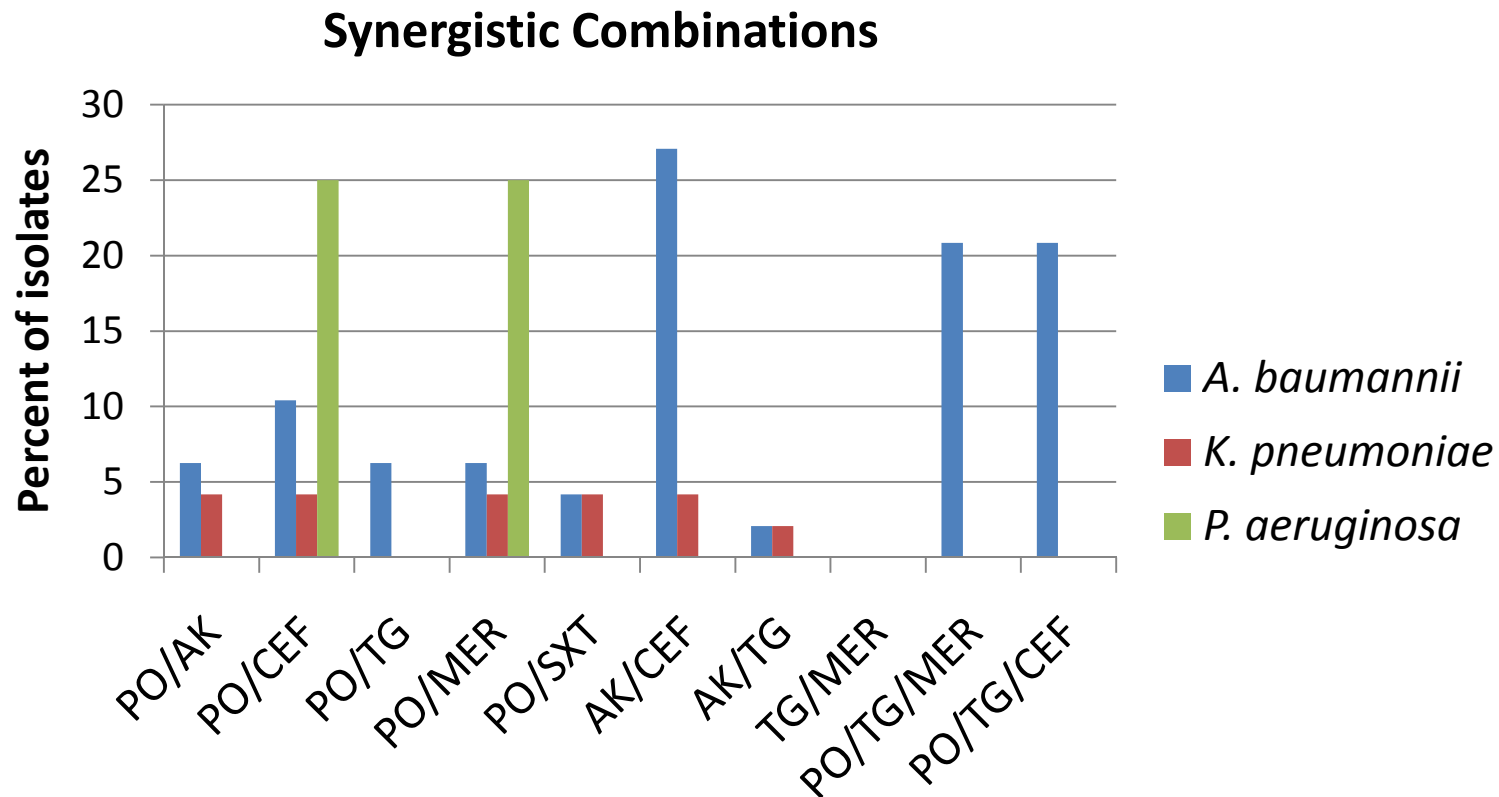
3-agent combinations

$$\text{FIC} = \frac{\text{MIC A}_{\text{comb A/B/C}}}{\text{MIC}_{\text{agent A}}} + \frac{\text{MIC B}_{\text{comb A/B/C}}}{\text{MIC}_{\text{agent B}}} + \frac{\text{MIC C}_{\text{comb A/B/C}}}{\text{MIC}_{\text{agent C}}}$$

FIC VALUE	Interpretation	Abbreviation Used in Report
<=0.75	Synergistic	SY
>0.75 - 1.5	Additive	AD
>1.5 - <=6.0	Indifferent	IN
>6	Antagonistic	AN
	Not clinically achievable	**

Synergy by MbD

- The best 2-agent combinations were cefepime with amikacin (15% overall) or with polymyxin B (6% overall)
- 3-agent combinations were only synergistic for *Ab* (21%; 10% overall)



Interpretive Criteria

MIC Lowering

- For a given drug, MIC Lowering is achieved when the concentration for a single drug was not clinically achievable, but the concentration for that drug is lowered into the clinically achievable range when it is present in a 2- or 3-agent combination
- It is possible that MIC Lowering is observed for fewer than the total number of agents in a given combination

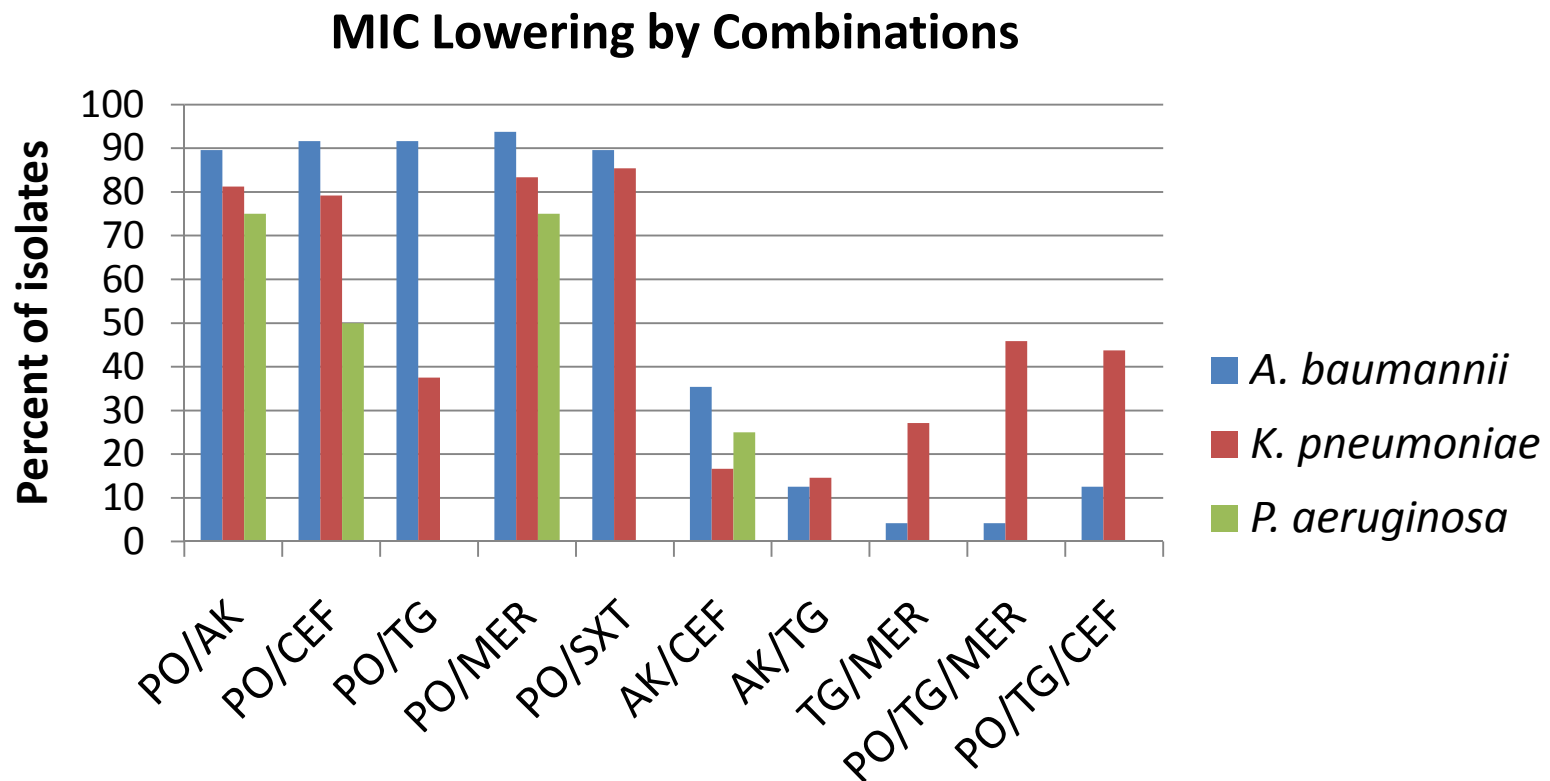
Interpretive Criteria

Agent	(S)	(I)	(R)	PD breakpoint (intravenous)
Amikacin	≤16	32	≥64	8
Aztreonam	≤8	16	≥32	4-8
Ertapenem	≤4	8	≥16	0.25
Gentamicin	≤4	8	≥16	2
Meropenem	≤4	8	≥16	4
Cefepime	≤8	16	≥32	16
Polymyxin B	≤2	4	≥8	2
Rifampicin	≤1	2	≥4	1
Tigecycline	≤2	4	≥8	1
	<i>Pa: n/a</i>	<i>Pa: n/a</i>	<i>Pa: n/a</i>	
Tobramycin	≤4	8	≥16	2
Trimethoprim-sulfamethoxazole	≤2/38		≥4/76	4/76
	<i>Pa: n/a</i>		<i>Pa: n/a</i>	
Ampicillin-sulbactam	≤8/4	16/8	≥32/16	16/8
Imipenem	≤4	8	≥16	4
Levofloxacin	≤2	4	≥8	0.5
Piperacillin-tazobactam	≤16	32-64	≥128	16
	<i>Pa: ≤64</i>		≥128	

MIC Lowering by MbD

- The best 2-agent combinations overall contained polymyxin B:

with meropenem (88%), trimethoprim-sulfmethoxazole (89%), amikacin (84%), cefepime (83%), tigecycline (65%)



Summary

- XDR-GNB are highly resistant to first-line agents, but are often susceptible to polymyxin B and tigecycline *in vitro*
- A majority of patients with XDR-GNB HAIs receive polymyxin B and/or tigecycline as treatment, and 88% receive combination therapy with ≥ 2 agents
- *In vitro* testing may provide evidence for useful combination treatment regimens, but will require clinical correlation

Next Steps

- Examine Etest Susceptibility and Synergy Results
- Test 2-agent combinations containing Rifampin (with polymyxin B or meropenem)
- Test combinations containing doripenem
- Look at clinical outcomes of patients treated with specific combinations

Next Steps

Determine if the results from *in vitro* testing strategies performed on XDR-GNB

- (1) are actually used by healthcare professionals to choose or modify treatment regimens;
- (2) can predict clinical and microbiologic outcomes

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Thank you!

Please visit <http://nursing.columbia.edu/CIRAR> for more information about Antimicrobial Resistance.

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