



# Interactive Cases: Management of Multidrug-Resistant GNB

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**GRAM-NEGATIVE BACTERIA  
AND ANTIMICROBIAL  
RESISTANCE:**

**WHAT'S CHANGED? WHAT REMAINS THE SAME?**

# Disclosures

## **Honoraria:**

Merck (Advisory Boards, Speaker)

Verity (Advisory Boards)

Cipher (Advisory Board)

## **Travel Reimbursement:**

Merck (Symposium)

Copan (User Group, Scientific Workshop)

## **Research Support:**

Accelerate Diagnostics (Summer Student Funding)

# Objectives

By the end of this session, you should be able to:

1. Discuss case-based scenarios for the management of multi-drug resistant Gram-negative infections

# Question 1

**In which are do you primarily work?**

1. Infectious Disease
2. Microbiology
3. Antimicrobial Stewardship
4. Infection Control
5. Pharmacy
6. Other

# Case 1 - You're in Trouble

- 88F admitted to Gen Medicine from home admitted with fever and dysuria and frequency
- Recent admission for feeling unwell:
  - BC 2/2 negative
  - admission rectal swab positive for NDM+ *E. coli*
- Urine and BC 2/2 sent

# Question 2

**Which agent would you consider empirically?**

1. TMP-SMX
2. Ciprofloxacin
3. Oral fosfomycin
4. Ceftriaxone
5. Ertapenem
6. Meropenem
7. Piperacillin-tazobactam
8. Other antimicrobial agent
9. No treatment

# Case 1 – Preliminary Results

*Source:* **Blood Culture**

*Site:* **PERIPHERAL**

## **Test Results**

Culture and Sensitivity:

**No growth**

# Case 1 – Preliminary Results

Source: Urine

Site: \_\_\_\_.....

## Test Results

Culture and Sensitivity:

**Klebsiella pneumoniae**

>100 x E6 cfu/L



# Question 3

**Would this change your empiric choice?**

1. Yes – narrow
2. Yes – broaden
3. No

# Case 1 – Updated Results

Source: Urine

Site: \_\_\_\_.....

## Test Results

### Culture and Sensitivity:

**Klebsiella pneumoniae**

>100 x E6 cfu/L

NDM and OXA48 carbapenemase gene DETECTED by Cepheid Xpert CARBA-R Assay (for research use only). This assay is able to detect NDM, KPC, OXA48, OXA181, OXA232, IMP-1, and VIM carbapenemase genes.

# Case 1 – Susceptibility Results

	K. pneumo	
Amikacin	R	
Amoxicillin/Clavulanate	R	
Ampicillin	R	
Ceftriaxone	R	
Cephalexin	R	
Ciprofloxacin	R	
Doxycycline	R	
Ertapenem	R	
Gentamicin	R	
Meropenem	R	<b>Meropenem MIC <math>\geq</math> 16 mg/L</b>
Nitrofurantoin	R	
Piperacillin/Taz	R	<b>Pip-tazo MIC <math>\geq</math> 128/4 mg/L</b>
Tobramycin	R	
Trimethoprim/sulfa	R	

# Question 4

**What would you change your treatment to?**

1. Tigecycline
2. Colistin
3. Oral fosfomycin
4. Ceftolozane-tazobactam
5. Prolonged infusion
6. Combination treatment
7. Other antimicrobial agent

Culture and Sensitivity:

***Klebsiella pneumoniae***

>100 x E6 cfu/L

NDM and OXA48 carbapenemase gene DETECTED by Cepheid Xpert CARBA-R Assay (for research use only). This assay is able to detect NDM, KPC, OXA48, OXA181, OXA232, IMP-1, and VIM carbapenemase genes.

COLISTIN MIC is 0.125 mg/L.

There are no CLSI standards for this drug. EUCAST suggests MICs  $\leq 2$  mg/L correlate with susceptibility. Please consult the microbiologist-on-call with any questions.

TIGECYCLINE MIC = 4 mg/L

There are no CLSI standards for this drug. EUCAST suggests MICs  $> 0.5$  mg/L correlate with resistance. Please consult the microbiologist-on-call with any questions.

FOSFOMYCIN zone size = 19 mm

There are no CLSI standards for fosfomycin and this organism. CLSI suggests zones of inhibition  $\geq 16$  mm correlate with SUSCEPTIBILITY for *E. coli*. Please consult the microbiologist-on-call with any questions.

**Ceftolozane-tazobactam R MIC  $\geq 256$  mg/L**

# Question 5

**What would you change your treatment to?**

1. Tigecycline
2. Colistin
3. Oral fosfomycin
4. Ceftolozane-tazobactam
5. Prolonged infusion
6. Combination treatment
7. Other antimicrobial agent

# Question 6

**What if the patient's BC was also positive for this organism? Would you change your treatment to?**

1. Tigecycline
2. Colistin
3. IV fosfomycin
4. Ceftolozane-tazobactam
5. Prolonged infusion
6. Combination treatment
7. Other antimicrobial agent

# Question 7

**For confirmed CPO, does your microbiology laboratory reflex all  $\beta$ -lactam agents as resistant?**

1. Yes
2. No



# Case 2 – Abscess Angst

- 64M recent renal transplant with multiple past admissions for UTIs, admitted to the transplant unit after presenting with fever, flank pain, and surgical site drainage
- Found to have a peri-nephric collection on imaging
- A drain is placed and purulent material is sent for culture
- BC 2/2 are also sent

# Case 2 – Preliminary Results

*Source:* **Blood Culture**

*Site:* **PERIPHERAL**

## **Test Results**

Culture and Sensitivity:

**No growth**

# Case 2 – Preliminary Results

*Source:* Wound Drainage

*Site:* ABDOMINAL

## Test Results

### Gram Stain:

3+ pus cells

2+ gram negative bacilli

### Culture and Sensitivity:

UPDATED REPORT

Escherichia coli

Heavy growth

# Question 8

**Which antimicrobial agent would you start?**

1. TMP-SMX
2. Ciprofloxacin
3. Ceftriaxone
4. Ertapenem
5. Piperacillin-tazobactam
6. Meropenem
7. Other

# Case 2 – Susceptibility Results

## Test Results

	E. coli	
Amoxicillin/Clavulanate	R	
Ampicillin	R	
Cefazolin	R	
Ceftriaxone	R	
Ciprofloxacin	R	
Ertapenem	R	
Gentamicin	S	
Meropenem	S	
Piperacillin/Taz	R	
Tobramycin	S	
Trimethoprim/sulfa	R	

**Gentamicin S**  
**Tobramycin S**  
**Meropenem S**

# Question 9

**What would you change your treatment to?**

1. Gentamicin
2. Tobramycin
3. Meropenem
4. Other

# Question 10

**You note that the patient had a past meropenem-*E. coli* isolated from urine. What would you use?**

1. Gentamicin
2. Tobramycin
3. Meropenem
4. Tigecycline
5. Colistin
6. Ceftolozane-tazobactam
7. Combination treatment
8. Other

# Case 2 – Additional Results

## Culture and Sensitivity:

### UPDATED REPORT

Escherichia coli

Heavy growth

Tigecycline MIC = 0.25 mg/L

There are no CLSI standards for this drug. EUCAST suggests MICs  $\leq 0.5$  mg/L correlate with susceptibility. Please consult the microbiologist-on-call with any questions.

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Colistin MIC is  $\leq 0.25$  mg/L

There are no CLSI standards for this drug. EUCAST suggests MICs  $\leq 2$  mg/L correlate with susceptibility. Please consult the microbiologist-on-call with any questions.

**Ceftolozane/tazobactam S MIC 0.75 mg/L**



# Question 11

**Which agent would you consider using?**

1. Gentamicin
2. Tobramycin
3. Meropenem
4. Tigecycline
5. Colistin
6. Ceftolozane-tazobactam
7. Combination treatment
8. Other antimicrobial agent

# Case 2 – 1 Month Later

## Test Results

	E. coli	
Amoxicillin/Clavulanate	R	
Ampicillin	R	
Cefazolin	R	
Ceftriaxone	R	
Ciprofloxacin	R	
Ertapenem	R	
Gentamicin	S	
Meropenem	R	
Piperacillin/Taz	R	
Tobramycin	S	
Trimethoprim/sulfa	R	

**Gentamicin S**  
**Tobramycin S**  
**Meropenem R**

# Case 3 – Pseudo trouble

- 59M with bronchiectasis admitted to Gen Medicine from home admitted with increased sputum production and shortness of breath
- Multiple past sputum cultures positive for *Pseudomonas aeruginosa*, some intermediate to ciprofloxacin, ceftazidime, gentamicin, and piperacillin-tazobactam
- Sputum culture ordered

# Question 12

**Which agent would you use empirically?**

1. Ciprofloxacin
2. Ceftazidime
3. Piperacillin-tazobactam
4. Meropenem
5. Gentamicin
6. Tobramycin
7. Amikacin
8. Combination treatment
9. Other antimicrobial agent

# Case 3 – Culture Results

Source: Sputum

Site:

Gram Stai...

3+ pus cells

Few epithelial cells

2+ commensal flora

Culture and Sensitivity:

**Pseudomonas aeruginosa**

Heavy growth

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	P. aerug	
Ceftazidime	I	
Ciprofloxacin	I	
Gentamicin	I	
Meropenem	I	
Piperacillin/Taz	R	
Tobramycin	S	

**Tobramycin S**

# Question 13

## **What would you choose now?**

1. Tobramycin
2. Colistin
3. Ceftolozane-tazobactam
4. Meropenem prolonged infusion
5. Combination treatment
6. Other antimicrobial agent

# Case 3 – Additional Susc. Results

| P. aerug |

| |

Ceftazidime | I |

Ceftolozane-Tazobactam | S |

Ciprofloxacin | I |

Colistin | S |

Gentamicin | I |

Meropenem | I |

Piperacillin/Taz | R |

Tobramycin | S |

**Ceftolozane-tazobactam S**

**Colistin S**

**Tobramycin S**

# Question 14

**What would you change your treatment to?**

1. Tobramycin
2. Colistin
3. Ceftolozane-tazobactam
4. Meropenem prolonged infusion
5. Combination treatment
6. Other antimicrobial agent



# Performance of Ceftolozane-Tazobactam Etest, MIC Test Strips, and Disk Diffusion Compared to Reference Broth Microdilution for $\beta$ -Lactam-Resistant *Pseudomonas aeruginosa* Isolates

Romney M. Humphries,<sup>a\*</sup> Janet A. Hindler,<sup>a</sup> Paul Magnano,<sup>a</sup> Annie Wong-Beringer,<sup>b</sup> Robert Tibbetts,<sup>c</sup> Shelley A. Miller<sup>a</sup>

- 308  $\beta$ -lactam resistant *P. aeruginosa*
- BMD used as reference

Error	DD	Etest	Liofilchem
VME	0	0	0
ME	0	0	0.9%
mE	7.1%	3.2%	12.3%
EA	N/A	97.7%	87%

Cefto-tazo  
Etest vs.  
BMD:

Number of isolates with BMD MIC ( $\mu\text{g}/\text{mL}$ )

		S							I	R				
		0.12	0.25	0.5	1	2	4	8	16	32	>32			
Number of isolates with Etest MIC ( $\mu\text{g}/\text{mL}$ )	S	0.12	1											
	0.25		1	1										
	0.5			1	20	7	3							
	1				7	65	25	3						
	2					9	41	20						
	4						2	16	7					
I	8						1	10						
R	16							2	3			1		
32										1		3		
>32													58	

Cefto-tazo  
Liofilchem  
vs. BMD:

Number of isolates with BMD MIC ( $\mu\text{g}/\text{mL}$ )

		S							I	R				
		0.12	0.25	0.5	1	2	4	8	16	32	>32			
Number of isolates with MTS MIC ( $\mu\text{g}/\text{mL}$ )	S	0.12												
	0.25	1												
	0.5		1		2									
	1			1	19	5	2							
	2				9	58	25	4						
	4					16	39	16						
I	8					5	18	4						
R	16						2	14	2					
32								1	1					
>32										1		62		

# Case 4 – A Negative Future

- 63F with bronchiectasis admitted for double lung transplant
- Multiple past sputum cultures positive for MDR *Pseudomonas aeruginosa*
- Pre-lung transplant surveillance BAL sent for culture with the goal to direct post-transplant prophylactic antimicrobial treatment

# Case 4 – Preliminary Results

*Source:* Bronchial Alveolar Lavage

*Site:*

## Test Results

### Gram Stain:

Pus cells seen.

Epithelial cells seen.

Gram negative bacilli seen.

### Culture and Sensitivity:

*Pseudomonas aeruginosa*

=>10 x E6 cfu/L SIGNIFICANT RESULT. Organisms cultured  
in quantities =>10 x E6 cfu/L are consistent with pneumonia.

# Case 4 – Susceptibility Results

## Test Results

	P. aerug	
Amikacin	R	
Aztreonam	R	
Cefepime	R	
Ceftazidime	R	
Ciprofloxacin	R	
Colistin	R	
Gentamicin	R	
Meropenem	R	
Piperacillin	R	
Piperacillin/Taz	R	
Ticarcillin/Clav	R	
Tobramycin	R	

**Pip-tazo  $\geq$  128/4 mg/L**  
**Meropenem MIC  $\geq$  32 mg/L**

# Case 4 – Additional Susc. Results

*Pseudomonas aeruginosa*

=>10 x E6 cfu/L SIGNIFICANT RESULT. Organisms cultured in quantities =>10 x E6 cfu/L are consistent with pneumonia.

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CHLORAMPHENICOL disk diffusion zone size = 16mm

There are no CLSI standards for chloramphenicol and *Ps. aeruginosa*.

CLSI suggests zones of 16mm correlate with intermediate susceptibility for Enterobacteriaceae.

FOSFOMYCIN disk diffusion zone size = 6mm

There are no CLSI standards for fosfomicin and *Ps. aeruginosa*. EUCAST suggests combinations of fosfomicin and other agents may be useful for isolates with fosfomicin MIC <=128 mg/L (equivalent to zone sizes >=13mm based on extrapolation from CLSI fosfomicin interpretive criteria for *E. coli*.)

**Ceftolozane-tazobactam R MIC = 64 mg/L**

# Question 15

## **What would you use prophylactically?**

1. Inhaled colistin
2. Inhaled tobramycin
3. Inhaled colistin and tobramycin
4. Combination treatment
5. Other antimicrobial agent
6. Nothing

# Question 16

**What would you consider if this patient developed post-operative pneumonia due to this organism?**

1. Combination treatment
2. Special access request for ceftazidime-avibactam
3. Special access request for imipenem-relebactam
4. Special access request for meropenem-vaborbactam
5. Special access request for plazomicin
6. Phage therapy
7. New lung transplant
8. Other



Faces of

# ANTIMICROBIAL RESISTANCE



GLOBAL NATIONAL

March 26 2019 5:45pm

## B.C. man challenging Health Canada for phage treatment

A Vancouver Island man is hoping to become the first person in Canada to receive an experimental treatment for deadly superbugs. Phage therapy works by using viruses to target antibiotic-resistant bacteria. Jeff Semple reports on the new push to give Canadians access to the potentially life-saving treatment.

# Summary

- **Case 1 – NDM+ OXA48+ *K. pneumoniae* UTI**
  - CPO plasmids readily move between and in/out of organisms
  - Challenges with lack of breakpoints/delays for second line agents
- **Case 2 - ESBL *E. coli* perinephric abscess**
  - Potential for meropenem non-susceptibility due to porin changes
- **Case 3 MDR *P. aeruginosa* bronchiectasis**
  - Challenges with lack of breakpoints/delays for second line agents
- **Case 4 PDR *P. aeruginosa* lung transplant recipient lung**
  - Untreatable organisms & need for special access, phage, transplant?