Current and New Treatments
MDR GNB Infections
NDM, ESBL and KPC
The US Experience

Lilian Abbo, M.D., FIDSA
Chief Infection Prevention & Antimicrobial Stewardship
Jackson Health System
Associate Professor of Infectious Diseases
University of Miami Miller School of Medicine
Objectives

• **Bread and Butter**
  Appraise current treatment options MDR GN infections

• **Some of my nightmare cases**
  Assess treatment options in difficult clinical situations
  Explore the future antibiotic pipeline

• **Thinking outside the box**
  Consider alternatives for the treatment and decolonization of MDR Gram negatives
My office
1550 beds

60 beds with BMTU
World's most threatening superbugs ranked in new list

By Michelle Roberts
Health editor, BBC News online

2 hours ago | Health

The World Health Organization has drawn up a list of the drug-resistant bacteria that pose the biggest threat to human health.

Top of the list are gram-negative bugs, such as E. coli, which can cause lethal bloodstream infections and pneumonia in frail hospital patients.

The list will be discussed ahead of this summer's G20 meeting in Germany.

WHO PRIORITY PATHOGENS LIST FOR R&D OF NEW ANTIBIOTICS

Priority 1: CRITICAL#

- *Acinetobacter baumannii*, carbapenem-resistant
- *Pseudomonas aeruginosa*, carbapenem-resistant
- *Enterobacteriaceae* species, carbapenem-resistant, 3rd generation cephalosporin-resistant

Bread and Butter
Urinary tract infections

- 54 year old lady back from 3 week vacation in Asia
- Presents with 2 days of dysuria, fever
- Diagnosed with UTI
- She took antibiotics for a sinusitis 5 months ago

- Are you concerned about antimicrobial resistance?
Independent risk factors of ESBL positive community acquired urinary tract infection

<table>
<thead>
<tr>
<th>Variable</th>
<th>Level</th>
<th>Adjusted OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Travelling to Asia, Middle East or Africa&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- During the past 6 weeks</td>
<td>yes/no</td>
<td>21</td>
<td>4.5–97</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>- Between the previous 6 weeks to 24 months</td>
<td>yes/no</td>
<td>2.3</td>
<td>1.2–4.4</td>
<td>0.017</td>
</tr>
<tr>
<td>Use of fluoroquinolones the past 90 days</td>
<td>yes/no</td>
<td>16</td>
<td>3.2–80</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Use of β-lactams except mecillinam in the past 90 days</td>
<td>yes/no</td>
<td>5.0</td>
<td>2.1–12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>yes/no</td>
<td>3.2</td>
<td>1.0–11</td>
<td>0.051</td>
</tr>
<tr>
<td>Recreational freshwater swim past year</td>
<td>yes/no</td>
<td>2.1</td>
<td>1.0–4.3</td>
<td>0.040</td>
</tr>
<tr>
<td>Age</td>
<td>5 year increase</td>
<td>0.89</td>
<td>0.82–0.97</td>
<td>0.014</td>
</tr>
<tr>
<td>Number of fish meals per week</td>
<td>1 meal increase</td>
<td>0.68</td>
<td>0.51–0.90</td>
<td>0.008</td>
</tr>
</tbody>
</table>

<sup>a</sup>Only trips lasting ≥24 hours are included.
doi:10.1371/journal.pone.0069581.t004

Fecal Colonization ESBLs Risk Factors Systematic Review Implications For Stewardship

66 studies on 28,909 healthy subjects
Pooled prevalence ESBL class A colonization 14% → 69% CTX-M
Antibiotic used previous 4 or 12 months (RR=1.63 RR=1.58)
International travel RR=4.06

Fecal carriage of extended spectrum β- lactamase producing E. coli and K. pneumoniae after urinary tract infection – A three year prospective cohort study

61% - 39% at (4 and 13 months) → 15% > 3 years
Implications for Infection control and stewardship

# Treatment Options: Severe Infections ESBL/AMP-C Producers

- Microbiological activity (MIC), Toxicity and Source

<table>
<thead>
<tr>
<th>Source</th>
<th>1&lt;sup&gt;st&lt;/sup&gt;</th>
<th>2&lt;sup&gt;nd&lt;/sup&gt;</th>
<th>3&lt;sup&gt;rd&lt;/sup&gt;</th>
<th>4&lt;sup&gt;th&lt;/sup&gt;</th>
<th>5&lt;sup&gt;th&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respiratory</strong></td>
<td>Carbapenem</td>
<td>Colistin</td>
<td>Tigecycline</td>
<td>Fosfo</td>
<td>Aminoglyc</td>
</tr>
<tr>
<td><strong>Intra-abdominal</strong></td>
<td>Carbapenem</td>
<td>Tigecycline</td>
<td>Colistin</td>
<td>Fosfo</td>
<td>Aminoglyc</td>
</tr>
<tr>
<td><strong>Urinary</strong></td>
<td>Aminoglyc</td>
<td>Fosfo</td>
<td>Carbapenem</td>
<td>Colistin</td>
<td>Tigecycline</td>
</tr>
<tr>
<td><strong>Catheter/Primary</strong></td>
<td>Carbapenem</td>
<td>Colistin</td>
<td>Fosfo</td>
<td>Aminoglyc</td>
<td>Tigecycline</td>
</tr>
</tbody>
</table>

Case Scenario

64 y/o female with Hx. DM-2 developed *Clostridium difficile* colitis with toxic megacolon requiring total colectomy, TPN dependent short bowel syndrome

**Intestinal transplantation**

No MDROs identified on rectal and nasal surveillance cultures at the time of the transplant

**POD 12, bacteremic 4/4 GNR**

ELAP for evacuation of intra-abdominal hematoma, pancreatitis with peripancreatic collection
All central lines are changed
## Blood Cultures

<table>
<thead>
<tr>
<th>Klebsiella pneumoniae</th>
<th>MIC Interp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>Resistant</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>Resistant</td>
</tr>
<tr>
<td>Cefepime</td>
<td>Resistant</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>Resistant</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>Resistant</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>Resistant</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>Resistant</td>
</tr>
<tr>
<td>Meropenem</td>
<td>Resistant</td>
</tr>
<tr>
<td>Piperacillin/Tazobactam</td>
<td>Resistant</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>Resistant</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>Resistant</td>
</tr>
<tr>
<td>Trimethoprim/Sulfa</td>
<td>Resistant</td>
</tr>
</tbody>
</table>

KLEBSIELLA PNEUMONIAE CARBAPENAMASE PRODUCER
COLISTIN E TEST = 12uG/ML
CEFTAZIDIME AVIBACTAM = 25 mm
How would you treat our patient?

a. Colistin
b. Carbapenem and colistin
c. Dual carbapenems +/- colistin
d. Tigecycline plus colistin and a carbapenem
e. Try all of the above...if everything fails.. refer the patient to Miami!
Supporting evidence for the treatment of CPE

• Clinical data in humans (best available evidence)
  – NO randomized clinical trials
  – Case series
  – Observational (prospective/retrospective)
Clinical Data in Humans: CPE Treatment

Clinical Failure (%)

Combination Therapy for Treatment of Infections with Gram-Negative Bacteria

Pranita D. Tamma, Sara E. Cosgrove, and Lisa L. Maragakis

The Johns Hopkins Medical Institutions, Department of Medicine, Division of Pediatric Infectious Diseases, Baltimore, Maryland, USA, and The Johns Hopkins Medical Institutions, Department of Medicine, Division of Infectious Diseases, Baltimore, Maryland, USA

- **Mild infections** and fully active drugs (suitable for the source of infection) -> **Monotherapy**

- **Severe infections** -> Some cases **Combination therapy**
  - at least 2 active agents considering MIC and source
  - streamline based on susceptibilities
  - reassess clinical response
When and how should carbapenems be used?

• For infections caused by CPE, if combination therapy is indicated, a regimen with:
  \[\text{carbapenem}^* + (1 \text{ or } 2 \text{ active agents}^{**})\]

• Use extended infusion

\begin{itemize}
  \item \text{* recommended if the carbapenem MIC is } \leq 8 \text{ mg/L;}
  \item \text{** colistin, tigecycline, aminoglycosides or fosfomycin,}
\end{itemize}
Colistin and Polymixin

- As part of the empirical treatment (severe infections) CPE is suspected (i.e. outbreaks/colonization) and MDR Pseudomonas or Acinetobacter

- Dosing in critically ill patients (septic shock/severe sepsis):
  1. Loading dose: 9 MU
  2. Maintenance dose: 4.5 MU /BID if Cl$\text{_{creat}} > 50$ mL/min

- Loading dose in non-critically ill patients? - Not enough evidence
Fosfomycin as an alternative therapeutic option for treatment of infections caused by multi-resistant Gram-negative bacteria

**PROS**
- **Broad spectrum** including MDR GN and Gram positives
- **High bioavailability** (high concentrations in serum)
- **Good distribution**
  - soft tissues, lungs, bones, heart valves, urinary bladder, prostate and seminal vesicles, clinically high levels in (CSF)
- 95% urinary excretion unchanged/24 hours

**CONS**
- rapid development of resistance
- serious infections not as monotherapy
- US→ only ORAL not IV
Tigecycline

- Poor serum concentration
- Avoid monotherapy when possible
  - Selected patients with mild cIAI and cSSSI infection with other few adequate alternative options

- Considered as part of a combo (non UTI) when MIC is ≤1

- Higher dose 100 mg BID or TID should be considered for septic shock, VAP, ECMO or Enterobacteriaceae with MIC ≥1mg/L (adverse events should be carefully monitored)
Dual-carbapenem therapy for CPE
Dual Carbapenems: Does it work?

**PK/PD in vitro**

**In vivo model**

## Dual Carbapenems Case Reports

<table>
<thead>
<tr>
<th>Reference</th>
<th>Underlying disease(s)</th>
<th>Drugs and MICs (µg/ml) forever</th>
<th>Days of Treatment &amp; Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oliva et al. Italy</td>
<td>Hip joint replacement Blood, CVC</td>
<td>ERT (1 g q24h i.v.) + MER (2 g q8h i.v., 4-h infusion) + CST</td>
<td>21-d (7 d CST)</td>
</tr>
<tr>
<td>Chua et al. Singapore</td>
<td>Necrotizing pancreatitis Sputum</td>
<td>ERT (1 g q24h i.v.) + DOR (1 g q8h i.v., 4-h ) + POL-B (q12h i.v.) + CST (inhaled)</td>
<td>12-d . Cleared after 1-day Death heart failure 30 d</td>
</tr>
<tr>
<td>ADC and HCC</td>
<td>Blood, sputum, abdominal wound</td>
<td>ERT (0.5 g q24h i.v.) + DOR (0.5 g q8h i.v., + POL-B IV</td>
<td>10-d Relapse day 10 bacteremia</td>
</tr>
<tr>
<td>Camargo et al., United States</td>
<td>Intestinal transplant Abdominal wound, blood, urine, CVC</td>
<td>ERT 1 g q24h i.v. + MER 1 g q12h + CST IV q12h</td>
<td>breakthrough bacteremia after 12 days of treatment. CST resistance (MIC, 12)</td>
</tr>
</tbody>
</table>

Back to our KPC Case:

Successful Treatment of Carbapenemase-Producing Pandrug-Resistant Klebsiella pneumoniae Bacteremia

Jose F. Camargo, a Jacques Simkins, a Thiago Beduschi, b Akin Tekin, b Laura Aragon, c Armando Pérez-Cardona, d Clara E. Prado, e Michele I. Morris, a Lilian M. Abbo a

Rafael Cantón (Commentator) f g

My nightmare cases
The Friday Consult

- 35 y/o Turkish female with Gardner Syndrome (abdominal desmoid tumors)

- Dx in 2004 – multiple bowel resections/ short gut syndrome + kidney invasion (stent and nephrostomy tubes bilaterally)

- Hospitalized for multivisceral (bowel + kidney) transplant work-up

- Back pain and purulent discharge from right nephrostomy tubes

*Desmoid tumors are among the rarest of tumors—they occur in only 2–4 people per million per year in the United States. Benign histologic appearance, lack ability to metastasize BUT locally invasive, aggressively and repeatedly recur
**Urine culture: *Klebsiella pneumoniae***

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>MIC (μg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>&gt;=64</td>
</tr>
<tr>
<td>Amp/Sul</td>
<td>&gt;=32</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>&gt;=64</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>&gt;=64</td>
</tr>
<tr>
<td>Cefepime</td>
<td>&gt;=64</td>
</tr>
<tr>
<td>Cefoxitin</td>
<td>&gt;=64</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>&gt;=64</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>&gt;=64</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>&gt;=16</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>&gt;=8</td>
</tr>
<tr>
<td>Meropenem</td>
<td>&gt;=16</td>
</tr>
<tr>
<td>Pip-Tazo</td>
<td>&gt;=128</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>&gt;=16</td>
</tr>
<tr>
<td>TMP-SMX</td>
<td>&gt;=320</td>
</tr>
</tbody>
</table>
How would you treat our patient?

a) Dual carbapenems (ertapenem + M/I/D)
b) Tigecycline
c) Fosfomycin
d) Colistin
e) Aminoglycoside
f) Contact precautions and prayers
g) All of the above
E Test

CZA MIC > 256

AZT MIC > 256

TGC MIC 1
What is unusual?

- Carbapenemase Producer - NOT a KPC
- Two different cell morphologies
- Both contain NDM, OXA-48 and a group 1 CTX-M
When Does 2 Plus 2 Equal 5?

Current testing methods in microbiology are:
- simple valid, reliable and reproducible worldwide

Don’t consider

Dynamic Situations

Predictors of clinical outcomes
- immune status of the patient
- site of infection
- drug interactions
- up to 50% patients with septic shock (> 1 antibiotic)

Doern C. A review of Antimicrobial Synergy Testing. JCM. Dec 2014 52, 12 (4124-4128)
In vitro Synergy Testing: 4 fold decrease in MIC

TAZ-AVI + AZT
Synergy

MIC of AZT from >256 to 24 ug/ml
MIC of CZA from >256 to 12 ug/ml
Other Combos- not better than TAZ-AVI+ AZT

- Meropenem 6mm
- Taz/Avi + Azt + Polymyxin B 29mm
- Rifampicin 6mm
- Taz/Avi + Azt + Mero 28mm
- Polymixin B 15mm
- Taz/Avi + Azt + Rif 28mm

EUCAST resistance breakpoint for Enterobacteriaceae is 19 mm for Taz (ceftazidime), 21 mm for Azt (aztreonam) and 16 mm for meropenem;

Courtesey: Rossana Rosa, M.D. (in press)
Why Aztreonam and TAZ-AVI for NDMs?

- **AZT only beta-lactam inherently impervious to MBL**
  - Can be hydrolized by other ESBLs (CTX-M, CMY, etc)

- **Avibactam: diazabicyclooctanes (DBOs)**
  - No β-lactam core but capable to acylate β-lactamase targets
  - It efficiently restores the *in vitro* activities of cephalosporins against Ambler **class A, class C, and some class D (e.g., OXA-48)** β-lactamases, **but not MBLs and Acinetobacter OXA carbapenemases.**

Remember Key points
Combination Therapy and Synergy

• Theory → different B-lactams have different affinities for PBPs and combos might be synergistic or antagonistic

• Synergy → 4 fold reduction in the MIC of both of the tested antibiotics

• Cefoxitin -> b-lactamase inducer → ANTAGONISTIC

• *In vitro* results might not correlate with *in vivo* efficacy
New antibiotics and antimicrobial combination therapy for the treatment of gram-negative bacterial infections

Matteo Bassetti and Elda Righi


Polishing the tarnished silver bullet: the quest for new antibiotics

# New Cephalosporins

<table>
<thead>
<tr>
<th>Drug</th>
<th>In vitro activity</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftolozane/Tazobactam</td>
<td>Ceftazidime + side chain</td>
<td>• It is NOT active against (class B) carbapenemases</td>
</tr>
<tr>
<td></td>
<td>• <strong>Enhanced antipseudomonal activity</strong> (PBP mutations and efflux pumps): x8 more active than doripenem</td>
<td>• Phase 3: superior to levofloxacin for cUTI and non-inferior to meropenem for cIAI</td>
</tr>
<tr>
<td></td>
<td>• ESBL, AmpC</td>
<td>• FDA-approved in US Dec 2014</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• <strong>We have cases already developing resistance (CPEs and Pseudomonas)</strong></td>
</tr>
</tbody>
</table>

## New Beta-Lactamase Inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>In vitro activity</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Ceftazidime + Avibactam (CAZ/AVI) | Ceftazidime Plus: ESBL, AmpC, KPC, OXA-48 | • Potent against CREs/ CPEs  
• Non inferiority cUTI & cIAI  
• **Not active against MBL**  
• FDA approved 2015  
• Availability & development of resistance |
| Ceftaroline + Avibactam | Ceftriaxone Plus MRSA, ESBL, AmpC, KPC, KPC, OXA-48? | • Not active non-fermenters (A. baumannii and P. aeruginosa)  
• **Phase 3 trials** |
| Aztreonam + Avibactam | Aztreonam Plus KPC, Class D (OXA-48) | • Hydrolyzed by ESBL (class A) and AmpC  
• **Phase 2/3** |
New BLI

- Limited activity against MBL (class B carbapenemases)

<table>
<thead>
<tr>
<th>Drug</th>
<th>In vitro activity</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Imipenem</strong> + <strong>Relebactam</strong></td>
<td>Imipenem Plus:</td>
<td>Reains inactive against MBL</td>
</tr>
<tr>
<td></td>
<td>• ESBL (both)</td>
<td><strong>Phase 3</strong> trials cUTI and cIAI and VAP ongoing</td>
</tr>
<tr>
<td></td>
<td>• AmpC (both)</td>
<td>Can’t get compassionate use yet and some organisms already R in vitro</td>
</tr>
<tr>
<td></td>
<td>• KPC</td>
<td>(KPC)</td>
</tr>
<tr>
<td></td>
<td>• OXA-48</td>
<td></td>
</tr>
<tr>
<td><strong>Meropenem</strong> + <strong>RX7009 (anti-KPC)</strong></td>
<td>Meropenem Plus</td>
<td>Phase 3 clinical trials:</td>
</tr>
<tr>
<td></td>
<td>• KPC</td>
<td>- cUTI</td>
</tr>
<tr>
<td></td>
<td>• OXA-48</td>
<td>- Severe infections (VAP, HAP, BSI) caused by CRE</td>
</tr>
</tbody>
</table>
# New aminoglycosides

<table>
<thead>
<tr>
<th>Drug</th>
<th>In vitro activity</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plazomicin</td>
<td>- Enhanced activity against GNR Active against ESBL, AmpC, KPC, OXA, VIM</td>
<td>- Phase 3 clinical trial: BSI/VAP caused by CPE</td>
</tr>
<tr>
<td></td>
<td>- Non active against NDM (some)</td>
<td></td>
</tr>
</tbody>
</table>

# New tetracyclines

<table>
<thead>
<tr>
<th>Everacycline</th>
<th>Enhanced activity as compared with tigecycline</th>
<th>Phase 2 study (cIAI)</th>
</tr>
</thead>
</table>

Future inhaled options

Fosfomycin/Tobramycin for Inhalation in Patients with Cystic Fibrosis with Pseudomonas Airway Infection

Bruce C. Trapnell¹,², Susanna A. McColley³, Dana G. Kissner⁴, Mark W. Rolfe⁵, Jonathan M. Rosen⁶, Matthew McKeveitt⁷, Lisa Moorehead⁷, A. Bruce Montgomery⁷, and David E. Geller⁸, for the Phase 2 FTI Study Group∗


March 13, 2017

CURx PHARMA→ Phase 3 studies in CF FTI to be submitted to FDA
http://curxpharma.com/fti.html
More to come...

- Roche / Discuva
  24 February 2017
  €1.8M (£1.5M) grant from Innovate UK
  Roche €165M ($175M) per product

  “targeting Gram-negative pathogenic bacteria responsible for antibiotic-resistant infections”
Current Nightmare: XDR Pseudomonas

- 17 year old female with history of Cystic Fibrosis
- CF exacerbation
- CXR: increased bilateral infiltrates

- Current home antibiotics: inhaled colistin, inhaled aztreonam
- Has history of anaphylaxis with all cephalosporins

- Sputum: MDR Pseudomonas
  - R cephalosporins, aztreonam and carbapenems
  - S colistin → failed clinically
  - S tobramycin and ceftolozane/tazobactam
Case Continues

• Admitted to pediatric ICU for desensitization to ceftolozane/tazobactam

• Tolerated treatment well in combination with IV tobramycin
• Discharged home

• 5 weeks into treatment the patient is readmitted with fever, GI symptoms and another CF exacerbation productive cough...

• Sputum culture
BAD BUGS.. No drugs

Ceftolozane/tazo = R

Fosfomycin=S

Ceftaz/avi = zone of inhibition with some colony growth within
STRONGER TOGETHER
Our OFF Label Management
XDR Pseudomonas Pneumonia

- IV ceftazidime/ avibactam + aztreonam + Oral fosfomycin 3 g every 6 h
- Weekly surveillance sputum cultures

- **Alternatives?**
  - Trying to get IV formulation in US
  - Compassionate use of plazomicin
  - Imipenem/ relebactam (not available compassionate use)
  - Hospice
Fighting MDROs with antibiotics...
.. maybe we should try to think out of the box?
What if we could fight MDR bacteria with a healthier microbiome?
Fecal Microbiota Transplantation and Successful Resolution of Multidrug-Resistant-Organism Colonization

Nancy F. Crum-Cianflone, a,b Eva Sullivan, c Gonzalo Ballon-Landa a
Infectious Disease Division, Scripps Mercy Hospital, San Diego, California, USA a; Infectious Disease Division, Naval Medical Center San Diego, San Diego, California, USA b; Pharmacy Department, Scripps Mercy Hospital, San Diego, California, USA c

We report a case in which fecal microbiota transplantation (FMT) utilized for relapsing Clostridium difficile colitis successfully eradicated colonization with several multidrug-resistant organisms (MDROs). FMT may have an additive benefit of reducing MDRO carriage and should be further investigated as a potential measure to eradicate additional potentially virulent organisms beyond C. difficile.
Is Fecal Microbiota Transplantation an option to eradicate high drug-resistant enteric bacteria carriage?

- French multicenter study
- 8 patients (6 CRE and 2 VRE) with GI colonization confirmed by rectal swabs
- Single FMT enema in immunocompetent patients
- Eradication of CRE and VRE carriage in 2/8 and 3/8 after 1 and 3 months
- FMT seems safe with an impact in MDRO decolonization

Antibiotic use **must be tailored** according to local resistance, epidemiological history source of infection, mechanism of resistance and previous antibiotic exposures.

Depending on the patient, the risk of infection, spectrum of organisms and outcomes will vary.
Take Home Points

- Get a good antibiotic history, travel and epidemiology
- Understand the mechanisms of resistance and tailor therapy
- Combination therapy works in XDR– choose them wisely
- Repopulating the microbiome to eradicate MDROs needs further studies.. We are getting there!!
- Call your colleagues for help!
Challenges In Antibiotic Resistance
Gram Negative Bacteria

https://www.futurelearn.com/courses/gram-negative-bacteria/
Thank you