CME-accredited Webinar: Managing Complicated Intra-abdominal Infections (cIAI) in Adults

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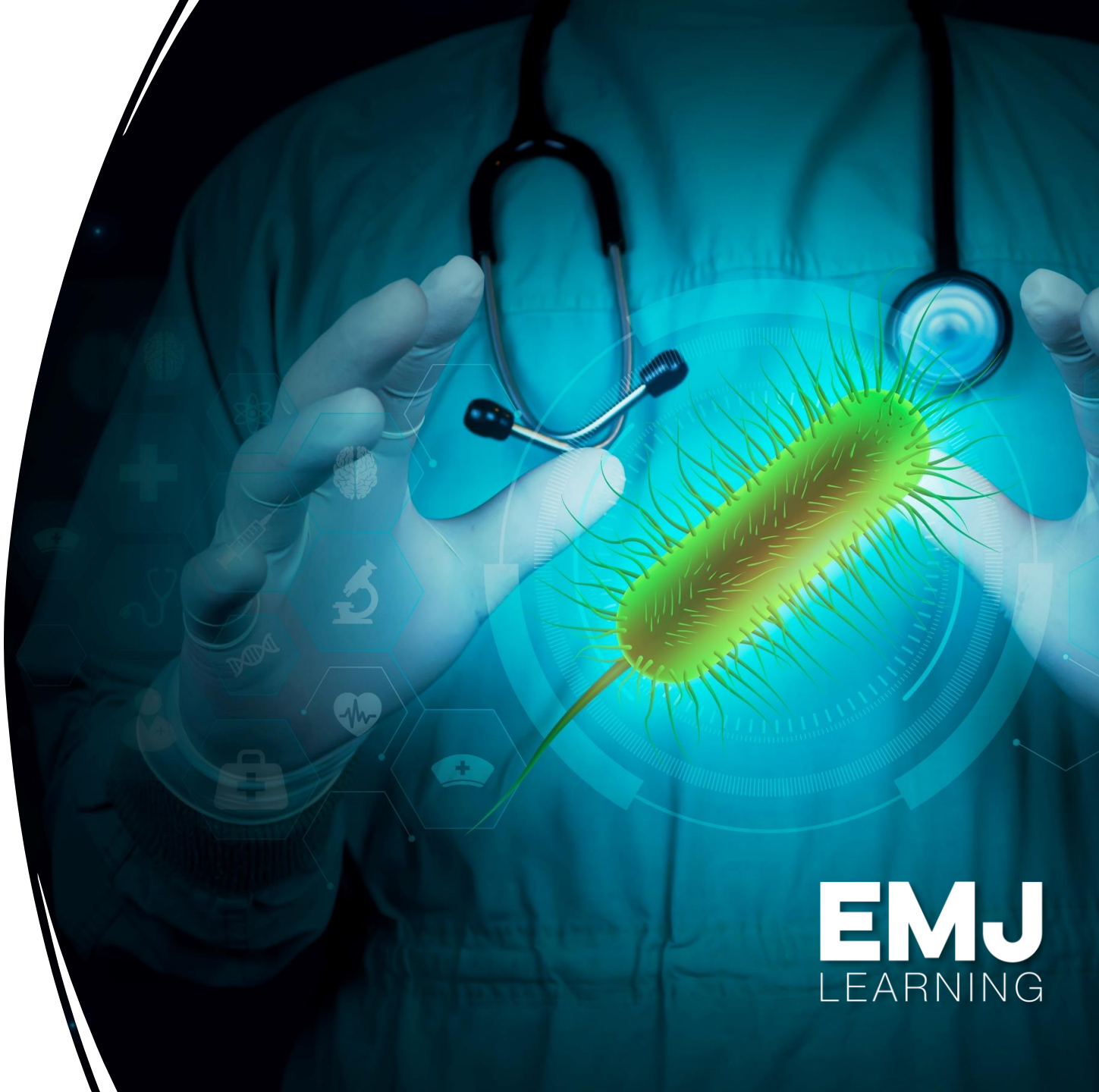
This webinar is intended for Healthcare Professionals and is supported by an educational grant from Viatris

Overview

- Describe complicated intra-abdominal infections (cIAI)
- Explain the safety and efficacy of treatments for cIAI
- Explore the use of alternative antibiotics and discuss the current trends in various antibiotic classes for cIAI.
- Define crucial aspects of antibiotic stewardship.
- Future strategies for the management and treatment of cIAI.



Introduction to Complicated Intra-abdominal Infections (cIAI)

The Burden of cIAI

Most frequent global gastrointestinal emergency.[1-3]

- Local or systemic infections due to gastrointestinal tract perforation or leak from necrotic gut wall.[1-3]

Urgent need for clinical management to address difficult-to-treat infections. [4]

- Patient health status, severity and diversity of infection, and likelihood of MDR pathogens pose a clinical challenge.[5]

cIAI: Complicated intra-abdominal infections; MDR: multidrug-resistant

1. Rodgers P et al. J Infect Dev Ctries.2022; 16(2): 305-13. **2.** Silva-Nunes J, and Cardoso T. BMC Infect Dis. 2019;19(1):980. **3.** Montravers P et al. Expert Rev Anti-Infective Thera. 2019; 17(11):851-63. **4.** Ferrer R et al. Revista Espanola de Quimioterapia. 2021; 34(6): 639-650. **5.** Mancuso G et al. Pathogens. 2021;10(10):1310.

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Principles of Clinical Diagnosis

Adequate detection and treatment are essential to minimise cIAIs.

Effective treatment and management is reliant on timely and early diagnosis so that the most appropriate intervention and treatment may be selected.

1. Sartelli M et al. WSES/GAIS/SIS-E/WSIS/AAST global clinical pathways for patients with intra-abdominal infections. World J Emerg Surg. 2021;16(1):49. 2. Mazuski JE et al. The Surgical Infection Society Revised Guidelines on the Management of Intra-Abdominal Infection. Surg Infect (Larchmt). 2017;18(1):1-76.

Principles of cIAI Management

Patient with cIAI

Source Control
- as soon as possible in critically ill patients

Empiric Antibiotic Therapy
Based on: - Local epidemiology;
- Individual risk factors for MDR pathogens;
- Clinical condition of the patient

Fluid Support
- if sepsis hypotension and septic shock

Microbiologic Evaluation / Culture
- identify pathogen(s); determine susceptibility
(always in those at risk of MDR and in critically ill)

Re-evaluate Antibiotic Therapy
- To expand or de-escalate antibiotic regimen

Vasopressors
- if hypotension persists following fluid loading

Re-intervention
- If ongoing infection

cIAI: complicated intra-abdominal infections; MDR: multidrug-resistant

Adapted from: **1.** Coccolini F et al., Source control in emergency general surgery: WSES, GAIS, SIS-E, SIS-A guidelines. World J Emerg Surg. 2023;18(1):41. **2.** Sartelli M et al. WSES/GAIS/SIS-E/WSIS/AAST global clinical pathways for patients with intra-abdominal infections. World J Emerg Surg. 2021;16(1):49. **3.** Mazuski JE et al. The Surgical Infection Society Revised Guidelines on the Management of Intra-Abdominal Infection. Surg Infect (Larchmt). 2017;18(1):1-76.

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Source Control

Microbiologic Evaluation

- Obtain cultures of peritoneal fluid or infected tissue from the site of infection and susceptibility results in higher-risk patients with CA-IAI and in patients with HA-IAI to identify potential resistant or opportunistic pathogens
- Consider obtaining cultures in all patients with IAI for epidemiologic purposes if adequate resources are available to guide empiric antimicrobial therapy
- Blood cultures should be performed before the administration of antibiotic agents in critically ill patients.

CA-IAI: community-acquired intra-abdominal infection; HA-IAI: healthcare or associated intra-abdominal infection

1. Sartelli M et al. WSES/GAIS/SIS-E/WSIS/AAST global clinical pathways for patients with intra-abdominal infections. World J Emerg Surg. 2021;16(1):49. **2.** Mazuski JE et al. The Surgical Infection Society Revised Guidelines on the Management of Intra-Abdominal Infection. Surg Infect (Larchmt). 2017;18(1):1-76.

Secondary Peritonitis

Common aetiologies include aerobic and anaerobic gram-negative rods (*Bacteroides* spp., *E. coli, Klebsiella* spp.) and gram-positive flora (*Clostridium* spp., *Enterococcus* spp., *Bifidobacterium* spp., *Peptostreptococcus* spp.).

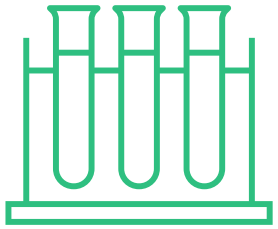
If typhlitis is suspected, *C. difficile* toxin testing, stool cultures for enteric pathogens, and blood cultures should be requested.

Additionally, *Clostridium septicum* should be considered in neutropenic enterocolitis.

- Infectious complications following bariatric surgery are frequently due to gram-positive cocci and yeast (*Candida* spp.)
- Multidrug-resistant organisms are of concern.

Miller M et al. A Guide to Utilization of the Microbiology Laboratory for Diagnosis of Infectious Diseases: 2018 Update by ASM/IDSA. Clin Infect Dis.2018:67(6), e1-e94.

Rapid Testing:
Evaluation of the Unyvero IAI cartridge



- 300 clinical samples
- Overall **sensitivity: 89.3% and specificity: 99.5%**
- Average time to results:
  - **↓~17 h** compared to identification (ID) results
  - **↓~41 h** compared to full antibiotic susceptibility testing (AST) results.
- Detected additional microorganisms compared with culture, in particular anaerobes, with most detections confirmed by sequencing.
  - The most frequent resistance markers detected were mecA/mecC (n = 25), aacA4 (n = 20), and $bla_{CTX\text{-}M}$ (n = 17) and carbapenemase genes (n=9).
- Further studies required to determine clinical impact which could play a role in the successful treatment of IAI.

Ciesielczuk H et al. Multicenter performance evaluation of the Unyvero IAI cartridge for detection of intra-abdominal infections. Eur J Clin Microbiol Infect Dis. 2018;37(11):2107-15.

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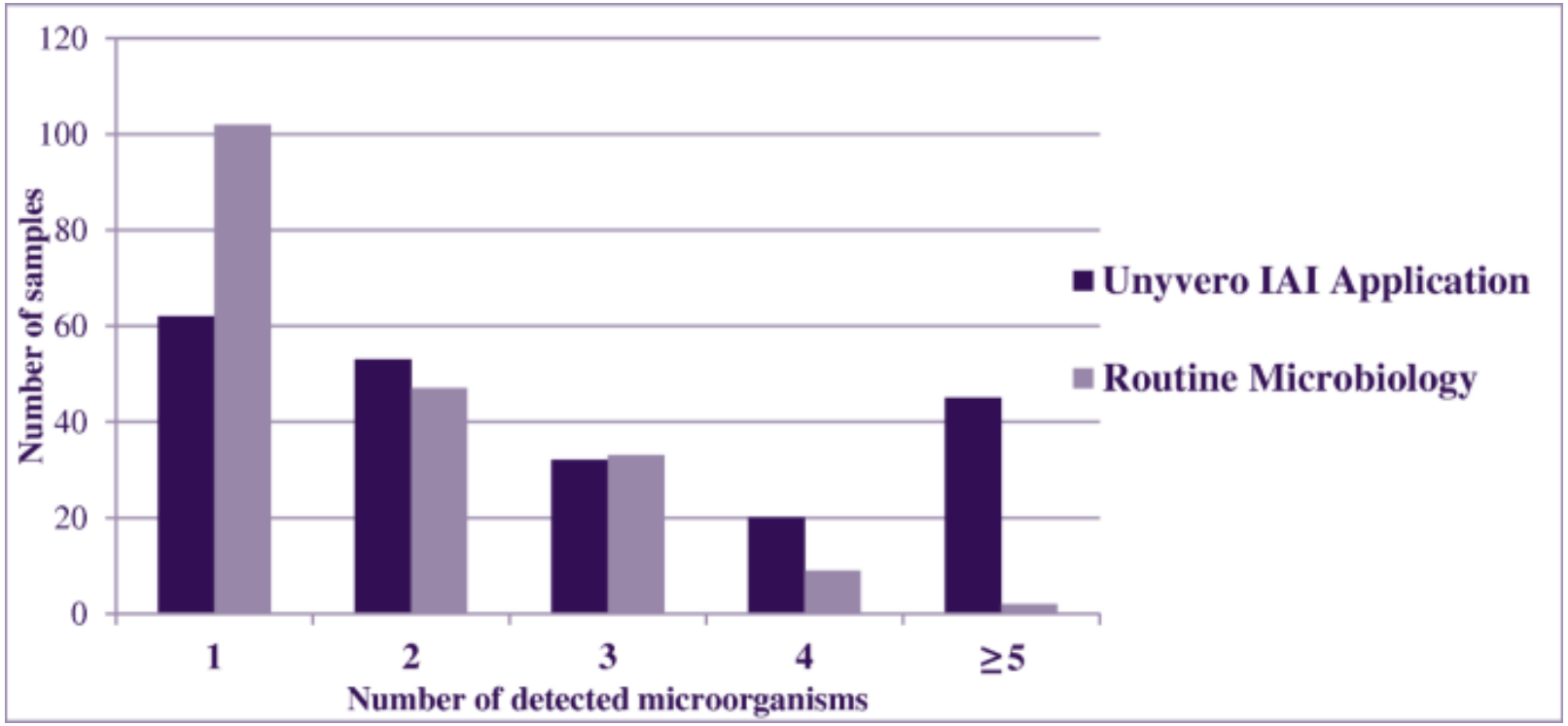
Number of IAI panel pathogen detections per sample by routine microbiology compared to Unyvero IAI Application



Results from the analyte "Universal Bacteria" were not included. To avoid double counting, *Bacteroides* spp../*Prevotella* spp.. was only counted if *Bacteroides* fragilis group was not detected and *Candida* spp.. was only counted, if *Candida albicans* or *Candida tropicalis* was not detected

Adapted from: Ciesielczuk H et al. Multicenter performance evaluation of the Unyvero IAI cartridge for detection of intra-abdominal infections. Eur J Clin Microbiol Infect Dis. 2018;37(11):2107-15.

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Detections of antibiotic resistance markers with the Unyvero IAI Application

Antibiotic substance class	Resistance marker on Unyvero IAI panel	Number of detections with IAI test	Number of detections with confirmed phenotypic resistance
3rd generation Cephalosporins	$bla_{\text{ctx-M}}$	17	14
Carbapenems	bla_{kpc}, bla_{imp}, bla_{ndm}, $bla_{\text{oxa-23}}$, $bla_{\text{oxa 24-40}}$, $bla_{\text{oxa-48}}$, $bla_{\text{oxa-58}}$, bla_{vim}	9	4
Oxacillin	*mec*A, *mec*C	25	5
Polymyxin/polypeptides	*mcr-1*	0	0
Vancomycin	*van*A, *van*B	13	6
Aminoglycosides	*aac*A4	20	16
Fosfomycin	*fos*A3	0	0
Nitroimidazole	*nim*A, *nim*B	3	0
Fluoroquinolones	*qnr*A, *qnr*B, *qnr*S	18	10
Tetracylines	*tet*A	15	8

Adapted from: Ciesielczuk H et al. Multicenter performance evaluation of the Unyvero IAI cartridge for detection of intra-abdominal infections. Eur J Clin Microbiol Infect Dis. 2018;37(11):2107-15.

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Empiric Antibiotic Therapy

Principles of Antibiotic Therapy

- Inappropriate antibiotic use associated with antimicrobial resistance.
- WSES 2023 - antibiotics should only be indicated in cases of cIAIs.
- Short-course antibiotic therapy after adequate source control is a reasonable option.
- With ongoing infection, an individualised approach should be mandatory and the patient's inflammatory response should be monitored regularly.
- Use local antibiogram data for choosing optimal antibiotics in the target population

WSES: World Society of Emergency Surgery

1. Coccolini F et al., Source control in emergency general surgery: WSES, GAIS, SIS-E, SIS-A guidelines. World J Emerg Surg. 2023;18(1):41. **2.** Sartelli M et al. WSES/GAIS/SIS-E/WSIS/AAST global clinical pathways for patients with intra-abdominal infections. World J Emerg Surg. 2021;16(1):49. **3**. Mazuski JE et al. The Surgical Infection Society Revised Guidelines on the Management of Intra-Abdominal Infection. Surg Infect (Larchmt). 2017;18(1):1-76.

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Empiric Antibiotic Therapy

Include agents with activity against aerobic Gram-negative bacteria (e.g., Enterobacteriaceae), aerobic streptococci, and obligate enteric anaerobic organisms found in the gastrointestinal tract,

- **Tigecycline and eravacycline** are viable treatment options, due to their favourable *in vitro* activity against anaerobic organisms, enterococci, several ESBL-producing and in association carbapenemase-producing Enterobacteriaceae, *A. baumannii,* and *Stenotrophomonas maltophilia*
- **Ceftolozone/tazobactam and ceftazidime/avibactam** have been approved for the treatment of cIAI (in combination with metronidazole) including infection by Gram-negative bacteria, though their role as empirical therapy remains to be defined.
- **Ceftolozane/tazobactam** is valuable for treating infections caused by multidrug-resistant Gram-negative bacteria in order to preserve carbapenems (it is active against ESBL but not against carbapenemases).

ESBL: extended-spectrum beta-lactamases;

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Multiple Regimens

- cIAIs may be managed by either single or multiple antibiotic regimens.
- **Beta-lactam/beta-lactamase inhibitor** combinations, including, **amoxicillin/clavulanate**, **ticarcillin/clavulanate**, **piperacillin/tazobactam**, have an *in vitro* activity against Gram-positive, Gram-negative and anaerobic bacteria.
- Broad-spectrum activity of **piperacillin/tazobactam**, including anti-pseudomonal and anaerobic coverage, still make it an attractive option in the management of severe IAIs.

1. Sartelli M et al. WSES/GAIS/SIS-E/WSIS/AAST global clinical pathways for patients with intra-abdominal infections. World J Emerg Surg. 2021;16(1):49. **2.** Mazuski JE et al. The Surgical Infection Society Revised Guidelines on the Management of Intra-Abdominal Infection. Surg Infect (Larchmt). 2017;18(1):1-76.

Experience with Piperacillin/ tazobactam continuous infusion

All Patients	Number (N)
Total N. Patients	382
Sex: Male	228
Sex: Female	154

Activity against ESBL, inoculum effect: High dose, continuous infusion

Parameters	Mean	Std Dev.	Median
Age (years)	70	15	72
Weight (Kg)	75	18	75
Height (m)	1.70	0.10	1.70
BMI (Kg/msq)	25.99	5.53	25.39
Creatinine (mg/dL)	1.50	1.29	1.05
eGFR (mL/min)	70.32	49.64	61.23
Mean Initial Dose (g)	15.16	4.50	18.00

BMI: body mass index; ESBL: extended-spectrum beta-lactamases ; eGFR: estimated glomerular filtration rate.
Sartelli M et al. WSES/GAIS/SIS-E/WSIS/AAST global clinical pathways for patients with intra-abdominal infections. World J Emerg Surg. 2021;16(1):49. From: Tascini unpublished data

Piperacillin (mg/L)	N.	Mean
All samples		
	701	82,71
Sex		
M	423	77,19
F	278	91,11
Age groups		
20-39	33	49,40
40-49	49	63,32
50-59	99	69,98
60-69	134	84,16
70-79	182	90,66
>=80	205	93,17
eGFR		
<20	67	101,91
20-39	125	111,42
40-89	315	82,85
90-119	109	62,91
>=120	85	50,20
BMI		
Underweight: <18	29	103,25
Healthy weight: 18 – 24.9	288	80,19
Overweight: 25 -29.9	242	85,73
Obese: > 30	142	78,47

Cephalosporin-based regimens and cephalosporin–β-lactamase inhibitor combinations

- **Cefepime plus metronidazole**
- **Ceftolozane/tazobactam:** Valuable for treating infections caused by MDR Gram-negative bacteria in order to preserve carbapenems (it is active against ESBL but not against carbapenemases).
- **Ceftazidime/avibactam:** demonstrated consistent activity against KPC and OXA-48-producing organisms (it has no activity against metallo-beta-lactamase-producing bacteria)
- **Aztreonam-based regimens:** aztreonam plus metronidazole plus vancomycin, but reserve this regimen primarily for higher-risk patients, particularly those with serious β-lactam allergies

→ Activity against AmpC, if MIC <= 2 mg/L
empiric use difficult to apply

Suspected or proven to be infected with resistant strains of *Pseudomonas aeruginosa*, for which other agents are not suitable

→ TOL/TAZ has activity against *E. coli* ESBL Klebsiella ESBL depends on the MIC

→ AmpC Enterobacterales depend on the MIC

→ Aztreonam alone might be weak although protected by avibactam

ESBL: extended-spectrum beta-lactamases: KPC: *Klebsiella Pneumonia* TOL/TAZ: Ceftolozane-tazobactam; MIC: minimum inhibitory concentration; MDR: multidrug resistant **1.** Sartelli M et al. WSES/GAIS/SIS-E/WSIS/AAST global clinical pathways for patients with intra-abdominal infections. World J Emerg Surg. 2021;16(1):49. **2.** Mazuski JE et al. The Surgical Infection Society Revised Guidelines on the Management of Intra-Abdominal Infection. Surg Infect (Larchmt). 2017;18(1):1-76.

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Carpanems

- For decades, carbapenems have been the antibiotics of first choice for ESBLs.
- The best option for targeting ESBLs (although lacking coverage of *P. aeruginosa*) is **ertapenem**, a once-daily administered carbapenem that otherwise shares the activity of imipenem, meropenem, and doripenem against most species, including ESBL producing pathogens.
- **Imipenem/cilastatin**, **meropenem**, and **doripenem** provide coverage for Gram-negative non-fermenting bacteria (e.g. *Pseudomonas aeruginosa* and *Acinetobacter baumannii*).
- The use of carbapenems should be limited to preserve the activity of this class of antibiotics because of the concern of emerging carbapenem resistance

ESBL: extended-spectrum beta-lactamases;

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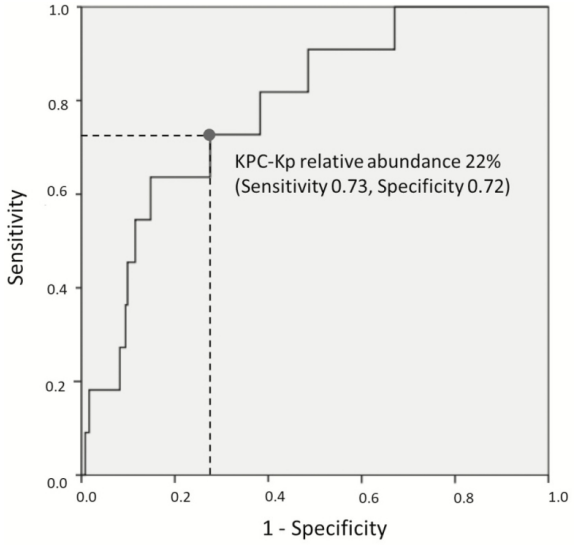
Carpanems - **Risk of selection of CRE**



ROC curve analysis of the relationship between relative abundance of KPC-Kp and subsequent KPC-Kp bloodstream infection.

Risk Factors Associated With ≥22% Relative Abundance of KPC-Kp in the Gut Microbiota

Clinical Predictor	Hazard Ratio (95% Confidence Interval)	*P* Value
Age, years	0.99 (0.97–1.02)	.549
Charlson comorbidity index	0.90 (0.74–1.09)	.277
Any medical device use	1.05 (0.25–4.48)	.943
Mechanical ventilation	0.82 (0.39–1.71)	.588
Gastrostomy tube	0.62 (0.30–1.29)	.204
Central line	1.17 (0.55–25)	.689
Hemodialysis	0.77 (0.23–2.54)	.666
Urinary catheter	0.73 (0.34–1.55)	.409
Any antibiotic exposure	0.70 (0.24–2.07)	.519
Carbapenem	2.19 (1.06–4.55)	.036
Beta-lactam/beta-lactamase inhibitor	0.66 (0.23–1.90)	.436
Vancomycin (intravenous)	0.79 (0.38–1.66)	.537
Metronidazole	0.50 (0.12–2.12)	.351

- A relative abundance cutoff of 22% predicted KPC-Kp bacteremia with sensitivity 73%, specificity 72%, and relative risk 4.2 (P=0.01).
- Increased relative abundance of KPC-Kp was associated with KPC-Kp bacteremia.

CRE: Carbapenem-resistant Enterobacteriaceae; KPC-Kp, *Klebsiella pneumoniae* carbapenemase-producing *Klebsiella pneumoniae*; ROC: Receiver operating characteristic. Adapted from: Shimasaki T et al. Increased Relative Abundance of *Klebsiella pneumoniae* Carbapenemase-producing Klebsiella pneumoniae Within the Gut Microbiota Is Associated With Risk of Bloodstream Infection in Long-term Acute Care Hospital Patients. Clin Infect Dis. 2019;68(12):2053-9.

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Tigecycline

- Other options include **aminoglycosides**, particularly for suspected infections by Gram-negative bacteria in critically ill patients, and tigecycline especially when multidrug-resistant bacteria are suspected, although caution is advised for the latter, in the setting of bacteremia.
- **Tigecycline** and **eravacycline** are viable treatment options, especially in empiric therapy, for complicated IAIs due to their favourable *in vitro* activity against anaerobic organisms, enterococci, several ESBL-producing and in association carbapenemase-producing Enterobacteriaceae, *A. baumannii*, and *Stenotrophomonas maltophilia*

- Tigecycline alone might have low concentrations in the blood
- Septic patients treated with monotherapy might risk breakthrough bacteraemia
- Eravacycline might be an alternative option, beta-lactams sparing strategy

ESBL: extended-spectrum beta-lactamases;

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Anti-enterococcal and anti-staphylococcal agents

- In patients at high risk for infection from enterococci including immunocompromised patients or patients with recent antibiotic exposure, consider the use of **ampicillin** 2 g every 6 h if patients are not being treated with **piperacillin/tazobactam** or **imipenem/cilastatin** (active against ampicillin-susceptible enterococci) or tigecycline.

1. Sartelli M et al. WSES/GAIS/SIS-E/WSIS/AAST global clinical pathways for patients with intra-abdominal infections. World J Emerg Surg. 2021;16(1):49. **2.** Mazuski JE et al. The Surgical Infection Society Revised Guidelines on the Management of Intra-Abdominal Infection. Surg Infect (Larchmt). 2017;18(1):1-76.

High risk of gram-negative MDR strains infections

Identify patients who have received substantial previous broad-spectrum antimicrobial therapy, had prolonged hospitalisations, undergone multiple invasive interventions, or are known to have been colonised or infected with a resistant gram-negative organism at risk for infection from a resistant gram-negative pathogen.

Consult local epidemiologic data and antibiograms for assistance in selecting empiric antimicrobial therapy in patients considered at risk for infection with resistant gram-negative pathogens

1. Sartelli M et al. WSES/GAIS/SIS-E/WSIS/AAST global clinical pathways for patients with intra-abdominal infections. World J Emerg Surg. 2021;16(1):49.
2. Mazuski JE et al. The Surgical Infection Society Revised Guidelines on the Management of Intra-Abdominal Infection. Surg Infect (Larchmt). 2017;18(1):1-76.

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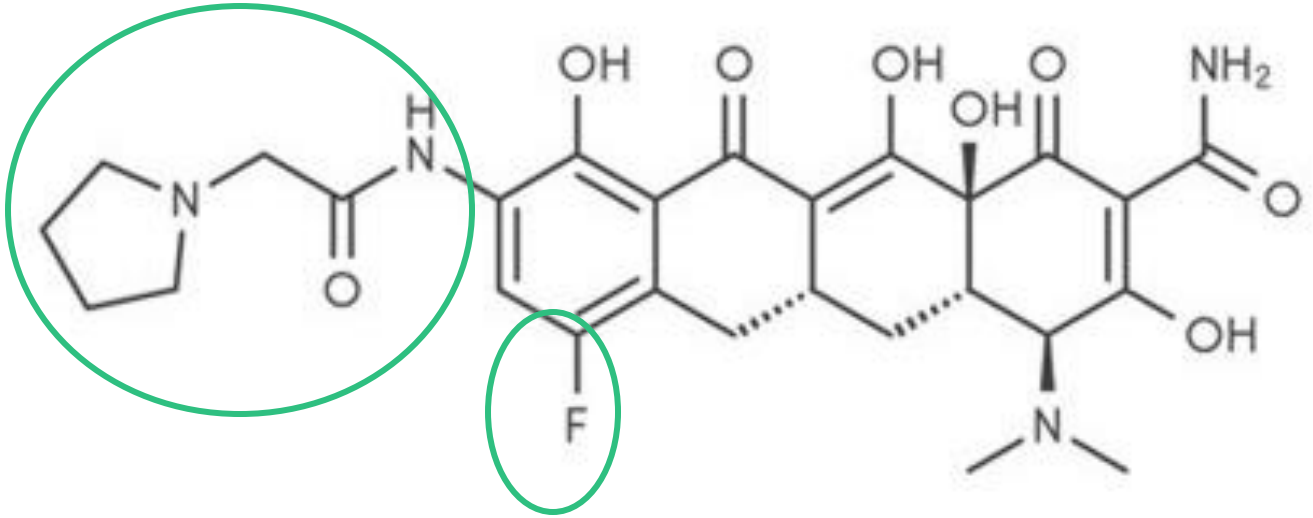
Emerging therapies for the treatment of cIAI

Tetracycline: Eravacycline



- Novel, fully-synthetic fluorocycline antibacterial for intravenous administration
- Retains activity against the most common tetracycline-specific acquired resistance mechanisms (i.e., efflux and ribosomal protection)
- Broad spectrum activity against certain Gram-negative, Gram-positive and anaerobic organisms

Approved in 2018 by USA (FDA)[1] and Europe (EMA)[2] Regulatory Agencies for the treatment of cIAI

1. US Food and Drugs Agency (FDA). Prescribing Information:. Xerava. 2018. Available at: Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/xerava. Last accessed: 21 February 2024. **2**. European Medicines Agency (EMA). Prescribing Information:. Xerava – Eravacycline. 2018. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/xerava. Last accessed: 21 February 2024

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Eravacycline: Tissue Distribution

- Rabbit models at a human dose, eravacycline concentrations were present in most tissues.
- Mean concentrations were greatest in renal cortex > liver > renal medulla > gallbladder > spleen > psoas muscle > lungs > bone marrow > pancreas > heart > vena cava > brain. Concentrations in the prostate and seminal vesicles were at relatively high concentrations
  - **Abdominal tissues**: bile > liver > gallbladder > spleen > pancreas
  - **Cardiopulmonary system**: lung > heart > vena cava > PAMs > BAL fluid
  - **Abdominal tissues**: bile > liver > gallbladder > spleen > pancreas
  - **Genitourinary system**: urine > renal cortex > renal medulla
  - **Musculoskeletal tissues**: psoas muscle > bone marrow > adipose tissue
  - **CNS Tissues/Fluid**: cerebrum > aqueous humor > CSF > choroid > vitreous humor
  - **Male reproductive organs**: seminal vesicles > prostate > vesicular gland > bulbourethral gland > testes

BAL: broncheoalveolar lavage; CSF: cerebral spinal fluid; PAM:pulmonary alveolar macrophages

Petraitis V et al. Pharmacokinetics and Comprehensive Analysis of the Tissue Distribution of Eravacycline in Rabbits. Antimicrob Agents Chemother. 2018;62(9):e00275-18.

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Comparing Tetracyclines

	Eravacycline	Tigecycline
Dose	1 mg/kg IV q12h over 60 mins	Initial dose of 100mg IV, followed by 50mg IV q12h infused over 30-60mins
Indication	cIAI	cIAI, SSSI, CAP
C_{max} (ng/mL)	1,825 (multiple 1 mg/kg q12h dose)	630 (multiple 50 mg q12h dose)
AUC_{0-24} (ng*h/mL)	12,618 (multiple 1 mg/kg q12h dose)	4,700 (multiple 50 mg q12h dose)
Protein binding	79-90% (100 to 10,000 ng/mL)	71-89% (100 ng/mL to 1,000 ng/mL)
Vss (L)	321 L	500 to 700 L
t1/2 (hr)	20 hours	42.4 hours
Metabolism	Liver (CYP3A4- and FMO mediated oxidation)	Liver (not extensively metabolised)

1. US Food and Drugs Agency (FDA). Prescribing Information:. Xerava. 2018. Available at: Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/xerava. Last accessed: 21 February 2024. **2.** European Medicines Agency (EMA). Prescribing Information:. Xerava – Eravacycline. 2018. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/xerava. Last accessed: 21 February 2024. **3.** Lashinsky J et al. Infect Dis Ther. 2017;6:199–211; **4.** Sklenar, et al. Agents Actions. 1977; 7(3): 369-77

Eravacycline EUCAST Breakpoints

Pathogen	MIC (µg/mL)		Disk Content (µg)	Disk Diffusion (zone diameter in mm)	
	S ≤	R >		S ≥	R <
E. coli	0.5	0.5	20	17	17
S. aureus	0.25	0.25	20	20[a]	20[a]
E. faecalis	0.125	0.125	20	22	22
E. faecium	0.125	0.125	20	24	24
Viridans group streptococci	0.125	0.125	20	17	17

MIC: minimum inhibitory concentrations (mcg/mL); S: susceptible; I: intermediate; R: resistant

[a] The zone diameter breakpoint is valid for MSSA (methicillin-susceptible *Staphylococcus aureus*) only. For MRSA (Methicillin-resistant *Staphylococcus aureus*), perform an MIC test, Susceptibility testing with eravacycline is not recommended for *Pseudomonas* spp. due to poor target for therapy. There is insufficient evidence that the following organisms/groups are good targets for therapy with eravacycline: *Acinetobacter* spp.., Streptococcus groups A, B, C and G, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, Gram-positive anaerobes (except *Clostridioides difficile*), Gram-negative anaerobes

European Committee on Antimicrobial Susceptibility Testing (EUCAST). Breakpoints tables for interpretation of MICs and zone diameters. Version 10.0. Available from: https://www.eucast.org/ Last accessed: 21 February 2024.

Eravacycline FDA Breakpoints

Pathogen	MIC (µg/mL)			Disk Diffusion (zone diameter in mm)		
	S	I	R	S	I	R
Enterobacteriaceae[a]	≤0.5	-	-	≥15	-	-
S. aureus	≤0.06	-	-	-	-	-
E. faecalis and *E. faecium*	≤0.06	-	-	-	-	-
S. anginosus group[b]	≤0.06	-	-	-	-	-
Anaerobes[c]	≤0.5	-	-	-	-	-

MIC: minimum inhibitory concentrations (mcg/mL); S: susceptible; I: intermediate; R: resistant

[a] Clinical efficacy was shown for *Citrobacter freundii, Enterobacter cloacae, Escherichia coli, Klebsiella oxytoca, Klebsiella pneumonia* [b] clinical efficacy was shown for *S. anginosus, S. constellatus, S. intermedius*. [c] clinical efficacy was shown for *Clostridium perfringens, Parabacteroides distasonis, Bacteroides caccae, Bacteroides fragilis, Bacteroides ovatus, Bacteroides thetaiotaomicron, Bacteroides uniformis, Bacteroides vulgatus.*

U.S. Food and Drug Administration (FDA). Antibacterial Susceptibility Test Interpretive Criteria. Eravacycline – Injection Products. Available at :https://www.fda.gov/drugs/development-resources/antibacterial-susceptibility-test-interpretive-criteria Last accessed: February 2024

EMJ LEARNING

Global Surveillance: MDR Gram-negative Pathogens

- *In-vitro* activity of ERV and comparators against global MDR Gram-negative clinical isolates (2013-2017)

Organism	N	ERV $MIC_{50/90}$	TGC $MIC_{50/90}$	MEM* $MIC_{50/90}$	PTZ $MIC_{50/90}$	AMK* $MIC_{50/90}$	FEP $MIC_{50/90}$
Acinetobacter baumannii	1,502	0.5/2	4/8	64/>64	>64/>64	>64/>64	>16/>16
Citrobacter spp..	247	0.25/1	0.5/2	0.06/1	>64/>64	1/8	2/>16
Enterobacter spp..	448	0.5/2	1/4	0.12/0.5	64/>64	1/4	4/>16
Escherichia coli	555	0.25/0.5	0.25/1	0.03/0.06	4/64	2/8	8/>16
Klebsiella spp..	801	0.5/2	1/4	0.06/>4	64/>64	2/16	>16/>16

In-vitro activity does not imply clinical efficacy

ERV: eravacycline; MDR: multidrug-resistant (defined as resistant to at least 1 agent in 3 or more antibiotic categories); MEM: meropenem; MIC:minimum inhibitory concentration; N: number of isolates; PTZ: piperacillin/tazobactam; TGC: tigecycline; MIC50/90 units are in µg/mL; * =was not tested during all years

Morrissey I et al. In Vitro Activity of Eravacycline against Gram-Positive Bacteria Isolated in Clinical Laboratories Worldwide from 2013 to 2017. Antimicrob Agents Chemother. 2020;64(3):e01715-19

In-Vitro Activity Against Anaerobic Pathogens

- In-vitro activity of ERV and comparators against anaerobic clinical isolates collected in USA and Europe (2012-2016).[1-3]

Organism	N	ERV $MIC_{50/90}$	TGC $MIC_{50/90}$	CLI $MIC_{50/90}$	MTZ $MIC_{50/90}$
Bacteroides fragilis	333	0.25/1	0.5/8	1/>32	0.5/1
Bacteroides caccae	28	0.5/2	1/8	8/128	1/2
Bacteroides thetaiotamicron	157	0.5/2	1/8	8/>128	<1/1
Clostridium difficile	193	0.03/0.06	<0.06/0.25	4/16	0.25/0.5
Clostridium perfringens	91	0.12/0.5	0.5/2	1/>8	<1/2
Prevotella spp..	208	0.12/0.5	0.12/0.5	<0.25/>8	<1/2

In-vitro activity does not imply clinical efficacy

ERV: eravacycline; CLI: clindamycin; MIC: minimum inhibitory concentration; MTZ: metronidazole; N: number of isolates; TGC: tigecycline; MIC50/90 units are in µg/mL

1. Snydman D et al. Antimicrob Agents Chemother 2018;62(5):e02206-17; **2.** Goldstein EC et al. Anaerobe. 2018;4:122-4; 3. Morrissey I et al. Open Forum Infectious Diseases. 2015: 2 (Suppl_1): 780 and 784.

EMJ LEARNING

IGNITE 1: Efficacy and safety of Eravacycline vs Ertapenem in cIAIs

Aim: To assess the efficacy and safety of eravacycline compared with ertapenem for treating cIAIs in hospitalised adults

Study description: Phase III, randomised, double-blind, double-dummy, multicentre study. To demonstrate noninferiority of eravacycline (1.0 mg/kg per 12 hours) *vs* ertapenem (1.0 g per 24 hours) parallel treatment

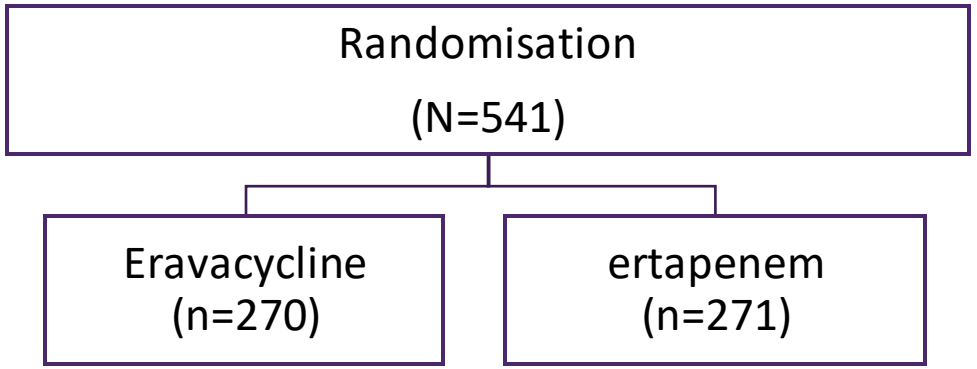
Primary outcome:

Clinical response at the TOC visit in the micro-ITT and CE populations (EMA) and the micro-ITT population (FDA)

Secondary outcomes:

- Clinical response at EOT, TOC, and FU visits in ITT, MITT, CE, micro-ITT (EOT and FU Visits) and ME
- Microbiologic responses at EOT and TOC visits in micro-ITT and ME populations
- Safety analysis

Study design:



CE: clinical evaluable; cIAIs,:complicated intra-abdominal infections; EMA: European Medicines Agency; EOT: end-of-treatment; IGNITE: Investigating Gram-Negative Infections Treated With Eravacycline trial; ITT: intent-to-treat; micro-ITT: microbiological intent-to-treat; ME: microbiloically evaluable; MITT: modified intent-to-treat; TOC, test-of-cure; US FDA, US Food and Drug Administration.

Solomkin J, Evans D, Slepavicius A, *et al*. Assessing the efficacy and safety of eravacycline vs ertapenem in complicated intra-abdominal infections in the investigating Gram-negative infections treated with eravacycline (IGNITE 1) trial: A randomized clinical trial. JAMA Surg. 2017;152(3):224-232.

EMJ LEARNING

IGNITE4: Safety and efficacy of Eravacycline vs meropenem in cIAIs

Aim: To evaluate the safety and efficacy of eravacycline compared to meropenem in acutely hospitalised patients diagnosed with cIAI requiring operative or percutaneous intervention

Study description: Phase 3, randomised, double-blind, double-dummy, multicentre, prospective trial designed to test the safety and efficacy of eravacycline *versus* meropenem in acutely hospitalised patients diagnosed with cIAI requiring operative or percutaneous intervention

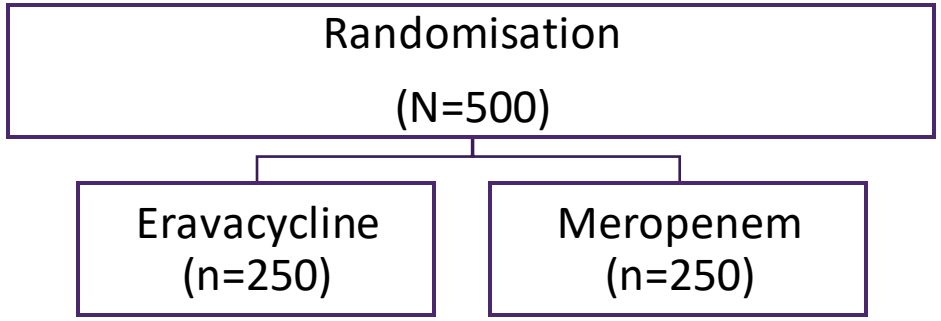
Primary endpoint:

Clinical response at the TOC visit 25–31 days after initiation of the study drug in the micro-ITT population, as required by the FDA. An NI margin of 12.5% was used as agreed to by the FDA.

Secondary endpoints:

- Clinical and microbiological responses for the micro-ITT, modified ITT, clinically evaluable, and microbiologically evaluable populations at EOT, TOC, and FU visits
- Safety analysis

Study design:



cIAIs: complicated intra-abdominal infections; EOT: end-of-treatment; FDA: US Food and Drug Administration; FU: follow-up; micro-ITT: microbiological intent-to-treat; NI: noninferiority; TOC: test-of-cure.

Solomkin JS, Gardovskis J, Lawrence K, et al. IGNITE4: Results of a phase 3, randomized, multicenter, prospective trial of eravacycline vs meropenem in the treatment of complicated intraabdominal infections. Clin Infect Dis. 2019;69(6):921-929.

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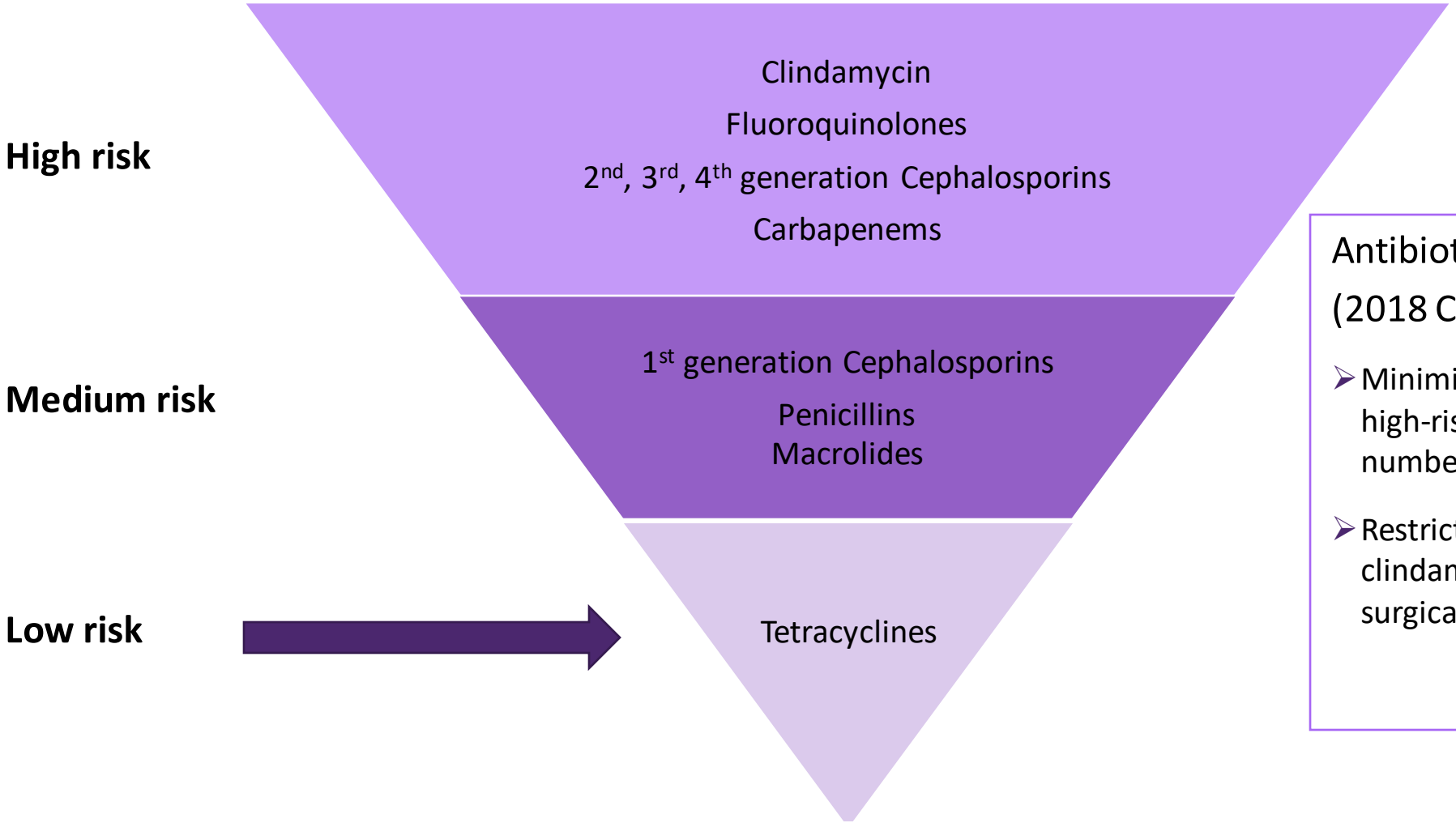
Summary of Results for IGNITE 1 and 4

- Primary Efficacy Endpoint (FDA) Clinical Response at TOC Visit micro-ITT Population
- Eravacycline demonstrated non-inferiority to ertapenem and meropenem in the primary analyses
- Recommended dose regimen is **1 mg/kg IV q12h** administered over approximately 60 minutes for a total duration of 4 to 14 days[1]
  - In clinical trials, eravacycline infusion was administered over up to 120 minutes[2]
  - Actual body weight is used for dose calculation
- Duration of treatment for cIAI is guided by the severity and location of infection and the patient's clinical response

ERV: eravacycline; ETP: ertapenem; MEM: meropenem; micro-ITT: microbiological intent-to-treat; TOC: test of cure

Solomkin et al. JAMA Surg. 2017;152(3):224-232; 2. Solomkin et al. Clin Infect Dis. 2019; 69(6):921-929

Antibiotics Associated with High, Medium, and Low Risk for CDI



Antibiotic Stewardship
(2018 CDI Guidelines)

- Minimised frequency and duration of high-risk antibiotic therapy and the number of antibiotic agents prescribed
- Restriction of fluoroquinolones, clindamycin, cephalosporins (except for surgical antibiotic prophylaxis)

McDonald, LC, et al. *Clin Infect Dis*. 2018;66(7):e1–e48; Mullane KM, et al. *Clin* Infect Dis. 2011;53(5):440-7; Tariq, R, et al. *Clin Infect Dis.* 2018;66(4):514-522.

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Clinical Case Review

Clinical Case 1: 80-year-old male, left emycolectomy for colon carcinoma

After 3 days

Secondary peritonitis for dehiscence of the anastomosis, closure of the viscus

Microbiological examination of the intra-abdominal material was negative

Empiric therapy with piperacillin/tazobactam and tigecycline was initiated

After 14 days

Intra-abdominal abscess with *K. pneumoniae* ESBL with MIC piperacillin/tazobactam 64 mg/L resistant and *E. faecium* VRE

Eravacycline: 1 mg/kg every 12 hrs for ten days

At 3 months follow up

No relapse of infection

Data provided by Tascini patient archive with authorisation.

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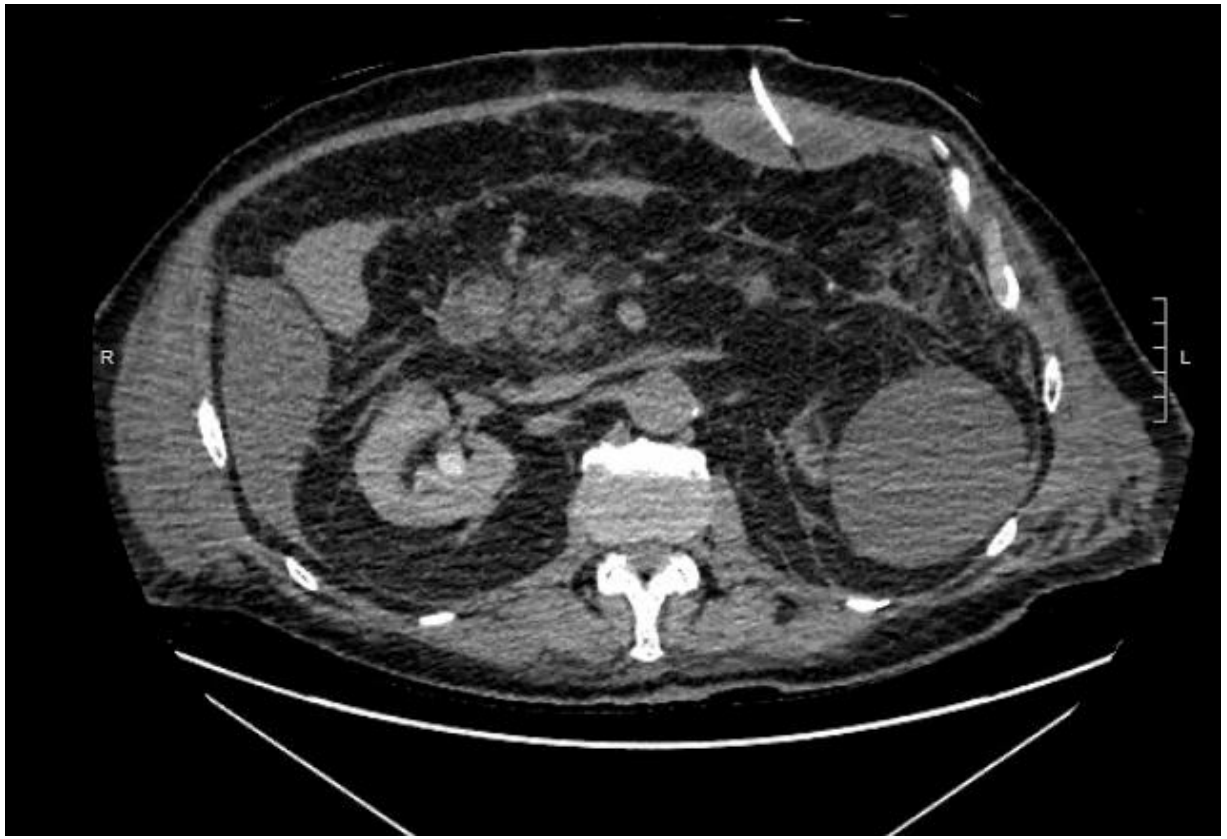
Abdominal wall abscess with a drainage inside, TDM of piperacillin



Weight	87	kg
Height	168	cm
Date/time pre-dose collection	12.10.23 8.30	
Piperacillin: Pre-dose conc.	123.89	mg/L
Date to monitor:	Monday	
Comments	**Concentration above therapeutic ranges**	

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Clinical Case 2: 65-year-old male, no co-morbidities, chronic diverticulosis

Patient History

Treated at home for **acute diverticulitis** for three weeks with **amoxicillin/clavulanate** 1 g every 8 hours and **rifaximine** 200 mg every 6 hours.

Previous hospital admission in 2019

14th December 2023

Admitted to the hospital for peritonitis with fever, acute abdominal pain,stable.

Submitted to abdominal surgery,

Antibiotic therapy with **piperacillin/ tazobactam**

16th December 2023

Rectal swab positive for *E. coli* NDM

Culture from abdominal material taken during surgery positive for E. coli NDM

18th December 2023

Started **aztreonam** and **imipenem/ relebactam**

Compassionate use of eravaciclin, urgent request to the hospital pharmacy

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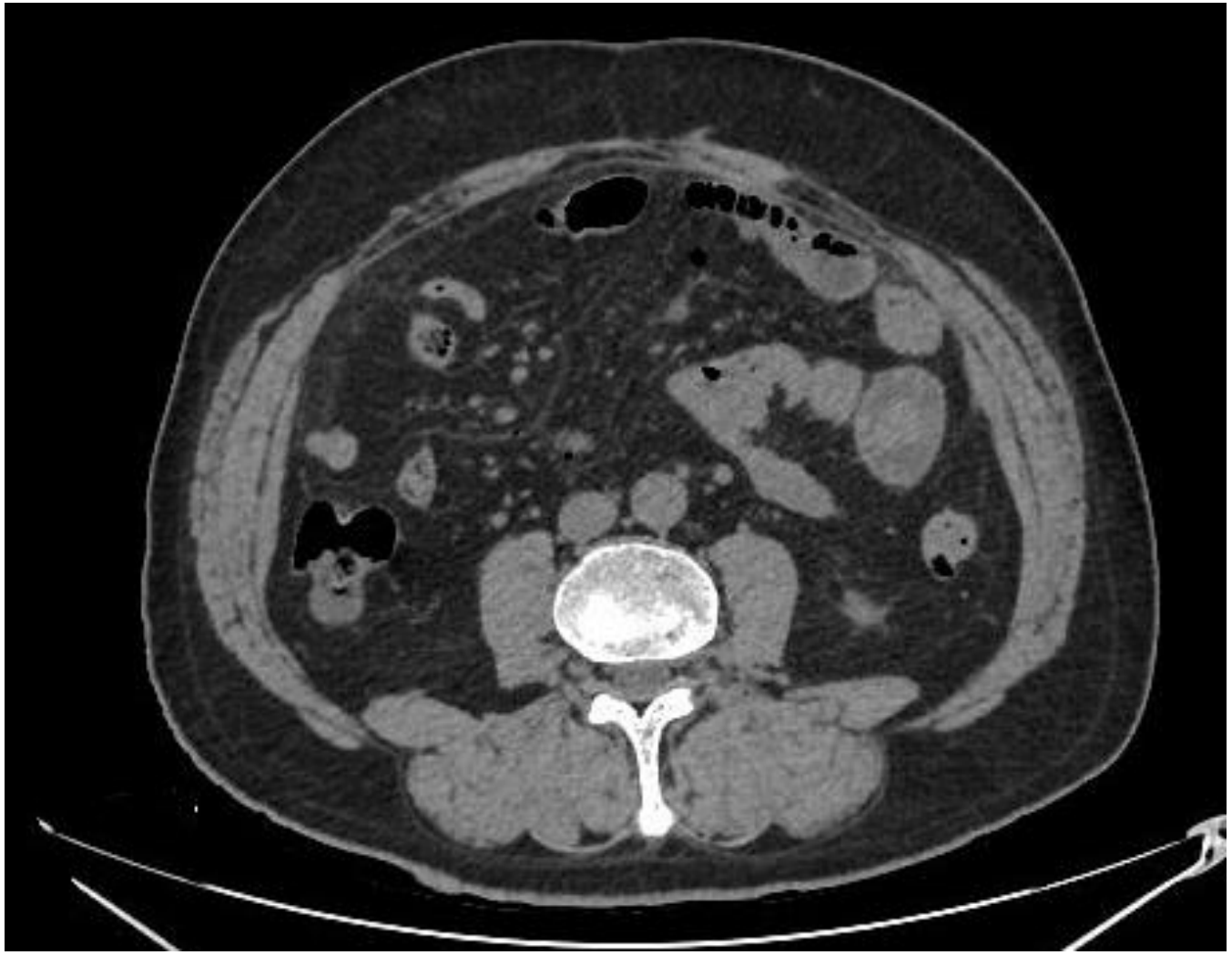
CT scan upon admission (13/12):



Perivisceral adipose tissue imbibition and air bubbles in lower abdominal region in the context of known sigmoid diverticulitis

Data provided by Tascini patient archive with authorisation.

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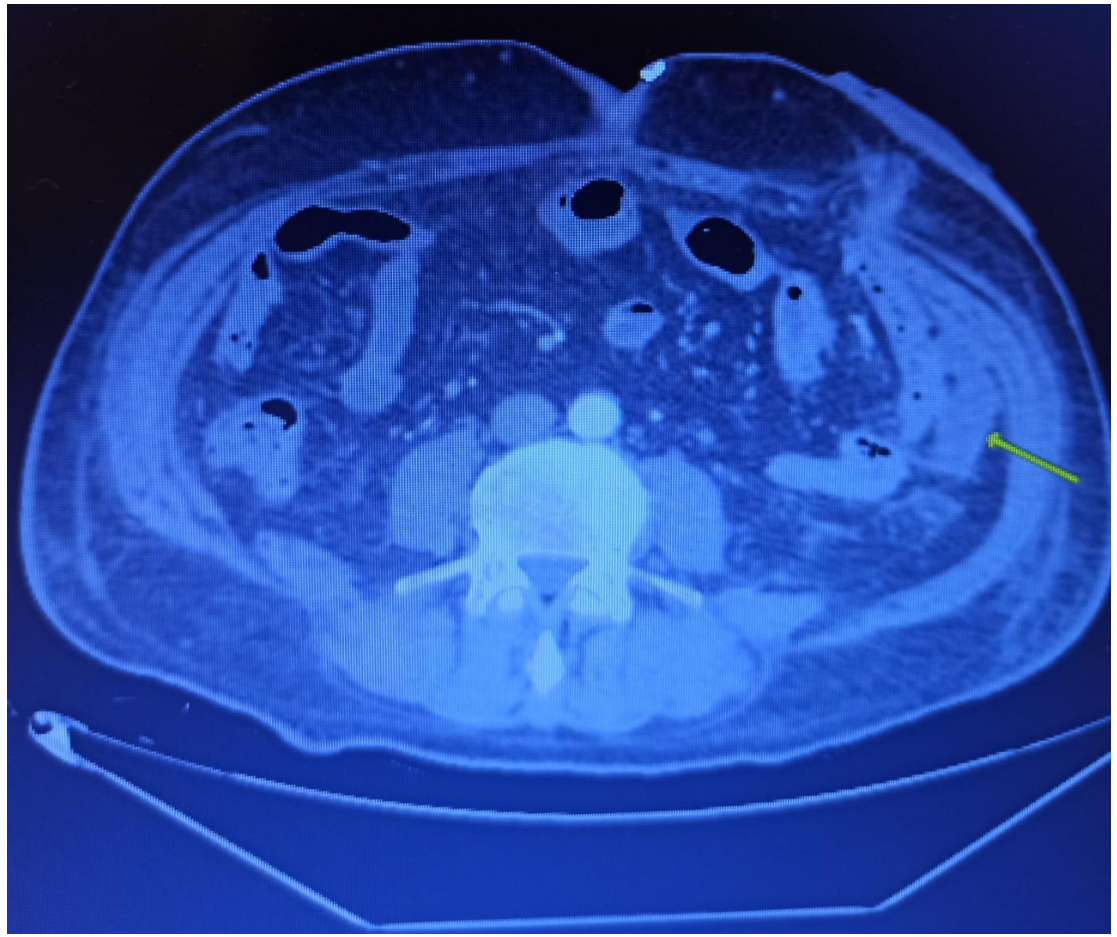
CT scan post-surgery (22/12):



Along the left iliac region, residual quote of intra-abdominal collection, partially organised, with fluid/supra content

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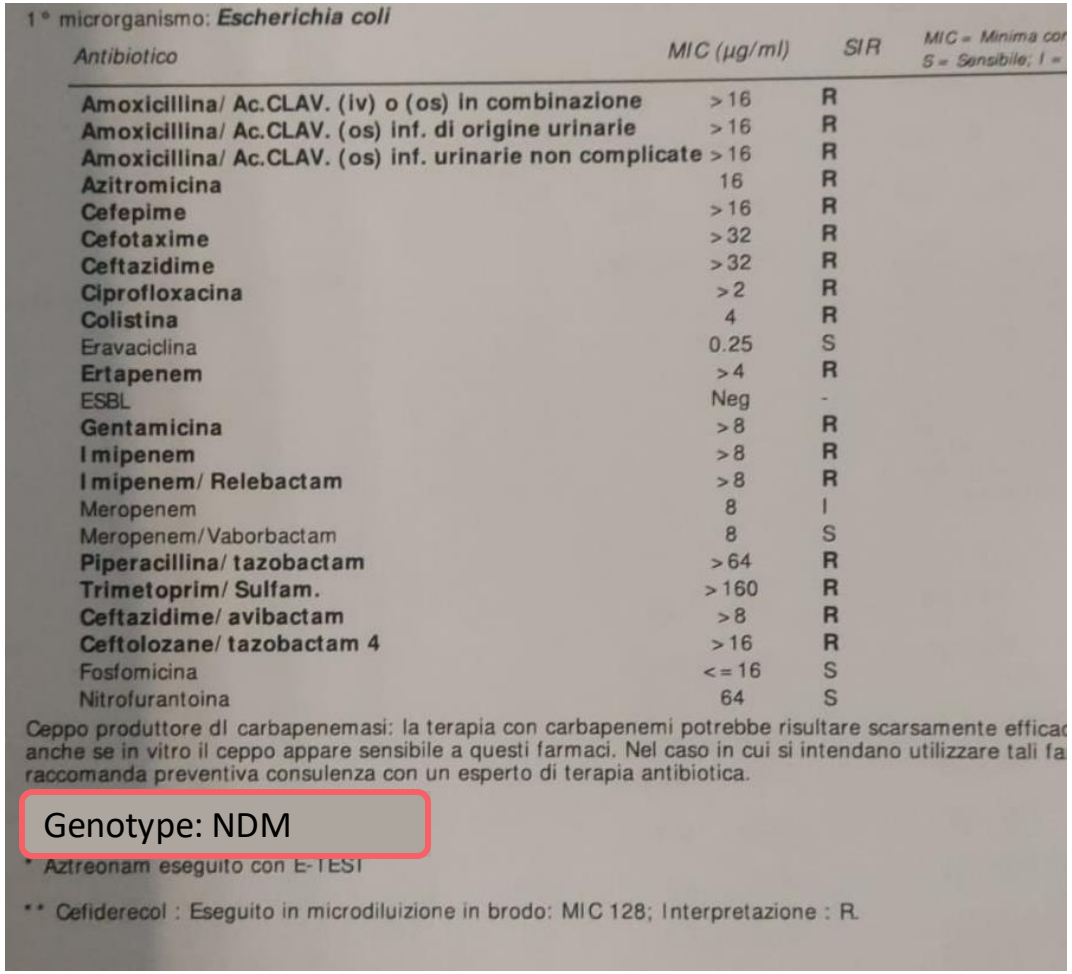
Clinical Case 2: *E. coli* NDM isolated from intra-abdominal material; **community-acquired strain**



1° microrganismo: ***Escherichia coli***

Antibiotico	MIC (µg/ml)	SIR
Amoxicillina/ Ac.CLAV. (iv) o (os) in combinazione	>16	R
Amoxicillina/ Ac.CLAV. (os) inf. di origine urinarie	>16	R
Amoxicillina/ Ac.CLAV. (os) inf. urinarie non complicate	>16	R
Azitromicina	16	R
Cefepime	>16	R
Cefotaxime	>32	R
Ceftazidime	>32	R
Ciprofloxacina	>2	R
Colistina	4	R
Eravaciclina	0.25	S
Ertapenem	>4	R
ESBL	Neg	-
Gentamicina	>8	R
Imipenem	>8	R
Imipenem/ Relebactam	>8	R
Meropenem	8	I
Meropenem/Vaborbactam	8	S
Piperacillina/ tazobactam	>64	R
Trimetoprim/ Sulfam.	>160	R
Ceftazidime/ avibactam	>8	R
Ceftolozane/ tazobactam 4	>16	R
Fosfomicina	<=16	S
Nitrofurantoina	64	S

Ceppo produttore dI carbapenemasi: la terapia con carbapenemi potrebbe risultare scarsamente efficac
anche se in vitro il ceppo appare sensibile a questi farmaci. Nel caso in cui si intendano utilizzare tali fa
raccomanda preventiva consulenza con un esperto di terapia antibiotica.

Genotype: NDM

* Aztreonam eseguito con E-TEST

** Cefiderecol : Eseguito in microdiluizione in brodo: MIC 128; Interpretazione : R.

Data provided by Tascini patient archive with authorisation.

Antibiotic	MIC (mg/L)/SIR
Cefepime	>16 R
Cefotaxime	> 32 R
Ceftazidime	> 32 R
Ciprofloxacin	> 4 R
Colistin	4 R
Eravaciclin	0.25 S
Ertapenem	> 4 R
Gentamicin	> 8 R
Imipenem	> 8 R
Imipenem/relebactam	> 8 R
Meropenem	8 I
Meropenem/relebactam	8 S
Piperacillin/tazobactam	> 64 R
Trimetoprim/sulfametoxazole	>160 R
Ceftazidime/avibactam	> 8 R
Ceftolozane/tazobactam	> 16 R
Fosfomicin	<= 16 S
Cefiderocol	128 R
Aztreonam	16 R

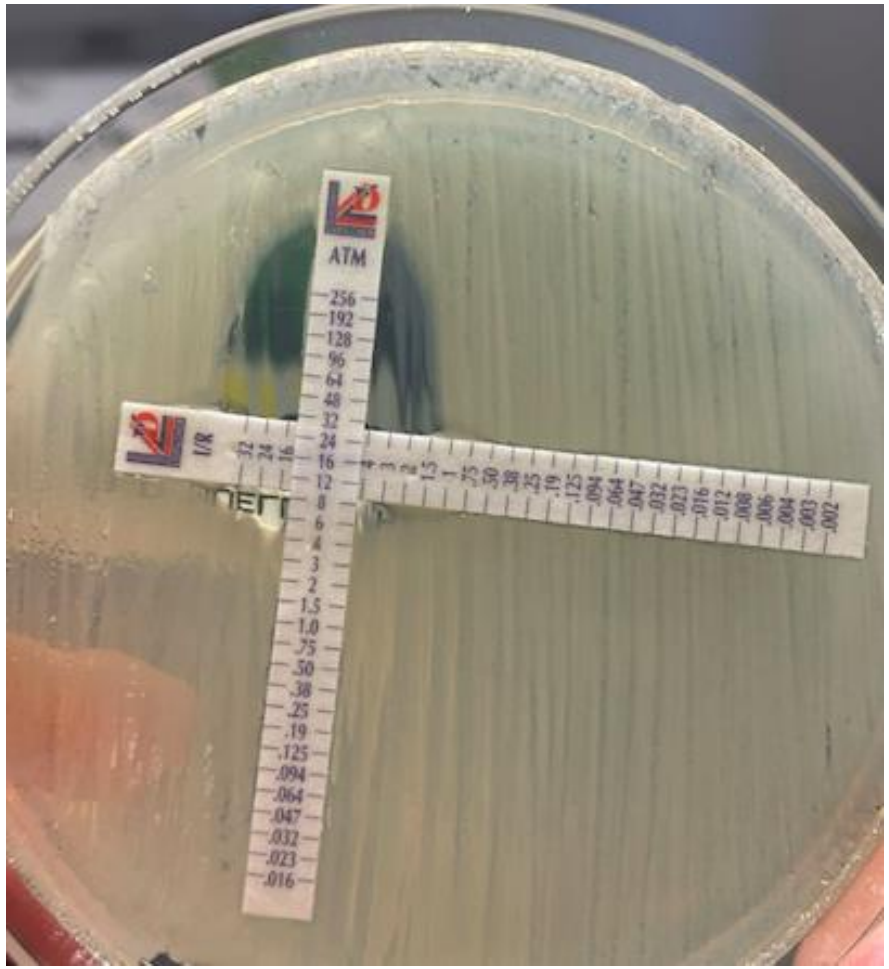
NDM: New Delhi metallo-β-lactamase; MIC: minimum inhibitory concentration; S: Sensitive; I: Intermediate; R: Resistant

E. Coli NDM

- MIC colistin only 1 dilution over the clinical breakpoint (CB)
- **Eravacycline** clinical breakpoint 0.5 mg/L
- **Meropenem/vaborbactam** clinical breakpoint 8mg/L
- **Meropenem alone** 2 mg/L,
- **Vaborbactam** no direct antibacterial activity
- **Relebactam** less potent on ESBL
- Resistance to **cefiderocol**

ESBL: extended-spectrum beta-lactamases; MIC: minimum inhibitory concentration; NDM: New Delhi metallo-β-lactamase

Synergism among Imipenem-Cilastatin-Relebactam (Imi/rel) and Aztreonam



Aztreonam MIC in combination with Imi/rel 4 mg/L ( ), Aztreonam MIC alone 8 mg/L, FIC aztreonam 4/8= 0.5.

Image provided by Tascini

MIC: minimum inhibitory concentration; FIC: Fractional inhibitory concentration; Imi/rel: Imipenem-Cilastatin-Relebactam

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Clinical Case 2: Vancomycin-Resistant Enterococci (VRE) isolated from intra-abdominal material; **community acquired strain**

2nd microorganism:
Enterococcus faecium

Antibiotic	MIC (µg/mL)	SIR
Ampicillin	> 16	**R**
Chinupristin/ Dalfopr	8	**R**
Ciprofloxacin	> 4	**R**
Imipenem	> 8	**R**
Kanamycin high conc.	SYN-R	**R**
Levofloxacin	> 4	**R**
Linezolid	2	S
Tigecycline	< = 0.12	S
Vancomycin	>16	**R**
High level of resistance to Gentamicin	Pos	+
High-dose streptomycin (synergy)	SYN-S	S
Teicoplanin	> 16	**R**

MIC: minimum inhibitory concentration; S: Sensitive; I: Intermediate; R: Resistant

Data provided by Tascini patient archive with authorisation.

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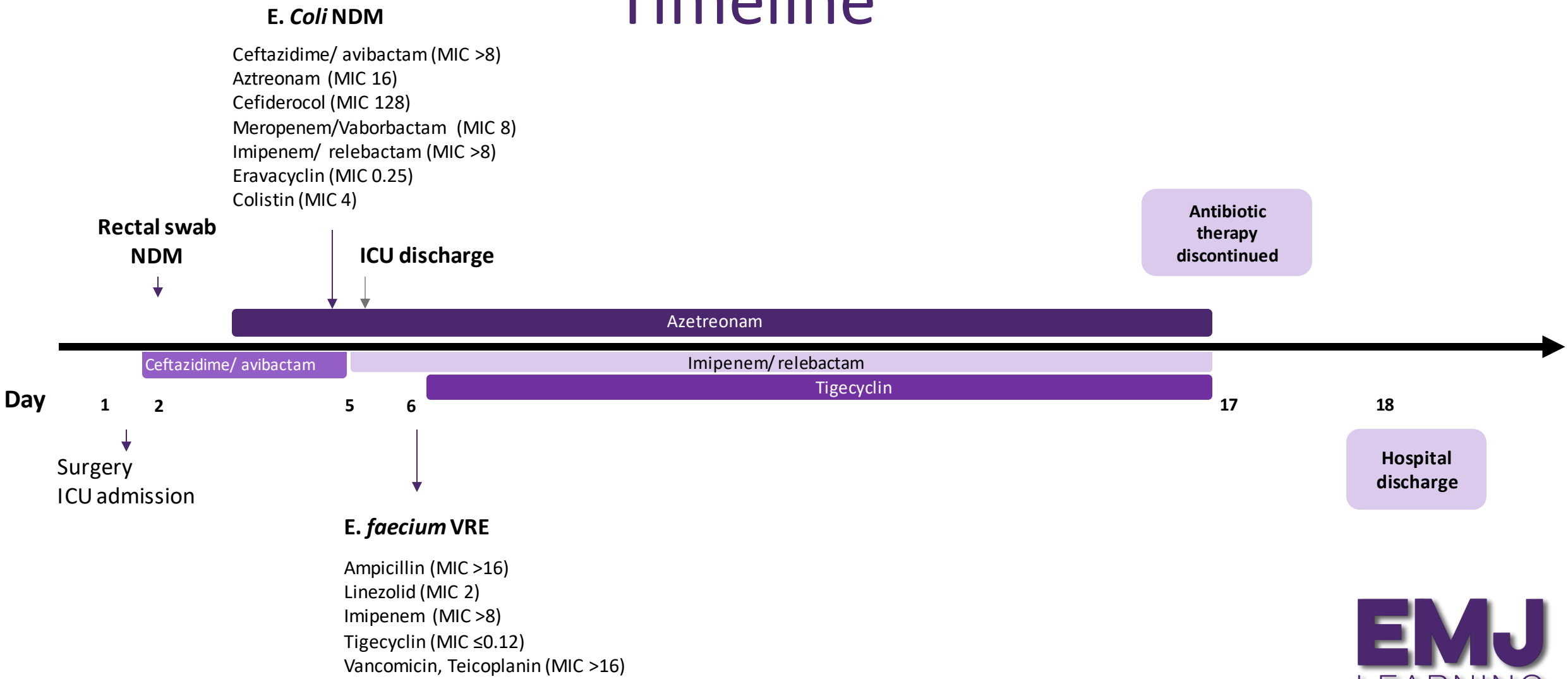
Timeline



ICU: Intensive care unit; MIC: minimum inhibitory concentration; NDM: New Delhi Metallo-β-Lactamase; VRE: vancomycin-resistant Enterococci

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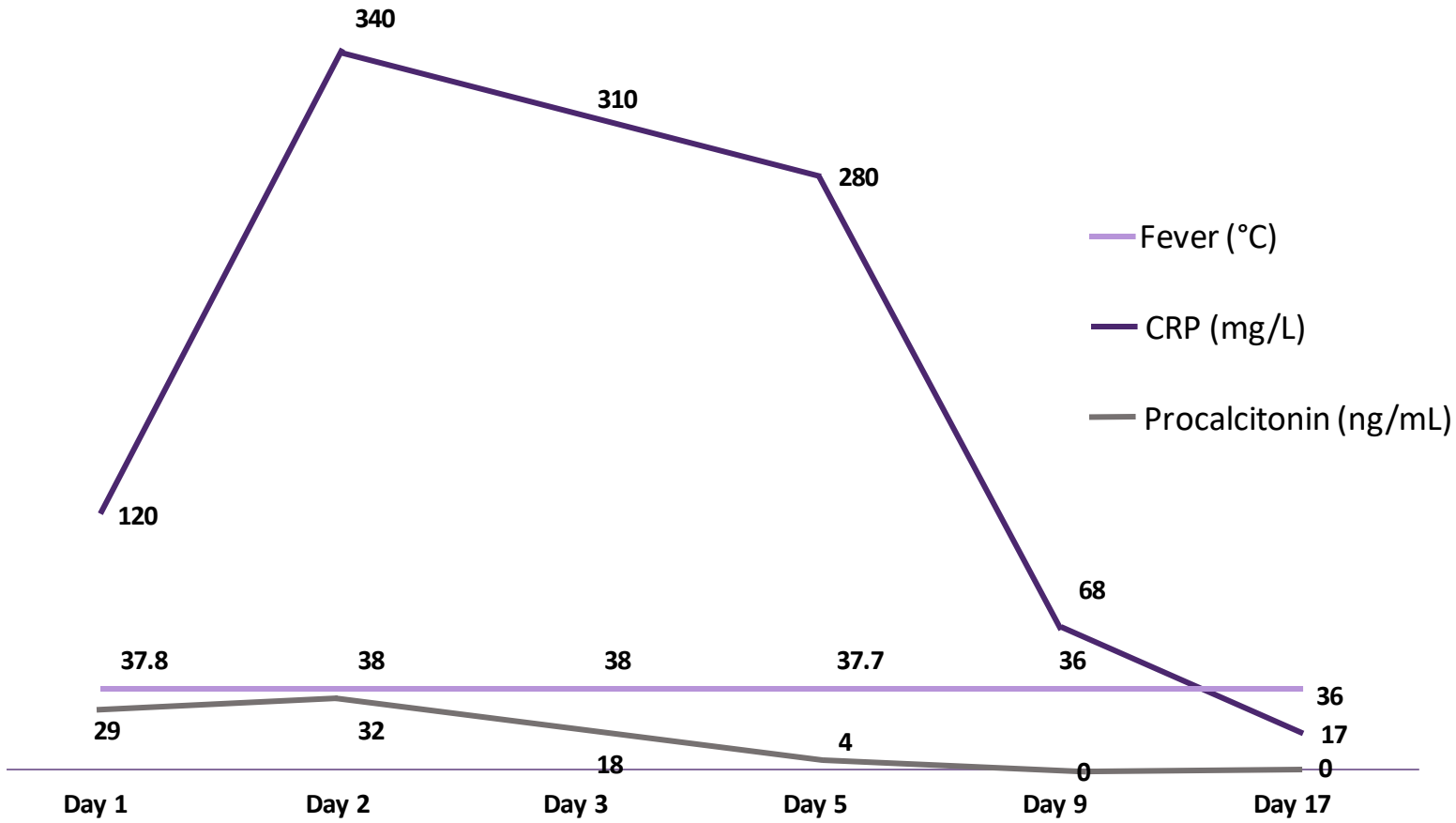
Fever and laboratory parameter



Data provided by Tascini patient archive with authorisation.

CRP: C-Reactive Protein

Clinical Case 2:

- **Tigecyclin -** standard dose was added
- **Eravaciclin** arrived after 10 days when the clinical picture was resolved

- **Clinical questions:**
  - Carbapenems in BLIC and selection of CRE
  - Cefalosporins and selection of resistance
  - Tetracycline alone to spare beta-lactams and avoid selection of resistance or persistence of colonisation

BLIC: *β*-lactamase inhibitor combinations; CRE: Carbapenem-resistant Enterobacterales

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Sequence Variants

Identified in *Escherichia coli* Isolates Recovered From Blood Before and After Treatment Failure With Ceftazidime-Avibactam Co-administered With Aztreonam (Isolate 2) and Cefiderocol (Isolate 3)

Isolate	Gene	Gene Product	Nucleotide Change	Amino Acid Change	Role in Antibiotic Resistance
1, 2, and 3	*ftsI*	PBP3	:TATCGA ATTAAA	Tyr-Arg-Ile-Lys insertion at position 333	Insertion in PBP3 mediates resistance to aztreonam and elevates MIC to cefiderocol[a]
2 vs 1	*acrD*	Multidrug efflux nodulation–cell division transporter permease AcrD	G:T	Gln997His	Mediates resistance to avibactam via efflux
	emrA	Multidrug efflux major facilitator superfamily transporter periplasmic adaptor subunit EmrA	G:A	Glu158Lysine	Mediates resistance to antibiotics via efflux
	barA	Sensor histidine kinase of the BarA/UvrY 2-component system	G:A	Glu362Lysine	Uncertain; may enhance biofilm formation and virulence
3 vs 1	*cirA*	Catecholate siderophore receptor CirA	C:T	Gln42Stop-codon	Truncated CirA prevents cefiderocol import[b]
	panF	Sodium/pantothenate symporter	A:G	Asp145Gly	Importer of transition metals (ie, Fe^{2+}) likely compensates for CirA
	artM	Arginine ABC transporter permease ArtM	A:C	Glu217Ala	Importer of metal ions (ie, Fe^{2+}) and Fe^{+3} siderophores likely compensates for CirA
	dadA promoter	D-amino-acid dehydrogenase a member of the FAD-dependent oxidoreductase family	A:G	–3 Promoter mutation	May reduce $Fe3^{+3}$ to Fe^{+2} to facilitate Fe^{+2} import to compensate for CirA
	tsr	Methyl-accepting chemotaxis protein	G:A	Asp174Asn	Uncertain; may enhance virulence
	I	Phage minor tail protein L	A:C G:A	Ser185His	Uncertain; may modify biofilm enzymatically
2 and 3 vs 1	*lacY*	Lactose permease	T:A	Trp151Arg	Uncertain; likely mediates resistance to antibiotics via efflux

ABC: ATP-binding-cassette; FAD: flavin adenine dinucleotide cofactor; Fe+2: ferrous; Fe+3: ferric; MIC: minimum inhibitory concentration; PBP3: penicillin-binding protein 3. [a]The MIC for aztreonam-avibactam was 16/4 µg/mL in isolate 1 and 64/4 µg/mL in isolate 2; isolate 3 was not tested. [b]The MIC for cefiderocol was 0.38 µg/mL in isolate 1, 0.5 µg/mL in isolate 2, and >256 µg/mL in isolate 3.

Adapted from: Senchyna F et al. Sequential Treatment Failure With Aztreonam-Ceftazidime-Avibactam Followed by Cefiderocol Due to Preexisting and Acquired Mechanisms in a New Delhi Metallo-β-lactamase–Producing Escherichia coli Causing Fatal Bloodstream Infection. Clin Infect Dis. 2024:ciad759. doi: 10.1093/cid/ciad759.

EMJ LEARNING

Importance of appropriate patient care

Effective antibiotic stewardship

EMJ LEARNING

Ten "golden rules" for optimal antibiotic use in hospital settings: the WARNING call to action
1. Enhancing infection prevention and control
2. Prescribing antibiotics when they are truly needed
3. Prescribing the appropriate antibiotic(s) at the right time
4. Administering antibiotics in adequate doses and routes
5. Initiating, as soon as possible, targeted treatment based on the results of culture and susceptibility testing
6. Using the short duration of antibiotics based on evidence
7. Achieving source control by identifying and eliminating the source of the infection or reducing the bacterial load
8. Supporting surveillance of HAIs and AMR, monitoring of antibiotic use, consumption, and the quality of prescribing
9. Educating staff and improving awareness
10. Supporting multidisciplinary ASPs and enhancing collaboration of HCPs from various disciplines.

AMR: antibiotic resistance; ASP:Antimicrobial Stewardship Programs; HAI:Hospital-acquired infections; HCP: healthcare professionals

Worldwide Antimicrobial Resistance National/International Network Group (WARNING) Collaborators. World J Emerg Surg. 2023;18(1):50.

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