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Treatment of carbapenemase-producing organisms: a case-based session

Karianne Gammelsrud, Oslo University Hospital / University of Oslo
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NordicAST workshop 27-28 May 2025

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International treatment guidelines/guidance

Clinical Infectious Diseases
IDSA GUIDELINES
IDSA Infectious Diseases Society of America · hivma hiv medicine association · OXFORD

Infectious Diseases Society of America 2024 Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections

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The Infectious Diseases Society of America (IDSA) is committed to providing up-to-date guidance on the treatment of antimicrobial-resistant (AMR) infections. This guidance document focuses on infections caused by extended-spectrum β-lactamase-producing Enterobacterales (ESBL-E), AmpC β-lactamase-producing Enterobacterales (AmpC-E), carbapenem-resistant Enterobacterales (CRE), *Pseudomonas aeruginosa* with difficult-to-treat resistance (DTR *P. aeruginosa*), carbapenem-resistant *Acinetobacter baumannii* (CRAB), and *Stenotrophomonas maltophilia*. This updated document replaces previous versions of the guidance document. A panel of 6 infectious diseases specialists with expertise in managing antimicrobial-resistant infections formulated questions about the treatment of infections caused by ESBL-E, AmpC-E, CRE, DTR *P. aeruginosa*, CRAB, and *S. maltophilia*. Because of differences in the epidemiology of AMR and availability of specific anti-infectives internationally, this document focuses on the treatment of AMR infections in the United States. Preferred and alternative suggested treatment approaches are provided with accompanying rationales, assuming the causative organism has been identified and antibiotic susceptibility results are known. Approaches to empiric treatment, transitioning to oral therapy, duration of therapy, and other management considerations are discussed briefly. Suggested approaches apply for both adult and pediatric populations, although suggested antibiotic dosages are provided only for adults. The field of AMR is highly dynamic. Consultation with an infectious diseases specialist is recommended for the treatment of AMR infections. This document is current as of December 31, 2023 and will be updated periodically. The most current version of this document, including date of publication, is available at www.idsociety.org/practice-guideline/amr-guidance/.

Keywords. ESBL; *Pseudomonas aeruginosa*; CRAB; *Stenotrophomonas maltophilia*.

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PMID: 39108079

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CMI CLINICAL MICROBIOLOGY AND INFECTION · ESCMID

Guidelines

European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for the treatment of infections caused by multidrug-resistant Gram-negative bacilli (endorsed by European society of intensive care medicine)

Mical Paul [1,2,§], Elena Carrara [3,§], Pilar Retamar [4,5], Thomas Tängdén [6], Roni Bitterman [1,2], Robert A. Bonomo [7,8,9], Jan de Waele [10], George L. Daikos [11], Murat Akova [12], Stephan Harbarth [13], Celine Pulcini [14,15], José Garnacho-Montero [16], Katja Seme [17], Mario Tumbarello [18], Paul Christoffer Lindemann [19], Sumanth Gandra [20], Yunsong Yu [21,22,23], Matteo Bassetti [24,25], Johan W. Mouton [26,†], Evelina Tacconelli [3,27,28,*,§], Jesús Rodríguez-Baño [4,5,§]

Clin Microbiol Infect. 2022 Apr;28(4):521-547. doi: 10.1016/j.cmi.2021.11.025. Epub 2021 Dec 16.
PMID: 34923128

Case 1

Male patient, 80 years old

Admitted with fever, no focal symptoms or signs, has nephrostomy

BP/HR normal, CRP 180, normal renal function

Working diagnosis: community-acquired UTI

No previous positive urine cultures available

Started empirically on ampicillin 2g x4 + Gentamicin 6 mg/kg x1

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Positive blood culture

Escherichia coli

Ampicillin	6 mm	=R
Amoxicillin-clav. acid	6 mm	=R
Piperacillin- tazobactam	10 mm	=R
Mecillinam	20 mm	
Cefuroxime	6 mm	=R
Cefotaxime	6 mm	=R
Cefpodoxime	6 mm	=R
Ceftazidime	15 mm	=R
Meropenem	27 mm	=screening for carbapenemase: positive

Gentamicin	=R
Ciprofloxacin	=R
Trimethoprim-sulfamethoxazole	=R

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Positive blood culture

Escherichia coli

Ampicillin	6 mm	=R
Amoxicillin-clav. acid	6 mm	=R
Piperacillin- tazobactam	10 mm	=R
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Cefuroxime	6 mm	=R
Cefotaxime	6 mm	=R
Cefpodoxime	6 mm	=R
Ceftazidime	15 mm	=R
Meropenem	27 mm	=screening for carbapenemase: positive

Gentamicin	=R
Ciprofloxacin	=R
Trimethoprim-sulfamethoxazole	=R

PCR (GeneXpert) on blood culture: OXA-48/OXA-181 POSITIVE

NDM, VIM, IMP, KPC neg.

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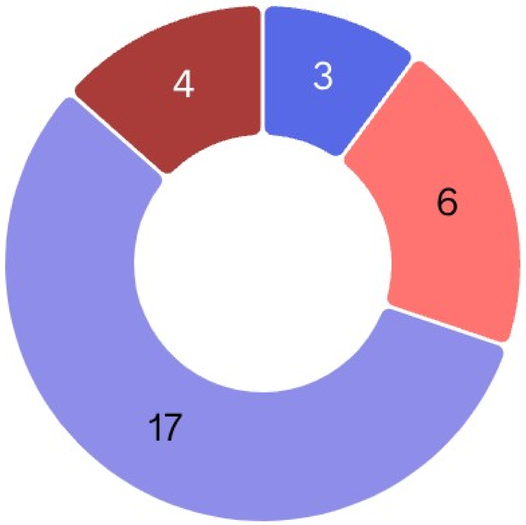
Bacteremia
E. coli
OXA-48
Resistant:
Aminoglyc.
Quinolones
Focus: UTI
Stable ☺

Which antibiotic treatment would you recommend?



3	Meropenem normal dose
6	Meropenem high dose
0	Meropenem-vaborbactam
17	Ceftazidime-avibactam
4	Aztreonam-avibactam
0	Any of the above, in combination with Colistin

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Beta-lactams and OXA-48 *Enterobacterales*

No effect

Amoxicillin-clavulanic acid, Piperacillin-tazobactam	Always R

Can be *in vitro* susceptible, but no good treatment option

2./3. generation cephalosporins without inhibitor	"pure" OXA-48 *in vitro* susceptible
Carbapenems without inhibitor	often *in vitro* susceptible according to clinical breakpoints
Meropenem-vaborbactam Imipenem-relebactam	Vaborbactam/relebactam do not inhibit OXA-48 no advantage compared to mother compound

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Beta-lactams and OXA-48 *Enterobacterales*

Treatment options

Ceftazidime-avibactam	Avibactam inhibits OXA-48, ESBL (ESBL-A) and AmpC (ESBL-M-C) **1. line treatment** acquired resistance seldom in OXA-48

Beta-lactams and OXA-48 *Enterobacterales*

Treatment options

Ceftazidime-avibactam	Avibactam inhibits OXA-48, ESBL (ESBL-A) and AmpC (ESBL-M-C) **1. line treatment** acquired resistance seldom in OXA-48
Aztreonam-avibactam	Avibactam inhibits OXA-48, ESBL (ESBL-A) and AmpC (ESBL-M-C) Less clinical experience than ceftazidime-avibactam Should be reserved for MBLs

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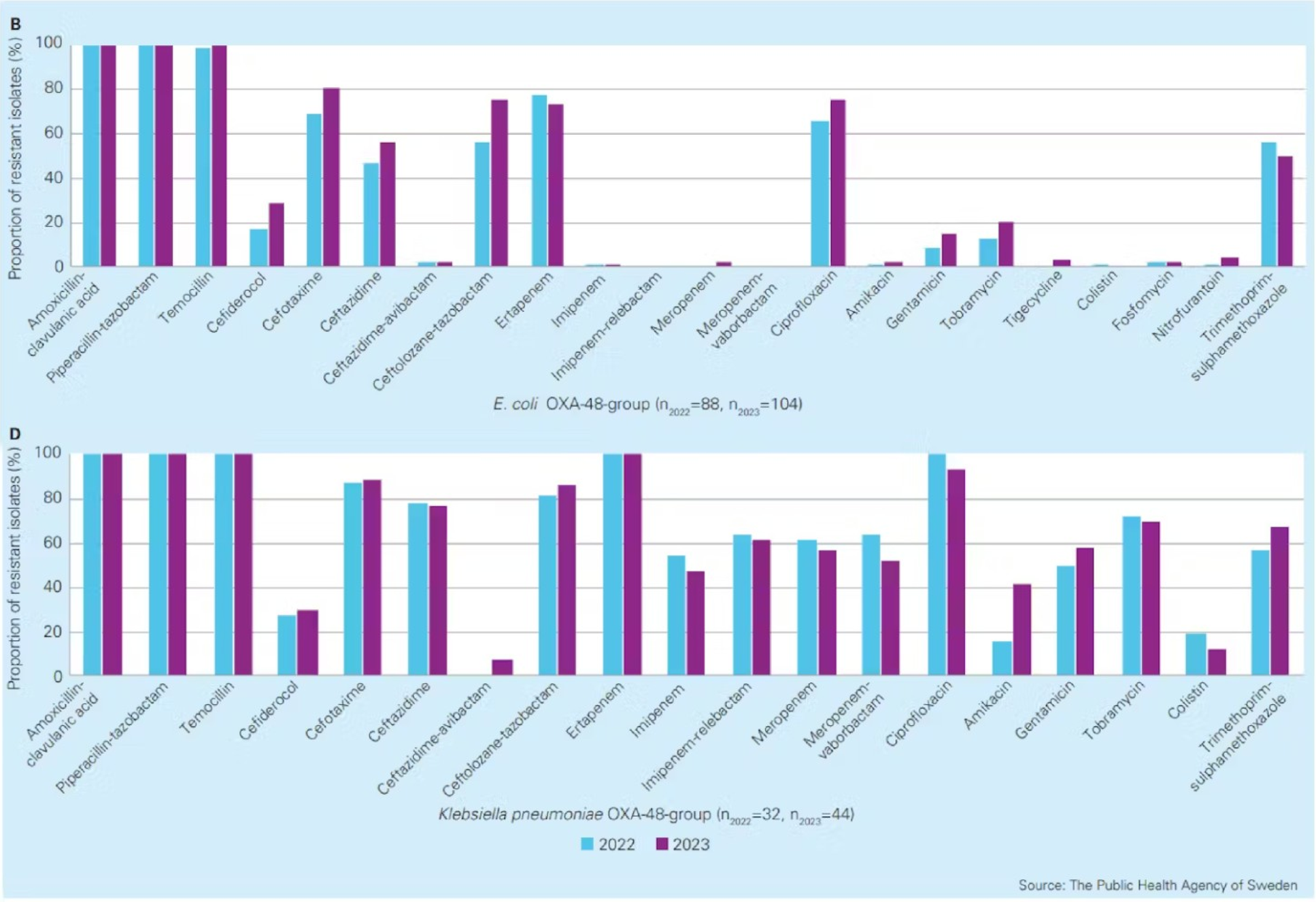
Beta-lactams and OXA-48 *Enterobacterales*

Treatment options

Ceftazidime-avibactam	Avibactam inhibits OXA-48, ESBL (ESBL-A) and AmpC (ESBL-M-C) **1. line treatment** acquired resistance seldom in OXA-48
Aztreonam-avibactam	Avibactam inhibits OXA-48, ESBL (ESBL-A) and AmpC (ESBL-M-C) Less clinical experience than ceftazidime-avibactam Should be reserved for MBLs
Cefiderocol	Often susceptible, treatment option if tested susceptible

?

Cefepime-enmetazobactam	Enmetazobactam inhibits ESBL (ESBL-A) Cefepime not a substrate for AmpC (ESBL-M-C) and OXA-48 Often good *in vitro* susceptibility, but no clinical data



https://www.sva.se/media/cegdew24/swedres-svarm-2023.pdf

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Case 2

- 44-yr old male from Ukraine
- Hospitalized after reconstructive surgery
- Deep wound infection and fever with growth of ***K. pneumoniae***
  - Cefotaxime, ceftazidime, piperacillin-tazobactam, imipenem, ertapenem, meropenem, ciprofloxacin, trimethoprim-sulfa all R
  - Colistin 2 mg/L
  - R to imipenem-relebactam, meropenem-vaborbactam and ceftazidime-avibactam with disk diffusion

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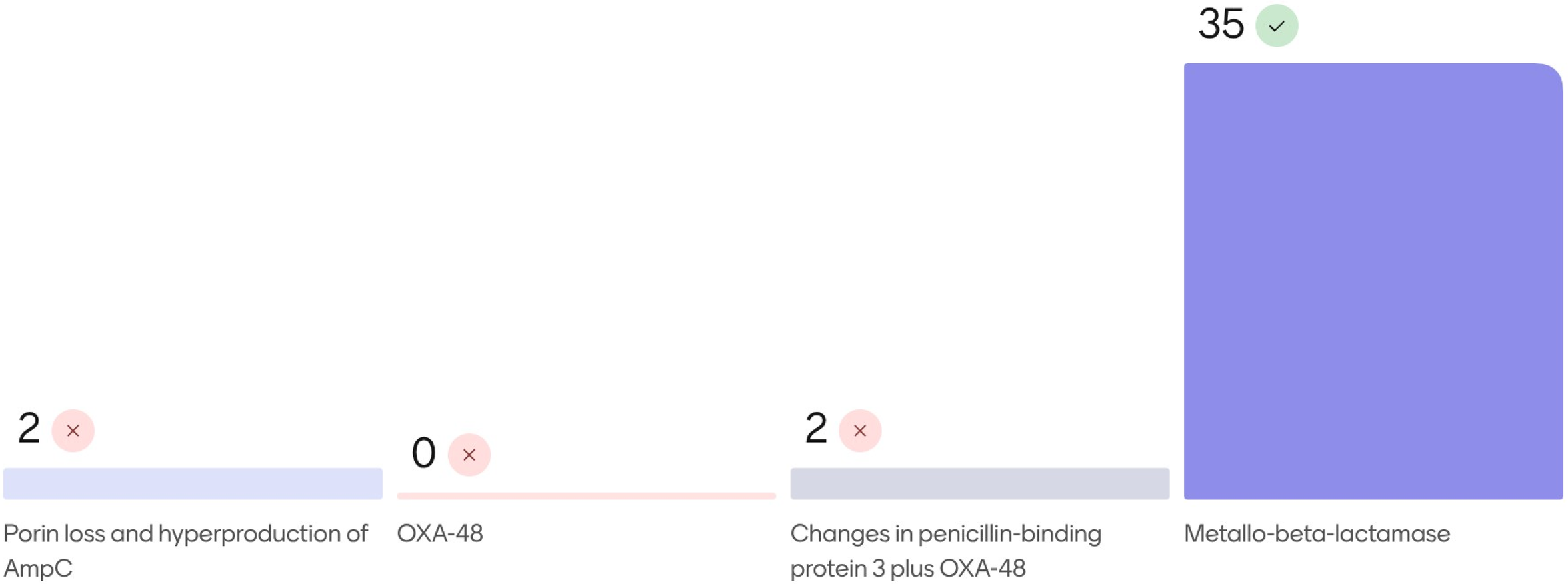
What is the most likely mechanism of resistance?



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You detect KPC and NDM with a lateral flow test. What is now your testing strategy for further agents?

0

Synergy testing with colistin, rifampicin and the most active carbapenem

2

Only cefiderocol

1

Switch to testing tigecycline plus aminoglycoside

1

Only aztreonam-avibactam

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Cefiderocol and aztreonam-avibactam

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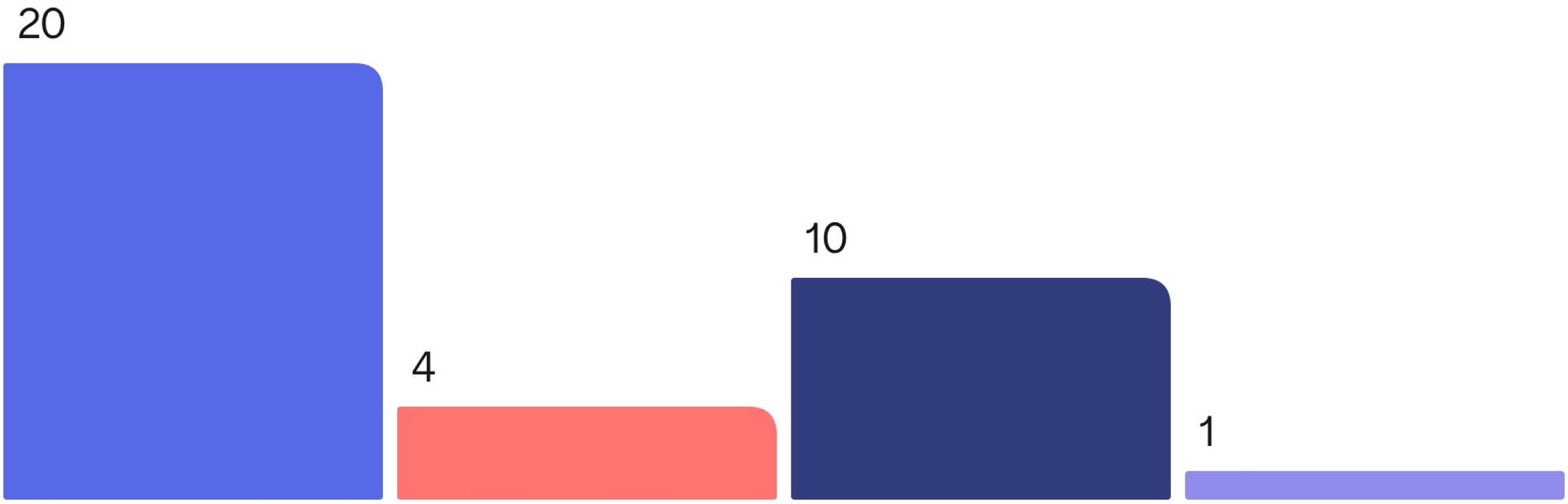
Cefiderocol is 21 mm (ATU) and aztreonam-avibactam is **S** with disk diffusion. What is your next action?



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1.1 *Enterobacterales* – inhibitor activity of relevant BLIs on clinically relevant β-lactamases[1]

β-lactamase inhibitor	β-lactam partner	ESBL (bla_{CTX-M})	Chromosomal/plasmid-mediated AmpC (bla_{CMY}, bla_{DHA})	Class A carbapenemases (bla_{KPC}, bla_{IMI})	Class B carbapenemases (bla_{NDM}, bla_{VIM}, bla_{IMP})	Class D carbapenemases[2] (bla_{OXA-48}, $bla_{OXA-181}$, $bla_{OXA-244}$)
Clavulanic acid[3]	Amoxicillin	+	-	-	-	-
Tazobactam	Piperacillin	+	-	-	-	-
Tazobactam	Ceftolozane	+	-	-	-	-
Enmetazobactam	Cefepime	+	-	+/-	-	-
Avibactam	Ceftazidime	+	+	+	-	+
Avibactam	Aztreonam	+	+	+	-[4]	+
Relebactam[5]	Imipenem	+	+	+	-	-
Vaborbactam	Meropenem	+	+	+	-	-
Taniborbactam[6]	Cefepime	+	+	+	+[7]	+
Zidebactam[6]	Cefepime	+	+	+	+	+

[1] +: inhibitory activity; -: No clinically useful inhibitory activity. Note that the activity of inhibitor can vary within and between variants in each β-lactamase group.
[2] Class D carbapenemases mainly associated with *A. baumannii* (e.g. OXA-23-like, OXA-24/-40-like and OXA-58-like) are rare among *Enterobacterales*, except for some reports mainly in *P. mirabilis*. The clinical effect of avibactam and taniborbactam is uncertain against these β-lactamases.
[3] β-lactam-β-lactamase inhibitor combination relevant for *E. coli*, *Klebsiella* spp. (except *K. aerogenes*), *Raoultella* spp. and *P. mirabilis*.
[4] Avibactam has not inhibitory activity against MBLs. However, aztreonam is not a substrate for MBLs.
[5] BLBLI relevant for Enterobacterales except *Morganellaceae* which have reduced susceptibility to imipenem.
[6] BLBLIs in phase 3 clinical trials.
[7] Limited in vitro inhibitory activity observed against some subclass B1 β-lactamases such as IMP and SIM, subclass B2 (PFM-like) and B3 (AIM-like). NDM- (e.g. NDM-9 and NDM-30) and VIM-variants (e.g. VIM-83) resistant to the inhibitory activity is described.

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Case 3

- 65 yr old female in the ICU following abdominal surgery for ileus
- Develops signs indicating ventilator associated pneumonia
- Growth in BAL of ***P. aeruginosa*** > 10^4 cfu/mL
- Resistance pattern: imipenem, meropenem, piperacillin-tazobactam, ceftazidime and ciprofloxacin **R** with disk diffusion

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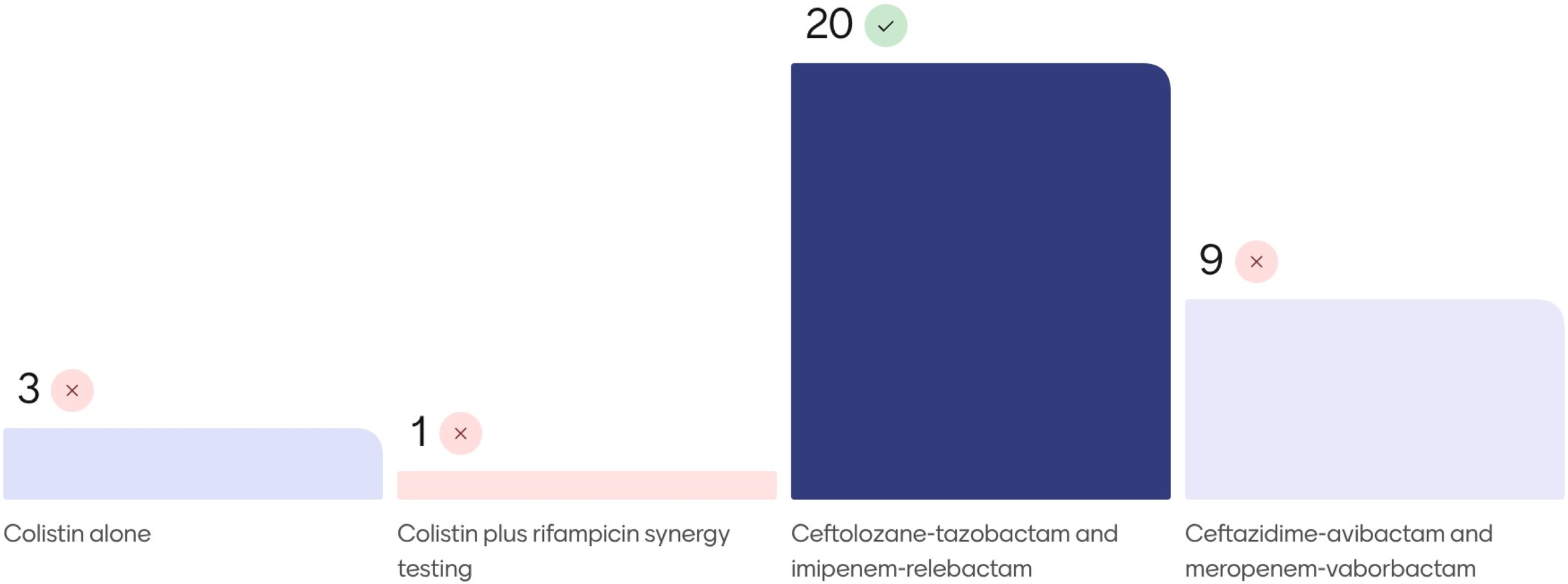
What do you test?



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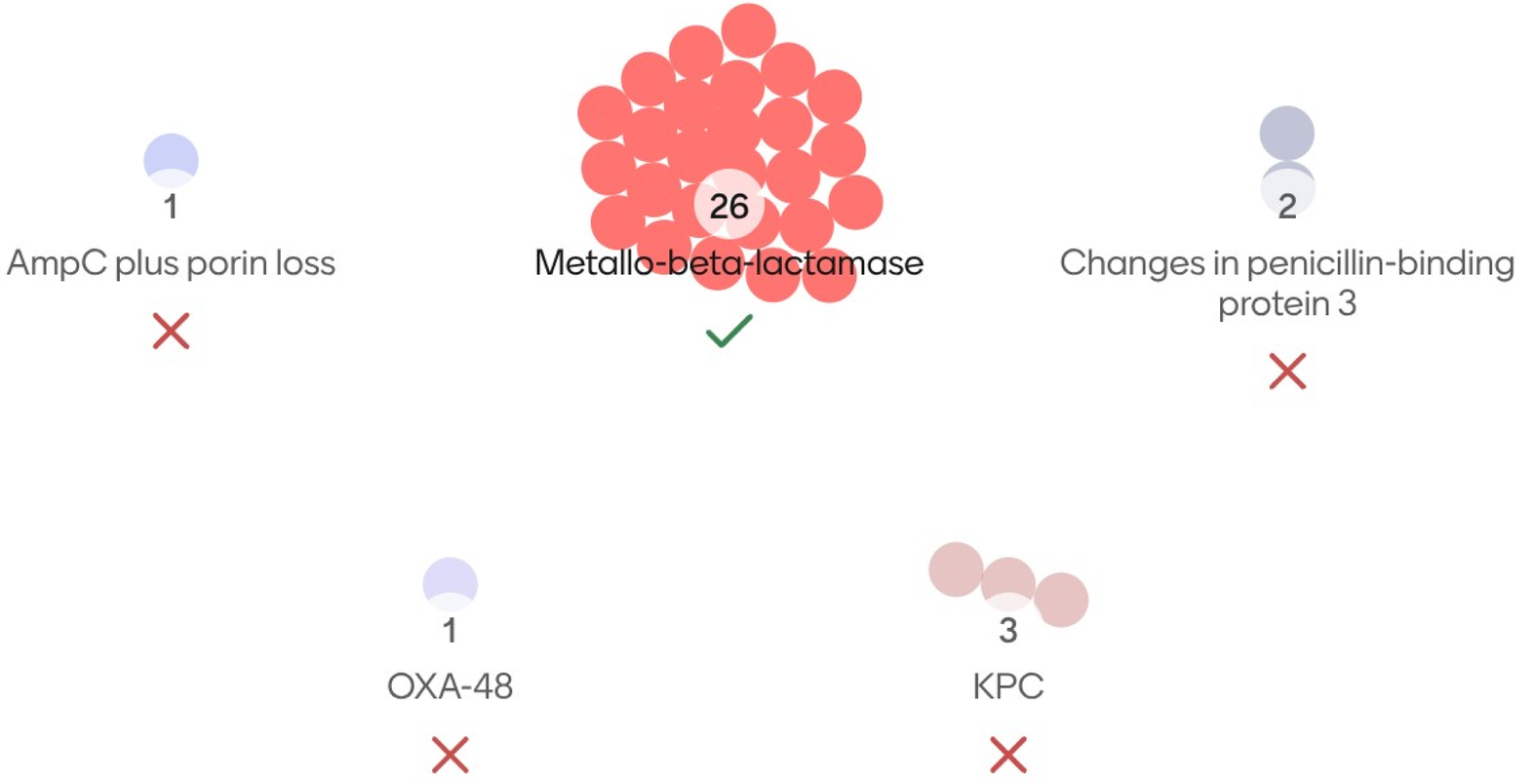
Resistance:

Ceftolozane-tazobactam

Imipenem-relebactam

Ceftazidime-avibactam

What is the most likely resistance mechanism?



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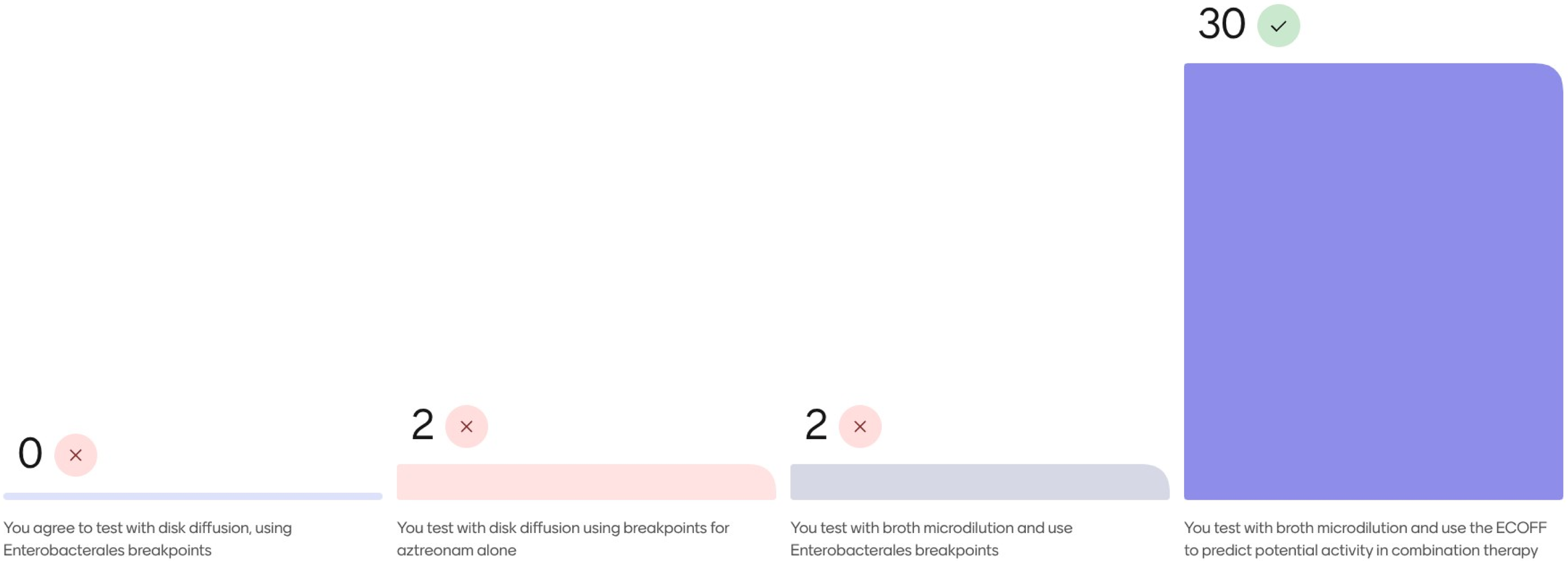
NDM+, cefiderocol 20mm, colistin 8 mg/L. The ID consultant wants you to test aztreonam-avibactam. What is your response?



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1.2 *P. aeruginosa* - inhibitor activity of relevant BLIs on clinically relevant β-lactamases[1]

β-lactamase inhibitor	β-lactam partner	ESBL (*bla*CTX-M/GES/PER)	Chromosomal AmpC	Class A carbapenemases (*bla*KPC/GES-varianter)	Class B carbapenemases (*bla*NDM/VIM/IMP)	Class D carbapenemases[2] (*bla*OXA-48/-181/-244/-23/-24/-40/-58)
Tazobactam[3]	Piperacillin	+	-	-	-	-
Tazobactam[3]	Ceftolozane	+	-[3]	-	-	-
Avibactam[2]	Ceftazidime	+	+	+	-	+
Relebactam[5]	Imipenem	+	+	+	-	-
Vaborbactam[5]	Meropenem	+	+	+	-	-
Taniborbactam[4]	Cefepime	+	+	+	+[5]	+[6]
Zidebactam[4]	Cefepime	+	+	+	+	+

[1] +: inhibitory activity; -: No clinically useful inhibitory activity. Note that the activity of inhibitor can vary within and between variants in each β-lactamase group.
[2] Class D carbapenemases are rare in *Pseudomonas* spp. and the clinical effect of relevant β-lactamase inhibitors is uncertain against these β-lactamases.
[3] The activity of the inhibitor is limited. The most relevant activity is due to the β-lactam partner.
[4] BLBLIs in phase 3 clinical trials.
[5] Limited inhibitory activity observed against some subclass B1 β-lactamases such as IMP and SIM, subclass B2 (PFM-like) and B3 (AIM-like). NDM- (e.g. NDM-9 and NDM-30) and VIM-variants (e.g. VIM-83) resistant to the inhibitory activity is described.
[6] In vitro inhibitory activity described, but clinical effect is unclear.

Case 4

- Patient, 20-something
- Multitrauma – traffic accident Northern Africa. Several severe fractures, including face. Surgery and hospitalization locally before transfer to Norway for further treatment.
- Clinically worse, meningitis symptoms (>2000 cells in CSF!)
  - Spinal fluid: *A. baumannii*
  - Blood, BAL, urine: *A. baumannii*
- Empiric treatment: meropenem iv. with some effect?

Case 4: **Primary AST**

Imipenem	R
Meropenem	R
Ciprofloxacin	R
Gentamicin	R
Trimethoprim-sulfamethoxazole	R

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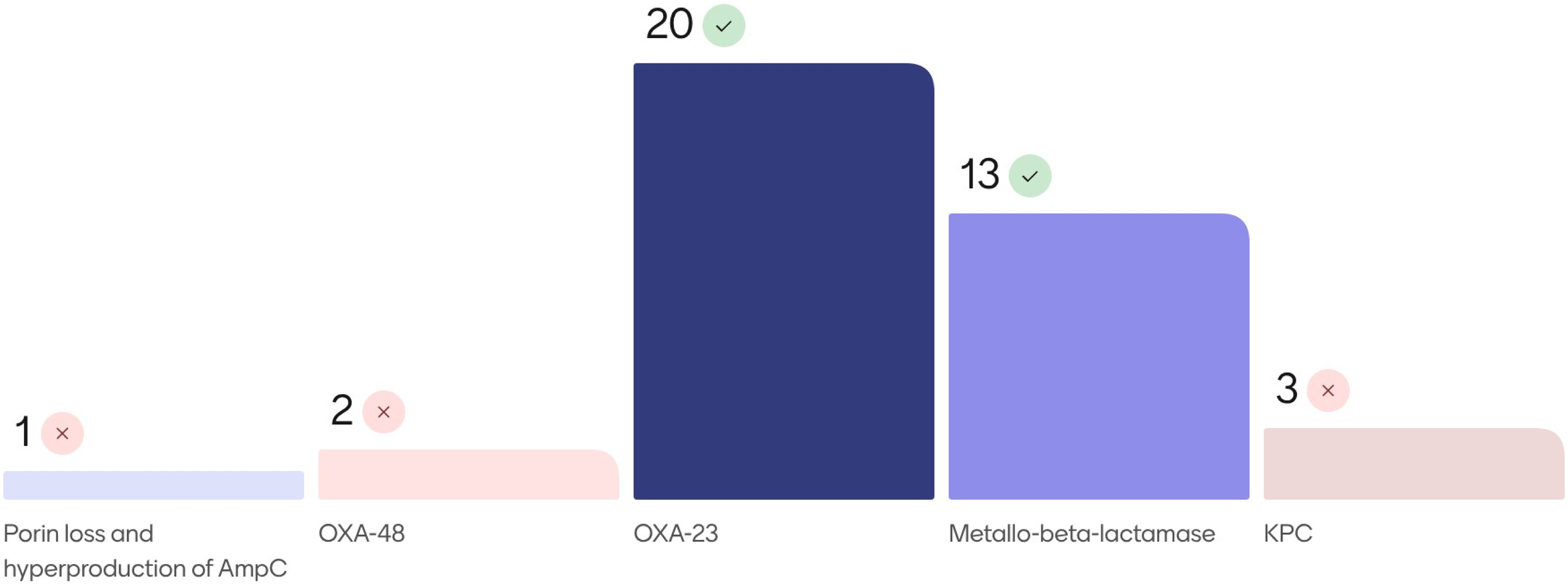
R: carbapenems, ciprofloxacin, gentamicin, trim-sulfa. What resistance mechanism is most likely?



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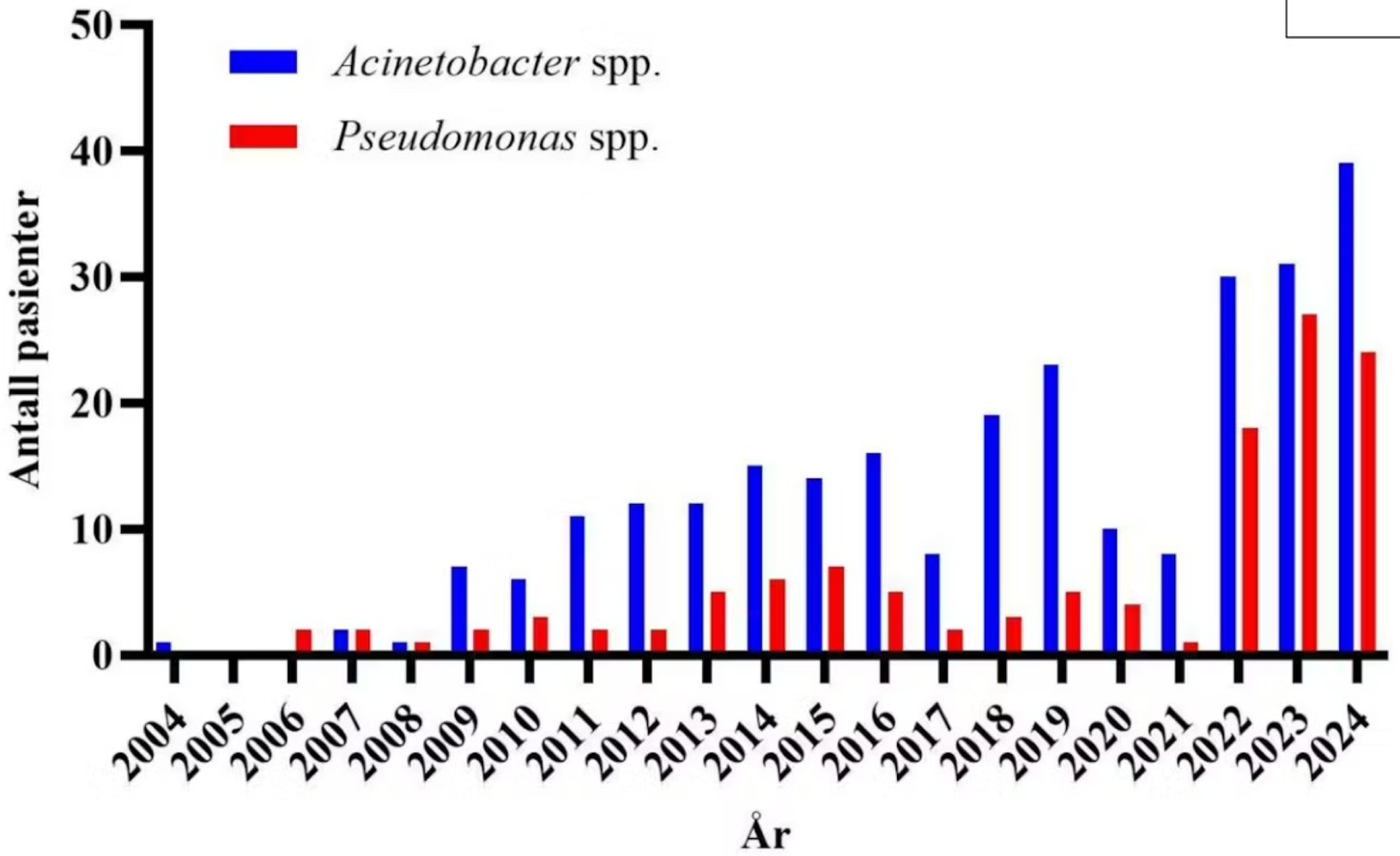
Forekomst og molekylærgenetiske analyser av bakterier med spesielle resistensmønstre i Norge 2024 – rapport fra nasjonalt referanselaboratorium



Figur 16. Antall personer med påvist karbapenemaseproduserende *Pseudomonas* spp. og *Acinetobacter* spp. i Norge 2004-2024.

Forekomst og molekylærgenetiske analyser av bakterier med spesielle resistensmønstre i Norge 2024 – rapport fra nasjonalt referanselab.

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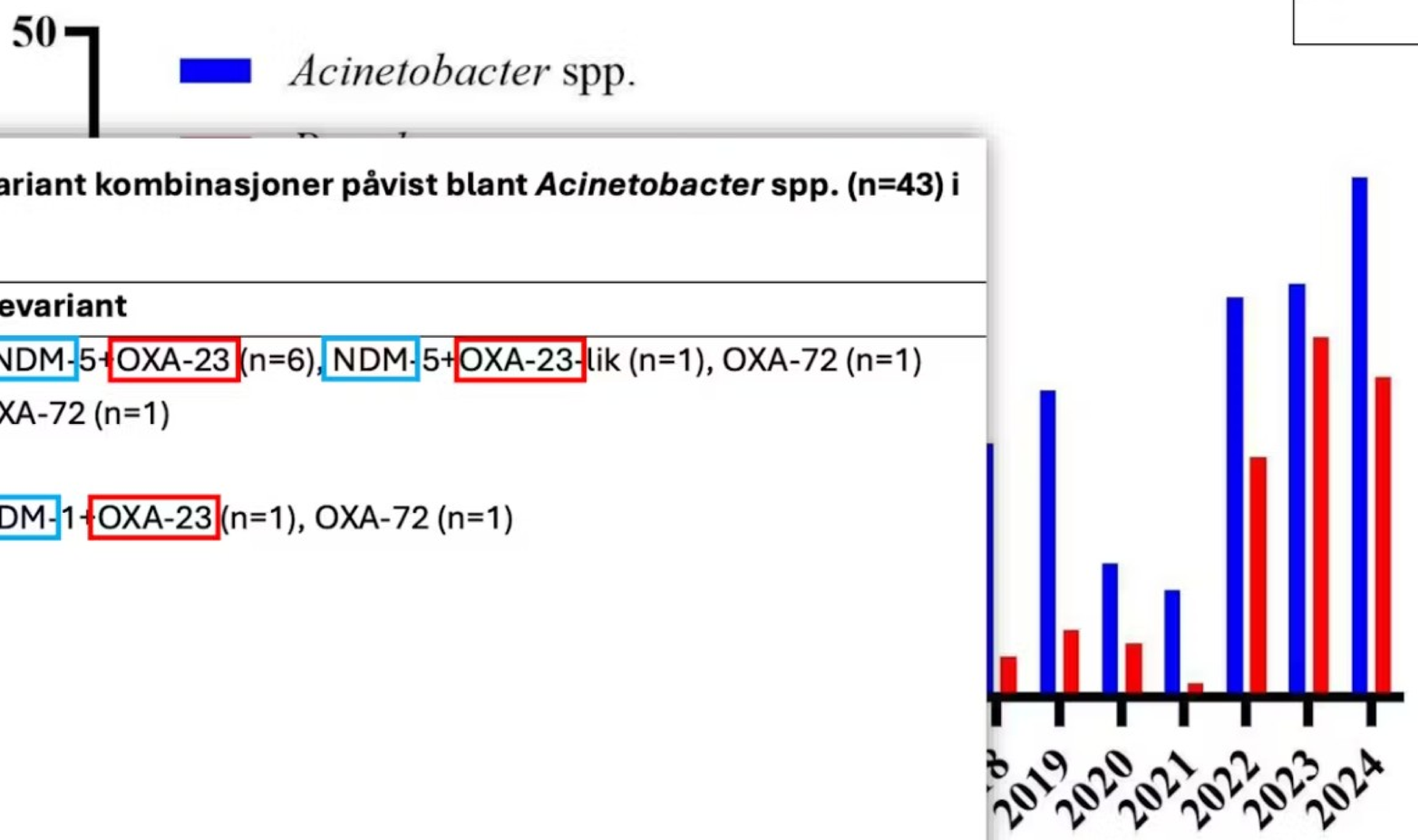
Tabell 4. Species/ST-karbapenemasevariant kombinasjoner påvist blant *Acinetobacter* spp. (n=43) i 2024

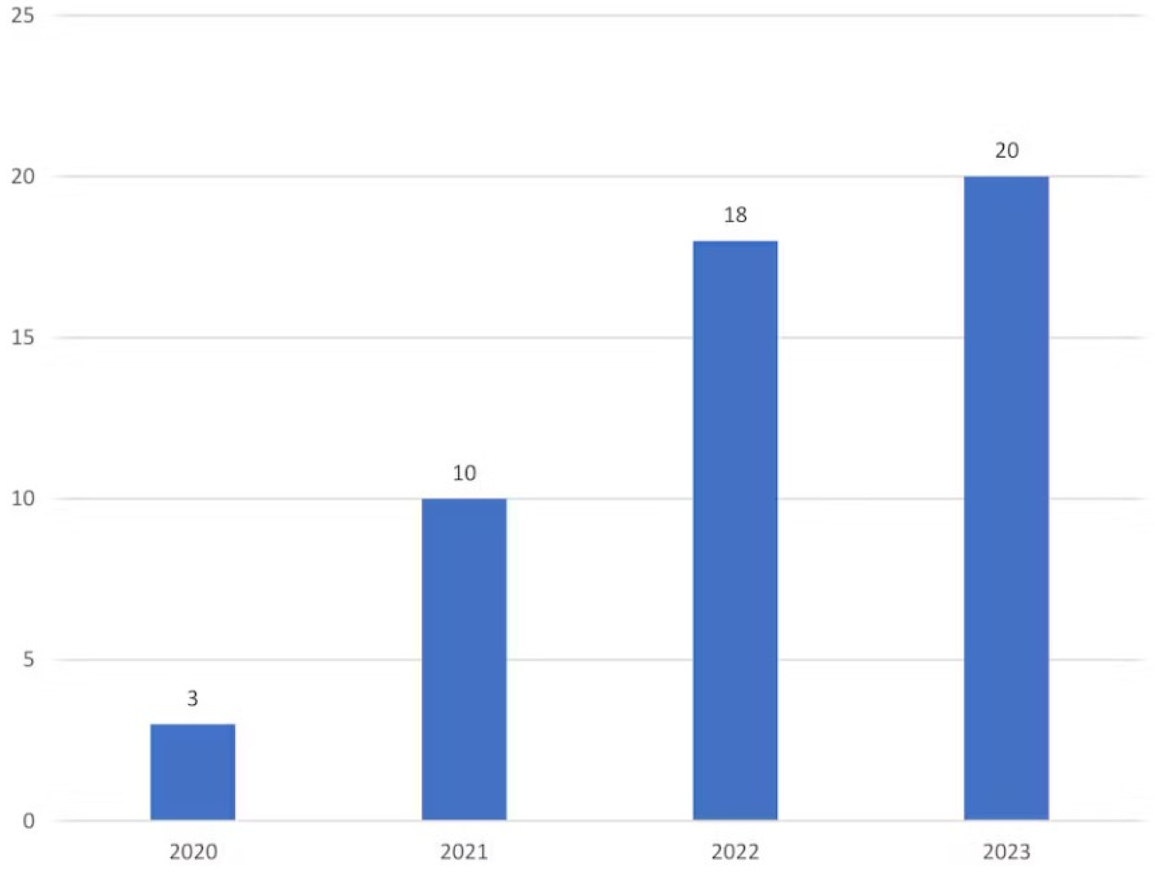
***A. baumannii* ST**	**Karbapenemasevariant**
ST2 (n=20)	OXA-23 (n=12), NDM-5+OXA-23 (n=6), NDM-5+OXA-23-lik (n=1), OXA-72 (n=1)
ST19 (n=6)	OXA-23 (n=5), OXA-72 (n=1)
ST78 (n=5)	OXA-72 (n=5)
ST164 (n=4)	OXA-23 (n=2), NDM-1+OXA-23 (n=1), OXA-72 (n=1)
ST1 (n=1)	OXA-72 (n=1)
ST15 (n=1)	NDM-1 (n=1)
ST158 (n=1)	OXA-23 (n=1)
ST29 (n=1)	NDM-1 (n=1)
ST-ny (n=2)	OXA-23 (n=2)
A. seifertii (n=1)[1]	OXA-72 (n=1)
A. johnsonii (n=1)[1]	NDM-1 (n=1)

[1] MLST ikke etablert.



Figur 16. Antall personer med påvist karbapenemaseproduserende *Pseudomonas* spp. og *Acinetobacter* spp. i Norge 2004-2024.

Utveckling *Acinetobacter baumannii*-komplexet med $ESBL_{CARBA}$ 2020-2023, Stockholm

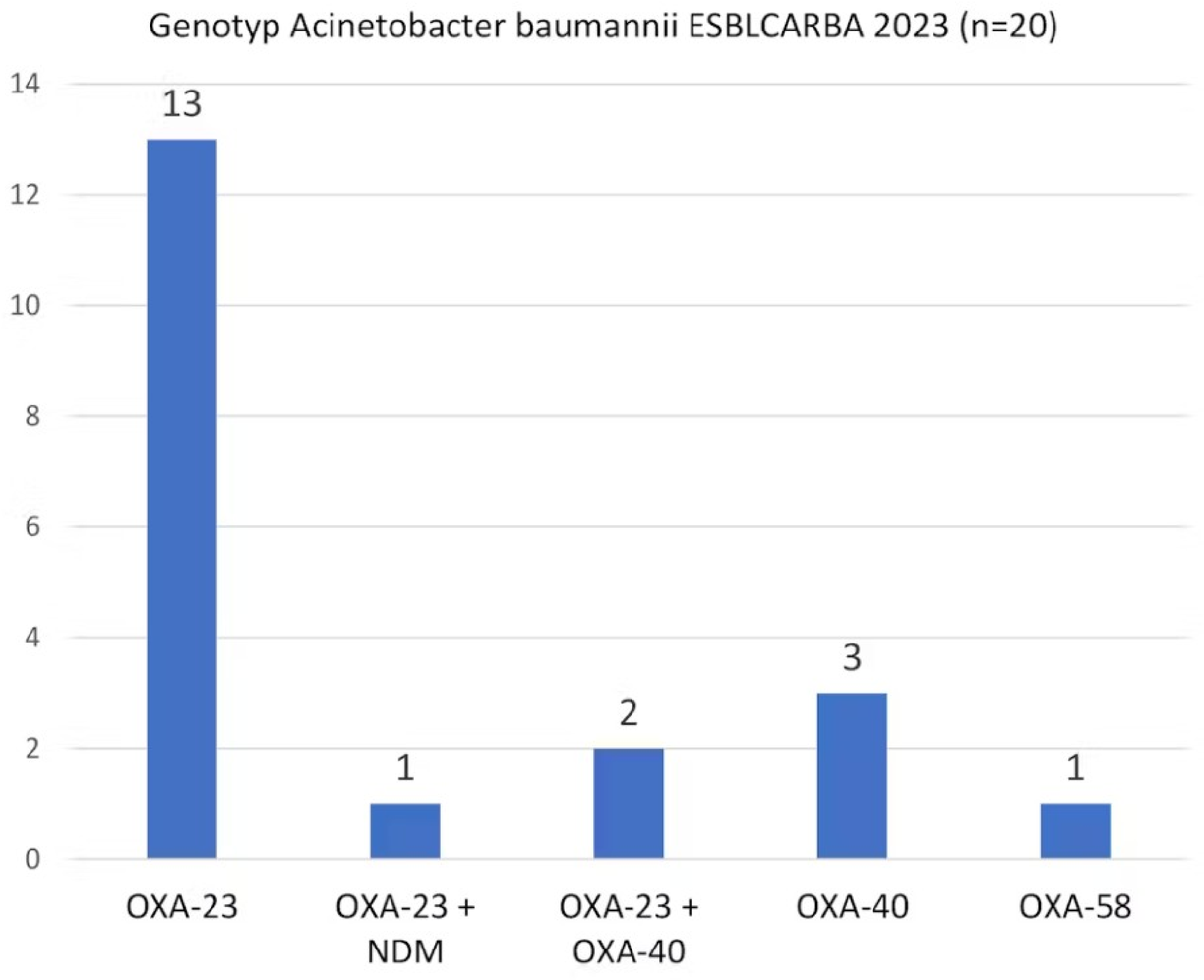


Nationell övervakning 2023 enligt SWEDRES

Microbiological surveillance programme, *Acinetobacter* spp.

In total, 46 isolates were received in 2023 within the microbiological surveillance program for *Acinetobacter* spp. with reduced susceptibility to meropenem (I+R). This is similar to what was seen in 2020 (n=46) and 2021 (n=45), however, less than in 2022 (n=67). Of the 46 isolates 38 carried a species-specific OXA-genes (23, 24 or 58-like), five encoded an NDM gene, and in three, no carbapenemase was detected. Four clusters were active during 2023, including samples from two (OXA-23), four (OXA-23), five (OXA-24) and nine (OXA-23) patients.

Acinetobacter baumannii-komplexet med $ESBL_{CARBA}$ 2023



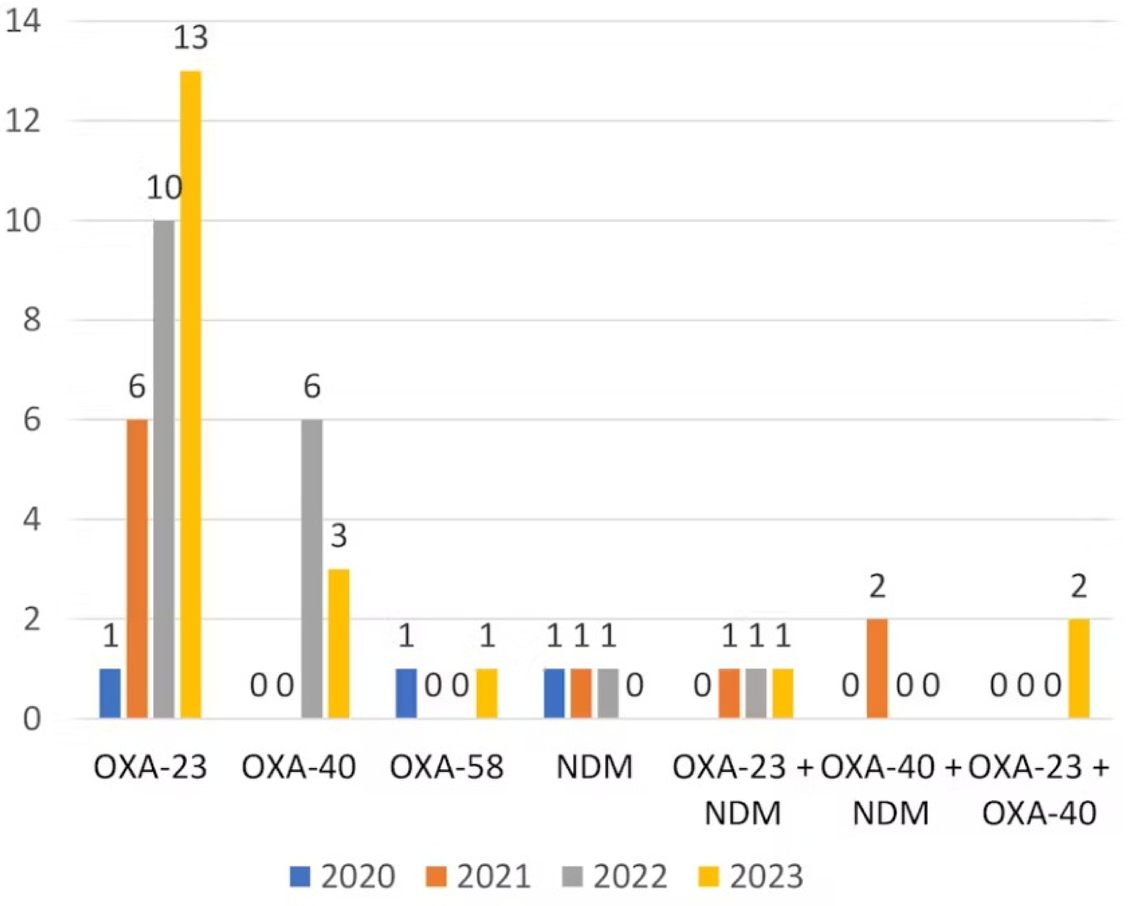


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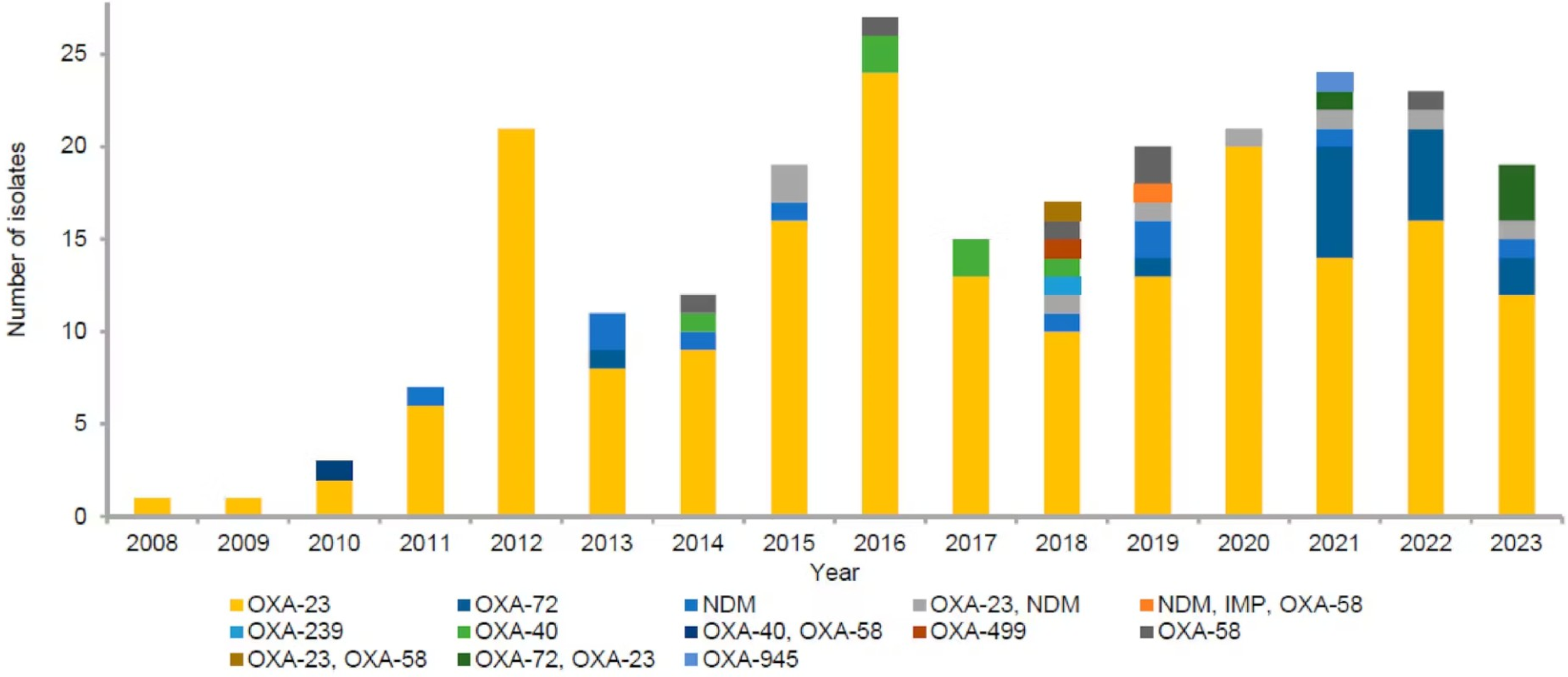
Figure 8.15 Carbapenemase-producing *Acinetobacter* spp. and enzymes identified, Denmark, 2008-2023

DANMAP 2023



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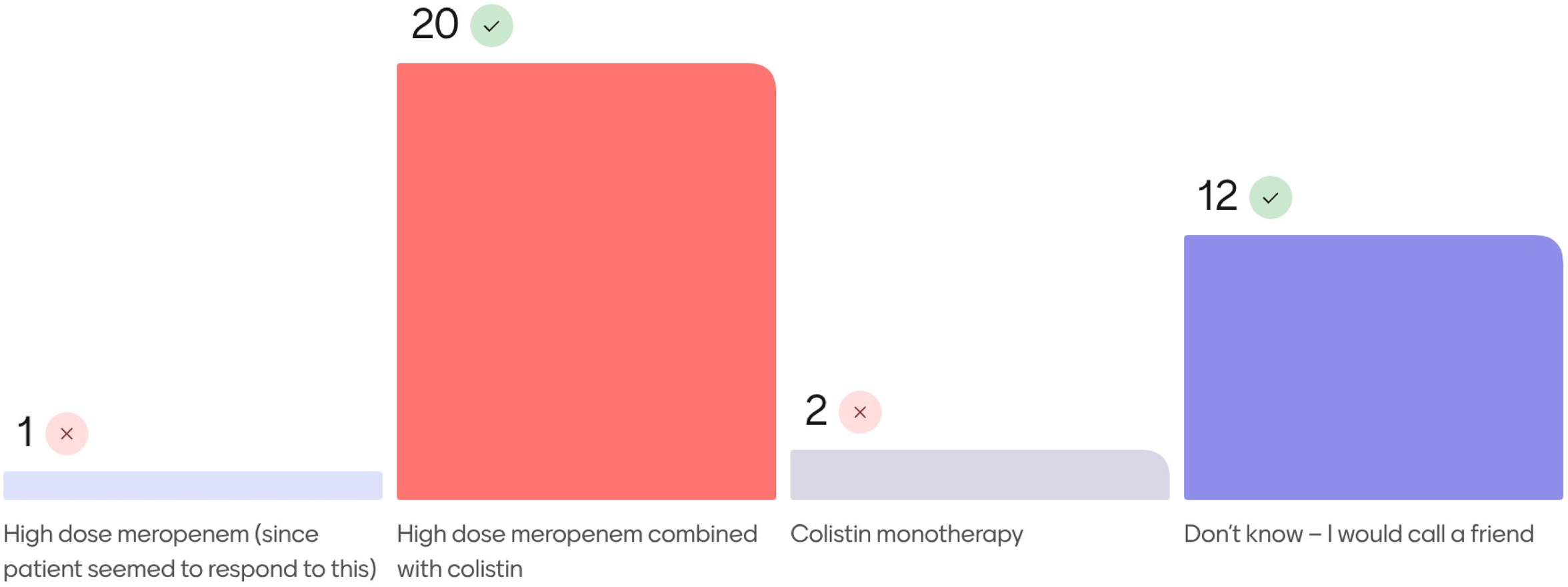
A. baumanni: OXA-23, R: carbapenems, cipro, genta, trim-sulfa. What empiric treatment would you suggest?



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Tabell 5. Andel (%) resistens blant karbapenemaseproduserende *Acinetobacter* spp. (n=43) i 2024

Antibiotikum	Resistente isolater (%)
Meropenem	100 %
Imipenem	100 %
Ciprofloxacin	98 %
Amikacin	84 %
Gentamicin	74 %
Tobramycin	65 %
Trimetoprim-sulfametoksazol	77 %
Kolistin	5 %

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Case 4: AST cont. (2019)

Penicillins	MIC (mg/L)
Ampicillin-sulbactam	>256
Amoxicillin-clavulanic acid	>64
Piperacillin-tazobactam	>128
Cephalosporins	
Cefotaxime	>8
Ceftazidime	128
Ceftazidime-avibactam	>16
Ceftolozane-tazobactam	16
Carbapenems	
Ertapenem	>2
Imipenem	>16
Meropenem	>32
Monobactams	
Aztreonam	32

Fluoroquinolones	MIC (mg/L)	
Ciprofloxacin	>16	
Levofloxacin	4	
Moxifloxacin	>32	
Aminoglycosides		
Amikacin	128	
Gentamicin	>128	
Tobramycin	128	
Tetracyclines		
Tigecycline	1 (4)	✸
Miscellaneous agents		
Colistin	2	✸
Daptomycin	>256	
Fosfomycin iv	>256	
Rifampicin	4	✸
Trimethoprim-sulfamethoxazole	8	

* Methods: BMD/MTS

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Case 4: AST cont. (2019)

Penicillins	MIC (mg/L)
Ampicillin-sulbactam	>256
Amoxicillin-clavulanic acid	>64
Piperacillin-tazobactam	>128
Cephalosporins	
Cefotaxime	>8
Ceftazidime	128
Ceftazidime-avibactam	>16
Ceftolozane-tazobactam	16
Carbapenems	
Ertapenem	>2
Imipenem	>16
Meropenem	>32
Monobactams	
Aztreonam	32

Fluoroquinolones	MIC (mg/L)	
Ciprofloxacin	>16	
Levofloxacin	4	
Moxifloxacin	>32	
Aminoglycosides		
Amikacin	128	
Gentamicin	>128	
Tobramycin	128	
Tetracyclines		
Tigecycline	1 (4)	✱
Miscellaneous agents		
Colistin	2	✱
Daptomycin	>256	
Fosfomycin iv	>256	
Rifampicin	4	✱
Trimethoprim-sulfamethoxazole	8	

2025:

- **Cefiderocol**? (guidelines: ESCMID vs IDSA)
- **Sulbactam-durolobactam**?
- Any other suggestions?

* Methods: BMD/MTS

NordicAST

Case 4: What actually happened?

- I called a few friends (Ørjan Samuelsen and Christian Giske are on speed-dial ☺)
- Close collaboration: ICU-doctors, ID-doctors, microbiologist, pharmacist
- Treatment: Intra thecal colisin combined with high dose meropenem iv
  - Contacted Shinogi about possible «rescue therapy with cefiderocol»
  - Contacted Swedish lab about serum concentration measurement of colistin
  - Litterature search
  - etc….
- After many weeks, the patient recovered completely!

Mentimeter

1.3 *A. baumannii* - inhibitor activity of relevant BLIs on clinically relevant betalactamases[1]

Relevant BLBLIs include only those containing carbapenems and sulbactam. Cephalosporins and monobactams in combination with BLIs are not considered relevant as there is insufficient evidence for clinical efficacy of cephalosporins and monobactams in the treatment of infections caused by Acinetobacter spp.

β-lactamase inhibitor	β-lactam partner	ESBL (bla_{CTX-M})	Chromosomal AmpC	Class A carbapenemases (bla_{KPC})	Class B carbapenemases ($bla_{NDM/VIM/IMP}$)	$ESBL_{CARBA-D}$/Class D carbapenemases[2] ($bla_{OXA-23/-24/-40/-58}$)
Relebactam[3]	Imipenem	+	+	+	-	-
Vaborbactam[3]	Meropenem	+	+	+	-	-
Durlobactam[4]	Sulbactam	+	+	+	-	+

[1] +: inhibitory activity; -: No clinically useful inhibitory activity. Note that the activity of inhibitor can vary within and between variants in each β-lactamase group.
[2] OXA-48-like class D/class A carbapenemases are rare in *Acinetobacter* spp.
[3] The β-lactamases produced by the organisms either do not modify the parent carbapenem or are insufficiently inhibited by the inhibitor. Therefore, the addition of the β-lactamase inhibitor does not add clinical benefit.
[4] BLBLI approved by FDA. Durlobactam has in addition to inhibitory activity against β-lactamases direct antibacterial effect activity due to anti-PBP-2 activity.
[5] β-lactam-β-lactamase inhibitor combination in clinical development.
[6] Limited inhibitory activity observed against some subclass B1 β-lactamases such as IMP and SIM, subclass B2 (PFM-like) and B3 (AIM-like). NDM- (e.g. NDM-9 and NDM-30) and VIM-variants (e.g. VIM-83) resistant to the inhibitory activity is described.
[7] Inhibitory activities are described, but clinical efficacy is unclear.

Mentimeter

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