

Nordic traditions for AST reporting in
Enterobacterales with risk of
hyperproducing AmpC

Meet the Expert

NordicAST workshop 28.5.2024

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Blood culture:

Enterobacter cloacae

• Ampicillin	R
• Amox-clav	R
• Cefuroxime	R
• Ciprofloxacin	S
• Cefotaxime	S
• Ceftazidime	S
• Ertapenem	S
• Meropenem	S
• Piperacillin-tazob	S
• Ciprofloxacin	S
• Tobramycin	S

How do you report 3rd gen cephalosporins?

- a. As tested (without any comment)
- b. As tested, but add a warning about the risk of developing resistance during treatment
- c. As tested, but discouraging use of cefotaxime or ceftazidime
- d. Suppress the results of cefotaxime and ceftazidime

Blood culture:

Serratia marcescens

• Ampicillin	R
• Amox-clav	R
• Cefuroxime	R
• Ciprofloxacin	S
• Cefotaxime	S
• Ceftazidime	S
• Ertapenem	S
• Meropenem	S
• Piperacillin-tazob	S
• Ciprofloxacin	S
• Tobramycin	S

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- d. Suppress the results of cefotaxime and ceftazidime

Enterobacter cloacae in blood culture

If you have access to clinical data, would it affect the way you report?

- a. No
- b. Yes, depends on the severity of infection
- c. Yes, depends on the site of infection
- d. Yes, depends on expected inoculum at the site of infection
- e. Yes, some other way

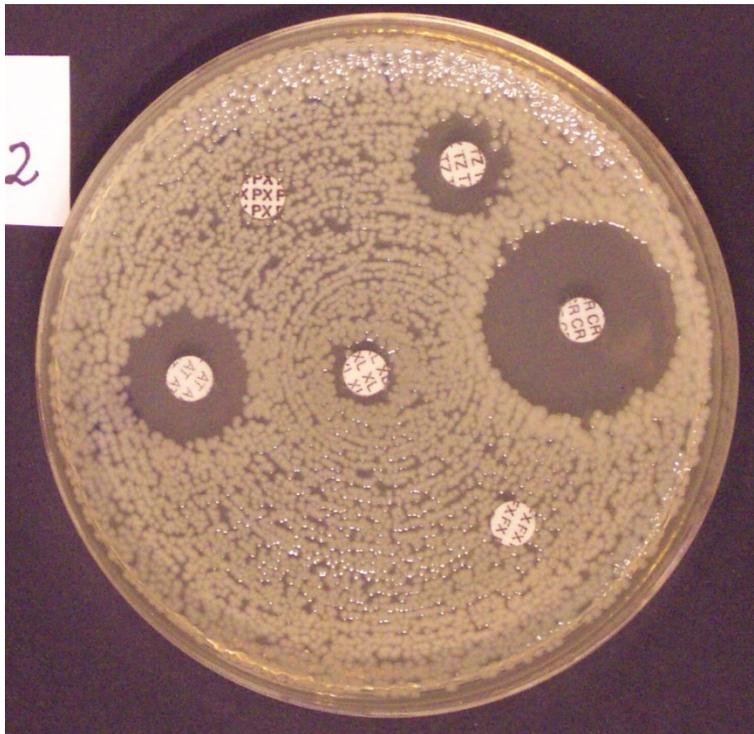
EUCAST Expert Rules v 3.2 on Enterobacterales

Rule No.	Organisms	Indicator Agent*	Agents affected*	Rule	Remarks	Grade	References
Beta-Lactams							
1	<i>E. coli</i> , <i>P. mirabilis</i>	ampicillin	ampicillin	IF resistant to ampicillin, THEN report		A	Drugg...
3	<i>Enterobacter</i> spp., <i>K. aerogenes</i> , <i>Citrobacter freundii</i> [†] , <i>Hafnia alvei</i>	cefotaxime, ceftriaxone, ceftazidime	cefotaxime, ceftriaxone, ceftazidime	IF susceptible in vitro to cefotaxime, ceftriaxone or ceftazidime, THEN EITHER add a note that monotherapy with cefotaxime, ceftriaxone or ceftazidime as well as combination therapy of these agents with an aminoglycoside should be discouraged owing to risk of selecting resistance, OR suppress the susceptibility testing results for these agents	Selection of AmpC de-repressed cephalosporin-resistant mutants may occur during therapy. The risk is relatively high in <i>Enterobacter</i> , <i>K. aerogenes</i> and <i>Citrobacter</i> and low in <i>Morganella</i> and <i>Serratia</i> . For <i>Hafnia alvei</i> in-vitro mutation rates are similar to <i>Enterobacter</i> or <i>Citrobacter</i> . The use of a 3rd generation cephalosporin in combination with an aminoglycoside may also lead to failure by selection of resistant mutants. the combination with a quinolone, however, has found to be protective, although the clinical utility of this combination is not known The selection risk is absent or much diminished for cefepime	A	Neu, 1981 Sanders & Sanders, 1988; Choi et al., 2008; Harris & Ferguson, 2012; Kohlmann, Bähr, & Gatermann, 2018

Rule No.	Organisms	Indicator Agent*	Agents affected*	Rule	Remarks	Grade	References
4	<i>Serratia</i> spp., <i>Morganella morganii</i> , <i>Providencia</i> spp	cefotaxime, ceftriaxone, ceftazidime	cefotaxime, ceftriaxone and ceftazidime	IF susceptible to cefotaxime, ceftriaxone or ceftazidime, THEN note that monotherapy with cefotaxime, ceftriaxone or ceftazidime may infrequently select resistant mutants		A	Sanders & Sanders, 1988; Choi et al., 2008; Harris & Ferguson, 2012; Kohlmann, Bähr, & Gatermann, 2018
5	<i>Enterobacter</i> spp.	cefotaxime	cefotaxime	IF susceptible to cefotaxime, THEN	Although the combination with	C	

Enterobacterales – selection of hyperproducing AmpC-strains

antimicrobial susceptibility testing and reporting



Arnfinn Sundsfjord

NordicAST, Malmö

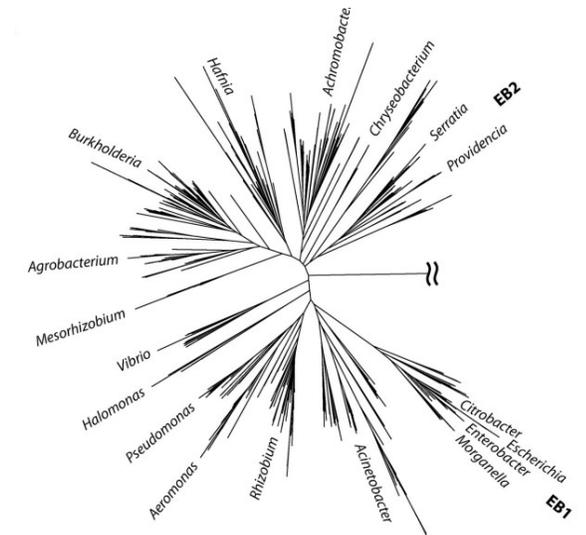
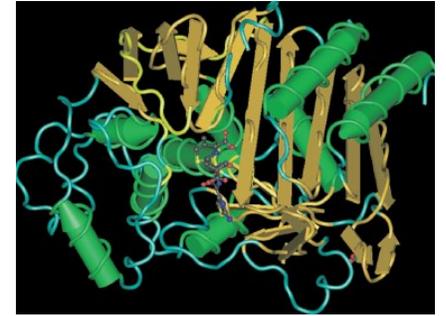
May 28, 2024



Arbeidsgruppen for
antibiotikaspørsmål og metoder
for resistensbestemmelse (AFA)

Agenda

- **Enterobacterales – risk for hyperproducing AmpC**
 - Clinically relevant species
- **Regulation of AmpC-expression**
 - Basal, induced, derepressed high-level
 - Antimicrobial substrate profile
- **Selection of stably derepressed AmpC-production**
 - Clinical studies
 - *In vitro* studies
- **Susceptibility testing and reporting**
 - Past
 - Revised



Relevant species

- *Enterobacter cloacae* complex
- *Klebsiella aerogenes*
- *Citrobacter freundii* complex
- *Hafnia alvei*
- *Providencia* spp.
- *Serratia* spp.
- *Morganella morganii*.

Philippon A et al. *Clin Micro Rev* 2022;35:3

Jacoby GA. AmpC β -lactamases. *Clin Microbiol Rev* 2009;22:161-82.

Livermore D. *Clin Micro Rev* 1995, p. 557–584

Enterobacterales (Karbapenemresistens) dyrkning (NPU58621)

1 Forhøyet kromosomal AmpC påvist

2 ENTEROBACTER CLOACAE COMPLEX

Amikacin	MIC: <2	mg/L	(S)
Meropenem+Vaborbactam	MIC: <0.06	mg/L	(S)
Avibaktam+Ceftazidim	MIC: 0.5	mg/L	(S)
Ceftolozan+Tazobaktam	MIC: 8	mg/L	(R)
Aztreonam	MIC: 32	mg/L	(R)
Cefotaksim	MIC: >16	mg/L	(R)
Cefoksitin	MIC: >32	mg/L	()
Ceftazidim	MIC: >32	mg/L	(R)
Ciprofloksacin	MIC: <0.06	mg/L	(S)
Eravasyklin	MIC: 0.25	mg/L	()
Kolistin	MIC: 0.5	mg/L	(S)
Cefepim	MIC: 2	mg/L	(I)
Cefepim (ESBL)	MIC: 2	mg/L	()
Cefepim + Klavulansyre (ESBL)	MIC: 1.5	mg/L	()
Ertapenem	MIC: 0.5	mg/L	(S)
Fosfomycin	MIC: 32	mg/L	()
Gentamicin	MIC: <0.25	mg/L	(S)
Imipenem	MIC: 0.25	mg/L	(S)
Imipenem+Relebaktam	MIC: 0.25	mg/L	(S)
Meropenem	MIC: 0.06	mg/L	(S)
Nitrofurantoin	MIC: 32	mg/L	()
Piperacillin+Tazobaktam	MIC: >32	mg/L	(R)
Temocillin	MIC: 16	mg/L	()
Tigesyklin	MIC: 0.25	mg/L	()
Tobramycin	MIC: <0.5	mg/L	(S)
Trimetoprim+Sulfametoksazol	MIC: <0.5	mg/L	(S)

Chromosomal AmpC - basal, induction and hyperproduction

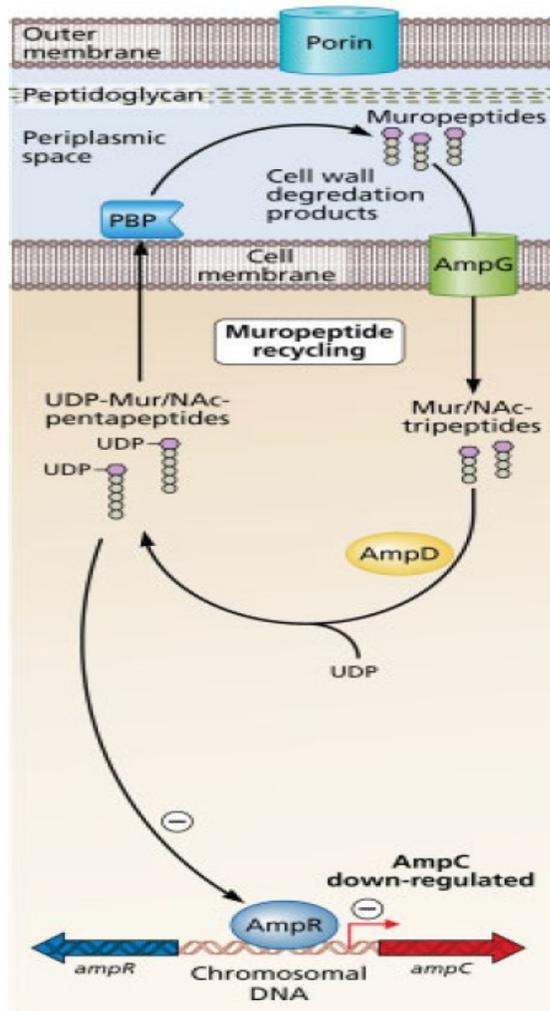
- Expression of the chromosomal AmpC β -lactamase is **normally low (basal)**
- A higher level of expression can be **induced (transient)** by specific beta-lactam antibiotics.
 - Resistance to ampicillin/amoxicillin-clavulanic acid, cefoxitin, and first generation cephalosporins (1GC).
- During ongoing antibiotic treatment, spontaneous mutants with **stably elevated expression (derepressed hyperproduction)** of chromosomal AmpC can be selected
 - Resistance to all penicillins, 2-3. generation cephalosporins (2-3GC), and aztreonam

Goldstein F. Clin Microbiol Infection 2002

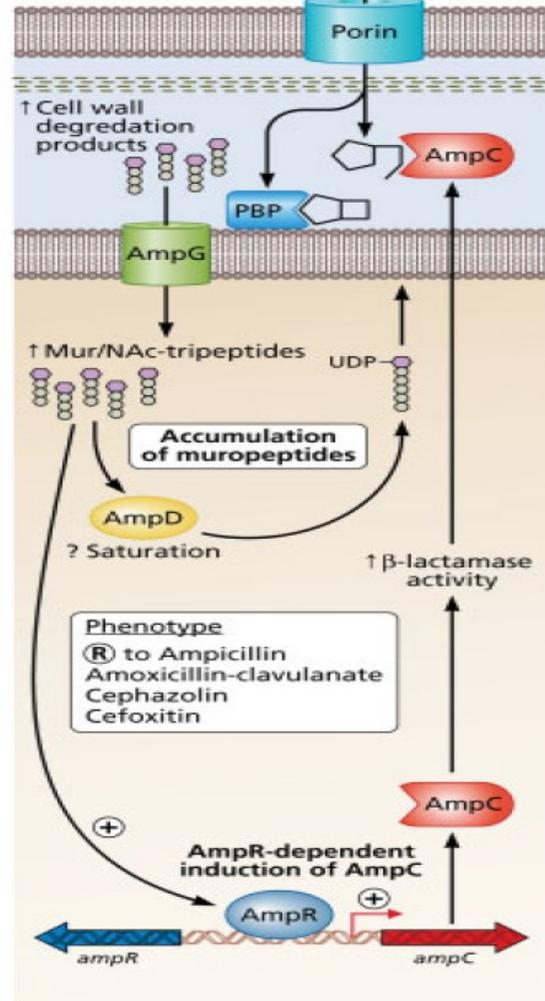
Jacoby GA. AmpC β -lactamases. Clin Microbiol Rev 2009;22:161-82.

Regulation of AmpC-expression

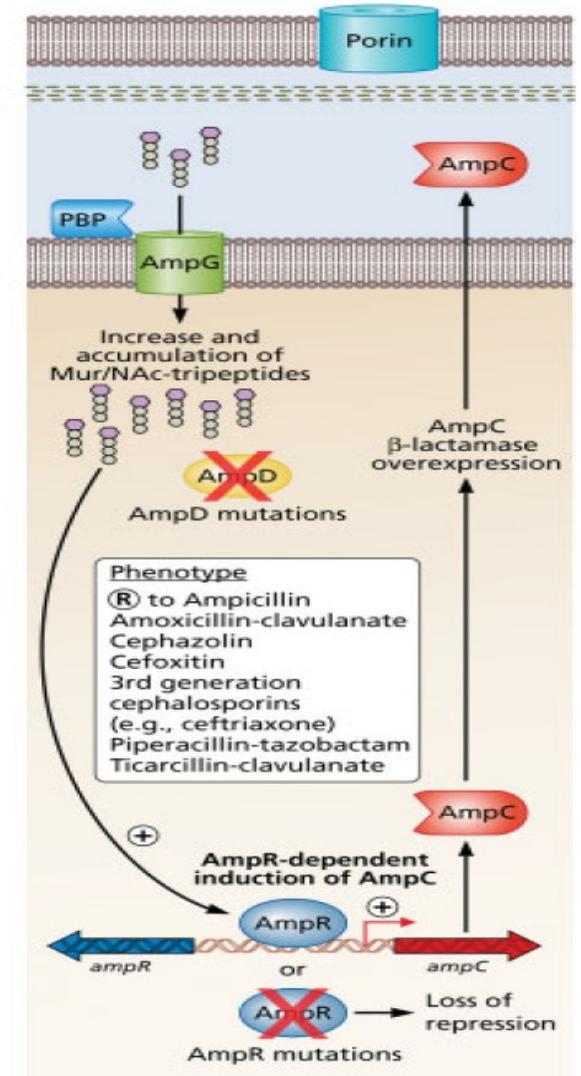
Wild-type basal level AmpC-expression



AmpC-induction (transient)



AmpC-derepressed (constitutive)



Betalactams: induction of AmpC and stability

- Strong induction and unstable (good substrate for hydrolysis)
 - 1GC, aminopenicillins, ceftioxin, ceftazidime, clavulanic acid
- Strong induction, but stable
 - Imipenem
- Weak/no induction and limited stability
 - 3GC, aztreonam, ureidopenicillins
 - Affected by stable hyperexpression/presence of a strong inducer
- No induction and relatively stable
 - Cefepime, cefpirome

Enterobacter bacteremia – emergence of resistance during therapy

- **Study design and setting:**

- Prospective observational study, six centres
- *Enterobacter* bacteremia, n=129, heterogenous AB-use
- MIC-determination of paired isolates
- Resistance development against 3GC
 - 6/31 (19%) during ongoing 3GC monotherapy, one patient died
- Appearance of resistance; mean 9 days (4-18 days).

- **Strengths**

- Prospective, molecular typing of paired isolates

- **Limitations**

- Few patients, infection focus not considered for those with resistance development
- Cefotaxime MICs pre-therapy strains varied between $\leq 0.25/2/4$ and 8 mg/L
 - Old CLSI cefotaxime breakpoints (high, R ≥ 16 mg/L)
 - Current breakpoints S ≤ 1 and R > 2 mg/L (EUCAST)
 - *Enterobacter cloacae* ECOFF 1 mg/L

Risk factors for emergence of resistance to 3GC among *Enterobacter* spp

- **Study design and setting:**
 - Single centre, retrospective cohort study
 - 447 patients with susceptible clinical isolates of *Enterobacter* spp.
 - Old CLSI breakpoints (R cefotaxime/ceftriaxone ≥ 16 mg/L).
 - Resistance development towards 3GC in 49/447 (10.3%)
 - Use of 3GC an independent risk factor (OR=2.3)
- **Strengths**
 - Large number of patients
- **Limitations**
 - Retrospective single centre
 - Many different infections – not defined (skin = 36%, colonisation?!)
 - Strains not genotyped, old CLSI-breakpoints, MIC-values not reported

Clinical consequences for reporting

- Report restricting the use of 3GC, piperacillin-tazobactam and aztreonam in invasive infections caused by those species
- Suppress reporting 3GC, piperacillin-tazobactam, and aztreonam
- *“Monotherapy with aztreonam, penicillins or cephalosporins should be avoided when treating serious infections due to the risk of developing resistance”.*

Recent reviews - infections by AmpC-producing Enterobacterales – can we use 3 GC?

International Journal of Antimicrobial Agents 55 (2020) 105834



Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents



..... indicate that the risk of selection of resistance is exaggerated and lays the foundation for the unnecessary use of carbapenems.

Review

Infection

Carbapenems

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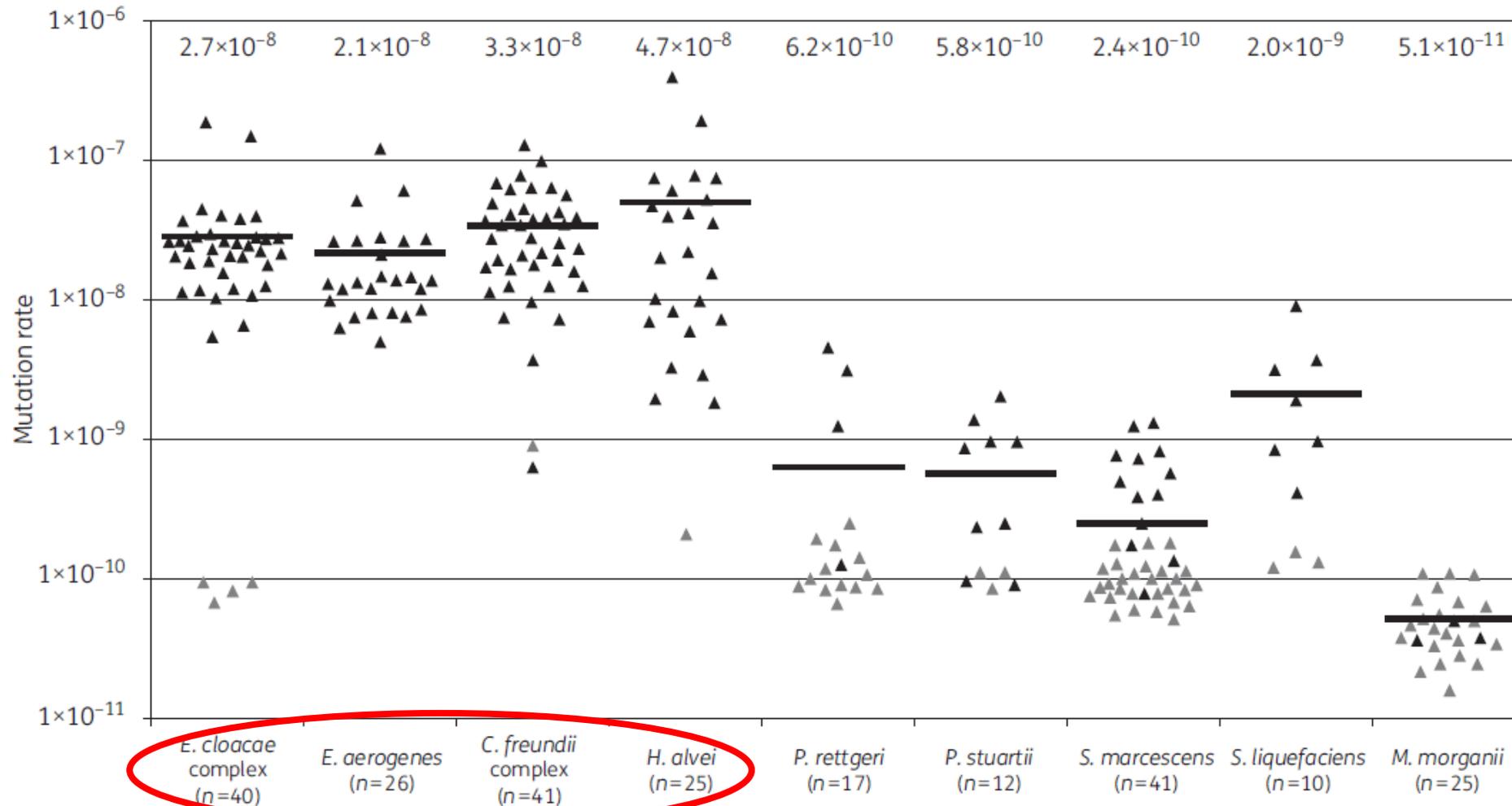
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Selection of derepressed AmpC during 3GC treatment

- **Study design and setting:**
 - Clinical infections with Enterobacterales with chromosomal AmpC
 - 01/2005 to 06/2005, N = 732
 - Overall resistance development during therapy 1.9%
- **Resistance development towards 3GC during 3GC treatment:**
 - CLSI-breakpoints, overall 5 % (11/218)
 - *Enterobacter* spp. (8.3%, 10/121) than in *C. freundii* (2.6%, 1/39), *S. marcescens* (0%, 0/37), or *M.morganii* (0%, 0/21).
 - Resistance appeared: mean 7 days (range (3-28 days)
 - One case of therapeutic failure, no mortality.
- **Strengths:** Prospective study, definition of clinical infection (CDC), molecular typing paired strains, and paired isolates MICs.
- **Limitations:** Single center study.

Spontaneous mutation rates – AmpC hyperproduction



N=237

Should we change our current reporting?

A carbapenem saving strategy

- *“In case of susceptibility, piperacillin-tazobactam, broad-spectrum cephalosporins or aztreonam can be used. Due to the risk of selection of resistance, the patient should be monitored for treatment failure. This applies in particular to critical ill patients, long treatment duration and unremedied foci of infection.” (AFA – in progress)*
- Differentiate between species?
 - *(i) Enterobacter cloacae species complex, Klebsiella aerogenes, Citrobacter freundii complex og Hafnia alvei (moderate to high risk)*
 - *(ii) Providencia spp., Serratia spp., og Morganella morganii (low risk)*

Thanks



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Questions for AmpC session

Christian Giske

May 2024

Question 1

- Enterobacter cloacae growing in blood cultures in a patient with pyelonephritis and underlying urinary tract disease. Testing S to cefotaxime (CTX), ceftazidime (CAZ) and piperacillin-tazobactam (PTZ). How do you manage reporting?
 - Report as tested without comment
 - Report as tested with a comment that PTZ, CTX and CAZ should be avoided due to risk of developing resistance
 - Report PTZ, CTX and CAZ as R
 - Report as tested with a comment that you should be vigilant if you continue with PTZ, CTX and CAZ
 - Suppress reporting of PTZ, CTX and CAZ

Question 2

- Enterobacter cloacae growing in blood cultures in a patient with neutropenic fever. Testing S to cefotaxime (CTX), ceftazidime (CAZ) and piperacillin-tazobactam (PTZ). How do you manage reporting?
 - Report as tested without comment
 - Report as tested with a comment that PTZ, CTX and CAZ should be avoided due to risk of developing resistance
 - Report PTZ, CTX and CAZ as R
 - Report as tested with a comment that you should be vigilant if you continue with PTZ, CTX and CAZ
 - Suppress reporting of PTZ, CTX and CAZ

Question 3

- *Serratia marcescens* growing in lower respiratory tract cultures in a patient with hospital-acquired pneumonia. Testing S to cefotaxime (CTX), ceftazidime (CAZ) and piperacillin-tazobactam (PTZ). How do you manage reporting?
 - Report as tested without comment
 - Report as tested with a comment that PTZ, CTX and CAZ should be avoided due to risk of developing resistance
 - Report PTZ, CTX and CAZ as R
 - Report as tested with a comment that you should be vigilant if you continue with PTZ, CTX and CAZ
 - Suppress reporting of PTZ, CTX and CAZ

Some suggestions for management

- Patient factors are decisive for the risk of development of resistance
- It is important to convey a balanced message, to avoid that clinicians will underestimate the risk of development of resistance
- Example of the comment recommended by SRGA (RAF)
 - In 10-20% of the cases resistance development can be observed when treating with cephalosporins and piperacillin-tazobactam. The risk is highest with complicated infections or in immunocompromised patients. Modify treatment when therapeutic failure is suspected