

ESBL_A & ESBL_{M-C}

KURS I RESISTENSBESTEMMELSE AV MIKROBER "AFA KURSET"
OSLO UNIVERSITETSSYKEHUS RIKSHOSPITALET, 15. NOVEMBER 2017

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HELSE NORD



AGENDA

- β-laktamer & β-laktamaser
- ESBL_A & ESBL_{M-C}:
 - Egenskaper og epidemiologi
 - Påvisning av ESBL_A og ESBL_{M-C}



β-LAKTAMER



		Eksempler			
Penicilliner	Smalspektrede	Penicillin G	Penicillin V	Cloxacillin	
	Bredspektrede	Ampicillin	Amoxicillin	Mecillinam	
	Utvidet spektrum	Piperacillin	Temocillin	Ticarcillin	
Cefalosporiner	1. gen.	Cefalexin	Cefalotin		
	2. gen.	Cefuroxim			
	2. gen. – cefamyciner	Cefoxitin	Cefotetan		
	3. gen.	Cefotaxime	Ceftazidim	Ceftriaxon	Cefpodoxime
	4. gen.	Cefepime			
5. gen.	Ceftaroline	Ceftolozane			
Monobaktam		Aztreonam			
Karbapenemer		Meropenem	Imipenem	Ertapenem	Doripenem
β-laktamase inhibitorer*		Klavulansyre	Tazobaktam	Sulbaktam	

* Avibaktam: ikke-β-laktam β-laktamase inhibitor

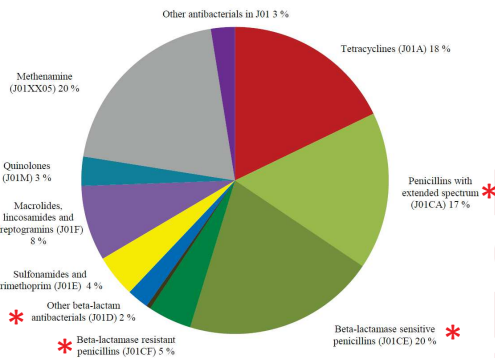


FIGURE 16. Relative amount of antibacterial agents for systemic use in 2015 in Defined Daily Doses (DDDs), total sales in the country.

NORM-NORM-VET 2016

β-LAKTAM RESISTENS

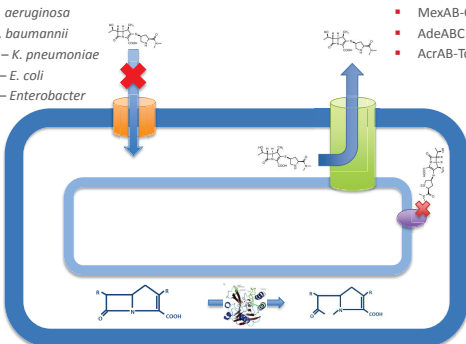
➤ Nedsatt permeabilitet

- OprD – *P. aeruginosa*
- CarO – *A. baumannii*
- OmpK36 – *K. pneumoniae*
- OmpC/F – *E. coli*
- OmpC/F – *Enterobacter*

➤ Efflux

- MexAB-OprM – *P. aeruginosa*
- AdeABC – *A. baumannii*
- AcrAB-TolC – *Enterobacteriaceae*

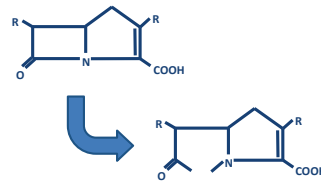
➤ Mutasjoner PBP



➤ β-laktamaser – ESBL_A, ESBL_{M-C} & ESBL_{CARBA}



β-LAKTAMASER



• Kromosomale bla påvist før den antibiotiske æra

- udefinert funksjon i celleveggmetabolismen?
- beskyttelse mot β-laktamer produsert i miljøet?

LETTERS TO THE EDITORS

The Editors do not assume responsibility for opinions expressed by their correspondents. The names mentioned in nature, or in connection with the names of natural substances, are intended for their use only and are not intended to be taken as recommendations by the editorial committee, unless otherwise stated.

An Enzyme from Bacteria able to Destroy Penicillin
 Penicillin, the most powerful antibiotic known, is destroyed by a group of enzymes called penicillinases. These enzymes are produced by certain bacteria, and their presence in the body of a patient may prevent the action of penicillin. The discovery of an enzyme from a bacterium which is able to destroy penicillin is of great importance. This enzyme, which has been named penicillinase, is a member of the class of enzymes known as β-lactamases. It is a water-soluble protein, and its activity is not affected by heat or by the presence of penicillin. The enzyme is able to destroy penicillin in a few minutes, and it is not affected by the presence of penicillinase inhibitors. The discovery of this enzyme is of great importance, as it may lead to the development of new antibiotics which are not destroyed by penicillinase.

(An Enzyme from Bacteria able to Destroy Penicillin)

Morphological Effects of Penicillin on Bacteria

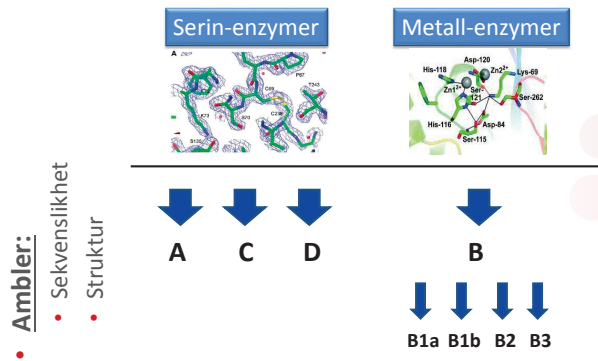
When working with these Penicillin and other antibiotics, it is important to know the morphological effects of these antibiotics on bacteria. Penicillin causes a change in the appearance of the bacteria, and this change is due to the action of the enzyme penicillinase. The enzyme is able to destroy penicillin, and this leads to the formation of penicillinase-resistant strains of bacteria. These strains are able to produce penicillinase, and this enzyme is able to destroy penicillin. The discovery of this enzyme is of great importance, as it may lead to the development of new antibiotics which are not destroyed by penicillinase.



«NOMENKLATUR»



KLASSIFISERING AV β -LAKTAMASER - Molekylær klassifisering



Ambler RP. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.* 1980; Bush K. et al. *Antimicrob. Agents Chemother.* 1995



KLASSIFISERING AV β -LAKTAMASER - Funksjonell klassifisering

TABLE 1. Classification schemes for bacterial β -lactamases, expanded from Bush et al. (16)

Bush-Jacoby group (2009)	Bush-Jacoby-Medeiros group (1995)	Molecular class (subclass)	Domestic substrate(s)	Inhibited by CA or TZP EDTA	Defining characteristic(s)	Representative enzyme(s)
1	1	C	Cephalosporins	No	Greater hydrolysis of cephalosporins than isoenzymes hydrolyze cephalosporins	<i>E. coli</i> AmpC, P92, ACT-1, CMPC-2, FOX-1, MBB-1, GC1, CMV-37
1c	NA*	C	Cephalosporins	No	Increased hydrolysis of cefazidime and other other oximino- β -lactams	
2a	2a	A	Penicillins	Yes	Greater hydrolysis of benzopenicillins than isoenzymes	PC1
2b	2b	A	Penicillins, early cephalosporins	Yes	Similar hydrolysis of benzopenicillins and cephalosporins	TEM-1, TEM-2, SHV-1
2bc	2bc	A	Extended-spectrum cephalosporins, monobactams	Yes	Increased hydrolysis of oximino- β -lactams (ceftriaxone, ceftazidime, ceftiofur, aztreonam)	TEM3, SHV-2, CTX-M15, PER-1, YEB-1
2br	2br	A	Penicillins	No	Resistance to clavulanic acid, sulbactam, and tazobactam	TEM-30, SHV-10
2br	NI	A	Extended-spectrum cephalosporins, monobactams	No	Increased hydrolysis of oximino- β -lactams combined with resistance to clavulanic acid, sulbactam, and tazobactam	TEM-50
2c	2c	A	Carbapenems	Yes	Increased hydrolysis of carbapenems	PSE-1, CARB-3
2d	NI	A	Carbapenems, cefepime	Yes	Increased hydrolysis of carbapenems, cefepime, and ceftipime	RTI-4
2f	2f	D	Clavulanic acid	Variable	Increased hydrolysis of clavulanic acid	OXA-11, OXA-10
2de	NI	D	Extended-spectrum cephalosporins	Variable	Hydrolyzes cloxacillin or oxacillin and oximino- β -lactams	OXA-11, OXA-15
2df	NI	D	Cephalosporins	Variable	Hydrolyzes cloxacillin or oxacillin and carbapenems	OXA-23, OXA-48
2e	2e	A	Extended-spectrum cephalosporins	Yes	Hydrolyzes cephalosporins, inhibited by clavulanic acid but not aztreonam	CepA
2f	2f	A	Carbapenem	Variable	Increased hydrolysis of carbapenems, oximino- β -lactams, cephalosporins	KPC-2, IME-1, SME-1
3a	3	B (B1)	Carbapenem	No	Broad-spectrum hydrolysis including carbapenems but not monobactams	IMP-1, VIM-1, GSA, IND-1
		B (B3)				L1, CAL-1, GOB-1, FEZ-1, CPM-1, SIB-1
3b	3	B (B2)	Carbapenem	No	Preferential hydrolysis of carbapenems	
NI	4	Utklass				

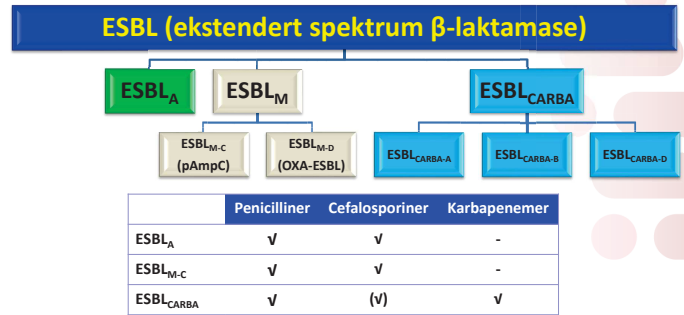
* CA, clavulanic acid; TZP, tazobactam; NI, not included.

Bush K. and Jacoby GA. *Antimicrob. Agents Chemother.* 2010



β -LAKTAMASER - Utvidet ESBL definisjon

- β -laktamaser med aktivitet mot ekstendert spektrum cefalosporiner og/eller karbapenemer
- Omfatter kun "mobile/ervert" β -laktamaser
- Benyttet av NordicAST/AFA



Giske CG. et al. *J. Antimicrob. Chemother.* 2009; Haldorsen BC og Samuelsen Ø. *Bioingenjøren* 2012



ESBL_A ESBL (ekstendert spektrum β -laktamase)

- ESBL_A den "klassiske" ESBL
- Varianter: CTX-M, TEM, SHV, OXA, YEB, PER, IMP, KPC
- Spektrum: GES-1, -2, -3, -4, -5, -6, -7, -8, -9, -10, -11, -12, -13, -14, -15, -16, -17, -18, -19, -20, -21, -22, -23, -24, -25, -26, -27, -28, -29, -30, -31, -32, -33, -34, -35, -36, -37, -38, -39, -40, -41, -42, -43, -44, -45, -46, -47, -48, -49, -50, -51, -52, -53, -54, -55, -56, -57, -58, -59, -60, -61, -62, -63, -64, -65, -66, -67, -68, -69, -70, -71, -72, -73, -74, -75, -76, -77, -78, -79, -80, -81, -82, -83, -84, -85, -86, -87, -88, -89, -90, -91, -92, -93, -94, -95, -96, -97, -98, -99, -100
- Infiserer alle kommersielle ESBL-enzymet fra *K. pneumoniae*, *P. aeruginosa*, *E. coli*, *S. pneumoniae*, *S. pneumoniae*, *S. pneumoniae*, *S. pneumoniae*

β -laktamgruppe	ESBL _A
Penicilliner (Ampicillin, Piperacillin)	✓
3. gen. cefalosporiner (Cefotaxime, Cefotaxidim)	✓
4. gen. cefalosporiner (Cefepime)	✓*
Cefamyciner (Cefoxitin, Cefotetan)	-
Monobaktamer (Aztreonam)	✓*
Karbapenemer (Meropenem, Imipenem, Ertapenem)	-
β -laktamase inhibitorer	ESBL _A
Klavulansyre, Tazobaktam, Sulbaktam, Avibactam	✓

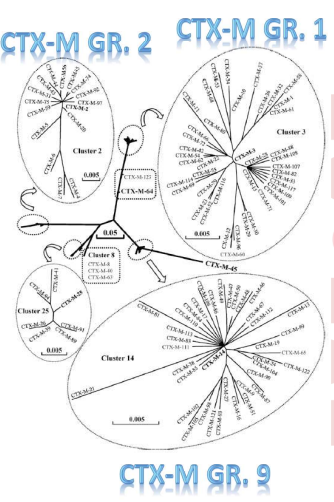
* variabel

Giske CG. et al. *J. Antimicrob. Chemother.* 2009; Haldorsen BC og Samuelsen Ø. *Bioingenjøren* 2012



ESBL_A (CTX-M)

- CTX-M: cefotaximase-Münich
- Først beskrevet i 1990
- ~180 varianter
- Mobilisert fra *Kluyvera* spp.
- CTX-M gr. 1 (CTX-M-15)
- CTX-M gr. 9 (CTX-M-14)

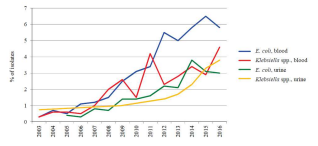
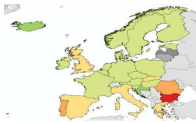


Zhao W-H. et al. *Crit. Rev. Microbiol.* 2012

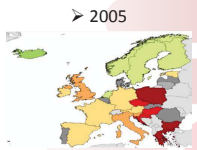


ESBL_A

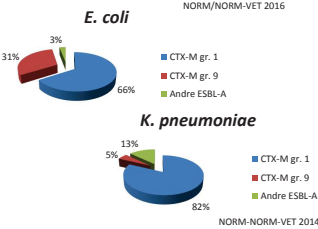
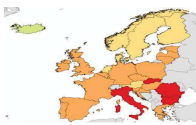
E. coli



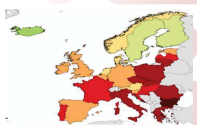
K. pneumoniae



2015



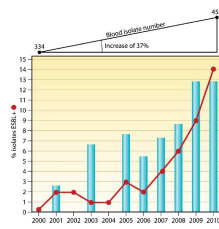
2015



ECD. Annual Reports of the European Antimicrobial Resistance Surveillance Network (EARS-Net) 2001; 2006; 2013



E. coli ST131 & bla_{CTX-M}



Nicolas-Chanoine M-H. et al. Clin. Microbiol. Rev. 2014

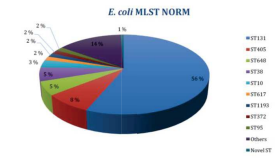


Figure 23. STs in NORM *E. coli* isolates. Presented in percentages of the total number of isolates. Andressen L et al. Unpubl. data

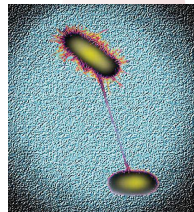
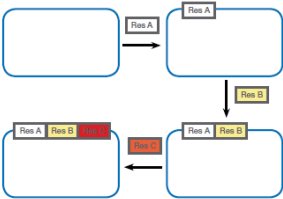
Nicolas-Chanoine M-H. et al. Clin. Microbiol. Rev. 2014



RESISTENS MOT ANDRE VIKTIGE ANTIBIOTIKA

	% R Fluorokinoloner	% R Aminoglykosider	% R Trim-sulfa	% R Karbapenemer
<i>E. coli</i> ESBL-A (NORM 2016)	77%	49%	75%	0%

NORM/NORM-VET 2016



Sundsford A. et al. Tidsskr. Nor. Lægefor. 2008

Spredning av multiresistens i en hendelse



ESBL_{M-C} & kromosomal AmpC

ESBL (ekstendert spektrum β-laktamase)



Kromosomal AmpC

- E. coli* & *Shigella*
- Enterobacter* spp.
- M. morgani*
- C. freundii*
- S. marcescens*
- P. aeruginosa*
- A. baumannii*

β-laktamgruppe	ESBL _{M-C} /kromosomal AmpC
Penicilliner (Ampicillin, Piperacillin)	✓
3. gen. cefalosporiner (Cefotaxime, Ceftazidim)	✓
4. gen. cefalosporiner (Cefepime)	-
Cefamyciner (Cefoxitin, Cefotetan)	✓
Monobaktamer (Aztreonam)	✓
Karbapenemer (Meropenem, Imipenem, Ertapenem)	-
β-laktamase inhibitorer	
Borsyre, Kloxacillin	✓

Giske CG. et al. J. Antimicrob. Chemother. 2009; Haldorsen BC og Samuelsen Ø. Bioingeniøren 2012; Jacoby G. Clin. Microbiol. Rev. 2009



ESBL_{M-C}

ESBL (ekstendert spektrum β-laktamase)



ESBL_{M-C}: plasmid-mediert AmpC

- ✓ CMY, FOX, MIR, MOX, DHA, LAT, BIL, ACT, ACC, CFE
- ✓ Omfatter ikke kromosomal AmpC (*E. coli*, *Enterobacter*, *C. freundii*, *M. morgani*, *P. stuartii*, *Serratia* spp., *Hafnia alvei*)

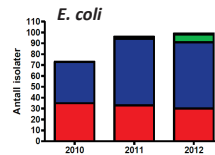
AmpC β-lactamase	Country of origin	Publication #	Species of first isolate	Likely source of AmpC gene	Similarity (%)	Reference(s)
CMY-1	South Korea	1989	<i>K. pneumoniae</i>	<i>A. hydrophila</i>	82	20, 23
CMY-2	Greece	1996	<i>K. pneumoniae</i>	<i>C. freundii</i>	96	22
MIR-1	United States	1990	<i>K. pneumoniae</i>	<i>E. cloacae</i>	99	142, 248
MOX-1	Japan	1993	<i>K. pneumoniae</i>	<i>A. hydrophila</i>	80	134
LAT-1	Greece	1993	<i>K. pneumoniae</i>	<i>C. freundii</i>	95	226
FOX-1	Argentina	1994	<i>K. pneumoniae</i>	<i>A. caviae</i>	99	95, 109
DHA-1	Saudi Arabia	1997	<i>S. cerevisiae</i>	<i>M. morgani</i>	99	186
ACT-1	United States	1997	<i>K. pneumoniae</i>	<i>B. subtilis</i>	98	41, 279
ACC-1	Germany	1999	<i>K. pneumoniae</i>	<i>B. subtilis</i>	99	21, 106
CFE-1	Japan	2004	<i>E. coli</i>	<i>C. freundii</i>	99	229

Giske CG. et al. J. Antimicrob. Chemother. 2009; Haldorsen BC og Samuelsen Ø. Bioingeniøren 2012; Jacoby G. Clin. Microbiol. Rev. 2009

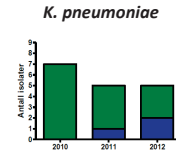


EPIDEMIOLOGI ESBL_{M-C}/Kromosomal AmpC

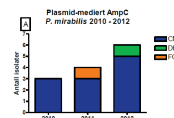
Isolater analysert K-res 2010-2012



Figur 1. Fordeling av cAmpC og ESBL_{M-C} blant innsendte *E. coli* isolater perioden 2010 - 2012.



Figur 2. Fordeling av ESBL_{M-C} blant innsendte *K. pneumoniae* isolater i perioden 2010 - 2012.



Figur 3. Fordeling av ESBL_{M-C} blant innsendte *P. mirabilis* (A) og *Salmonella* sp. (B) isolater i perioden 2010 - 2012.

Samuelsen Ø. AmpC rapport K-res 2013 (www.unn.no/kres);

EPIDEMIOLOGI ESBL_{M-C}/Kromosomal AmpC

E. coli NORM 2010-2012

Prøvemateriale	År	ESBL _{M-C}	cAmpC
Urin	2010	0,4%	0,3%
	2011	0,1%	0,0%
	2012	0,0%	0,2%
Blodkultur	2010	0,1%	0,4%
	2011	0,1%	0,6%
	2012	0,2%	0,4%



- *E. coli* ESBL_{M-C} (*bla*_{CMY-2})
- 35.7% av kjøtt kjøtt prøver:
- 28.9% av caecum prøver



Samuelsen Ø. AmpC-rapport K-res 2013; NORM-NORM-VET 2014; Berg ES et al. Clin. Microbiol. Infect. 2017

HVORFOR PÅVISE β-LAKTAMASER?

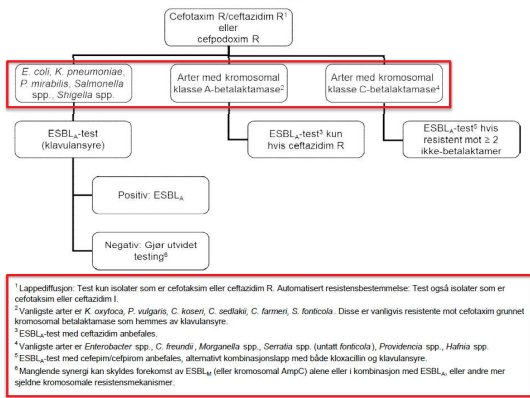
Importance of detection of resistance mechanism	
Required for clinical antimicrobial susceptibility categorization	No
Infection control purposes	Yes
Public health purposes	Yes



EUCAST guidelines for detection of resistance mechanisms and specific resistances of clinical and/or epidemiological value. v. 2.0 July 2017

ALGORITME FOR ESBL_A TESTING

Enterobacteriaceae
ALGORITME FOR PÅVISNING AV KLASSISK ESBL (ESBL_A)



NordicAST brytningspunktstabell v. 7.1

FENOTYPISKE METODER FOR PÅVISNING AV ESBL_A

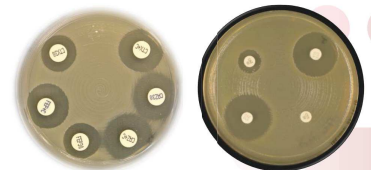
Basert på synergi mellom cephalosporiner og klavulansyre

Kombinasjons gradient-tester:



- Ceftazidim/ceftazidim+klavulansyre
- Cefotaxime/cefotaxime+klavulansyre
- Cefepime/cefepime+klavulansyre

Kombinasjons lapper/tabletter:



- Ceftazidim/ceftazidim+klavulansyre
- Cefotaxime/cefotaxime+klavulansyre
- Cefepime/cefepime+klavulansyre

- Positiv test:
 - ✓ Ratio ≥8
 - ✓ Fantomsone

- Positiv test:
 - ✓ Ratio ≥5

NB: Synergi med en av kombinasjonene nok!

EKSEMPEL *E. coli*

Enterobacteriaceae
ALGORITME FOR PÅVISNING AV KLASSISK ESBL (ESBL_A)

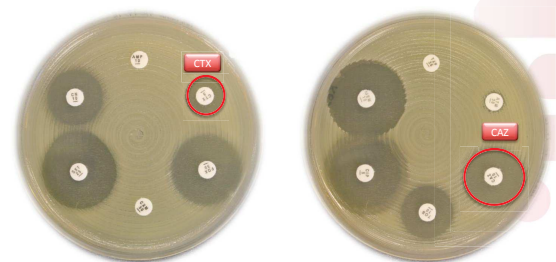
- PCR: CTX-M gr. 1

EKSEMPEL *K. oxytoca*

Enterobacteriaceae
ALGORITME FOR PÅVISNING AV KLASSISK ESBL (ESBL_A)

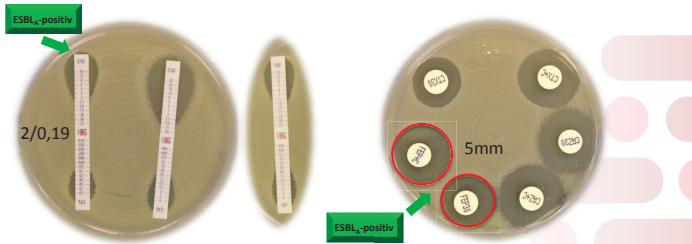


- *K. oxytoca*, *P. vulgaris*, *C. koseri*, *C. sedlakii*, *C. farmeri*, *S. fonticola*.....:
 - ✓ Kromosomale β-laktamaser – noen har lignende substratprofil som ESBL_A
 - ✓ Gir vanligvis resistens mot cefotaxime
 - ✓ Oftest lavgradig uttrykt



- ESBL_A-test kun hvis ceftazidim R

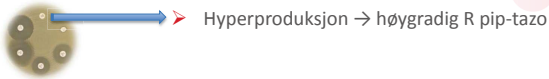
EKSEMPEL *K. oxytoca*



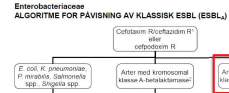
PCR: negativ for ESBL_A → Falsk positive ESBL_A tester (cefotaxime/cefepime)

ESBL_A-test med ceftazidim anbefales.

«Test kun for ESBL-A test med ceftazidim/ceftazidim-klavulansyre»



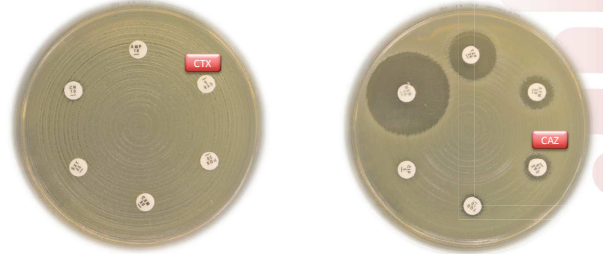
EKSEMPEL *Enterobacter*



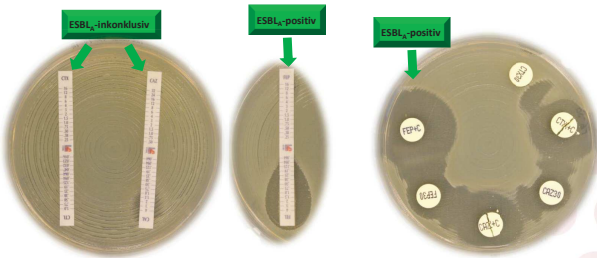
» "Arter med kromosomalt klasse C-β-laktamase": (*Enterobacter* spp., *C. freundii*, *Morganella* spp., *Serratia* spp. (untatt *fonticola*), *Providencia* spp., *Hafnia* spp.):

✓ Induserbar kromosomal AmpC

✓ Klavulansyre-synergi med ceftazidim/cefotaxime kan bli maskert



EKSEMPEL GRUPPE 3 (*Enterobacter*)

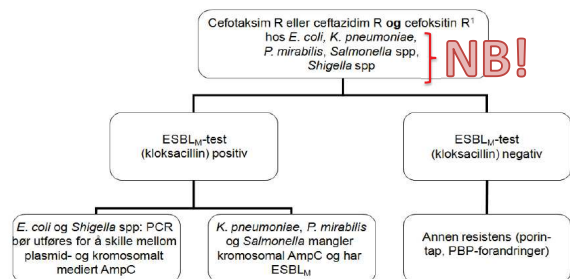


ESBL_A-test med cefepim/cefepim anbefales, alternativt kombinasjonslapp med både kloxacillin og klavulansyre.

» «ESBL-A test med cefepime/cefepime-klavulansyre nødvendig»

ALGORITME FOR ESBL_{M-C} TESTING

Enterobacteriaceae
ALGORITME FOR PÅVISNING AV PLASMIDMEDIERT AmpC (ESBL_M)



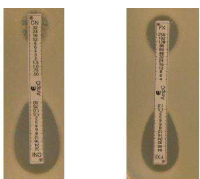
¹ Test isolater med cefotaxim R eller ceftazidim R (ved automatisert resistensbestemmelse: test også isolater som er cefotaxim eller ceftazidim I) i kombinasjon med cefoksitin R. Merk at ESBL_A-positive isolater også kan være ESBL_M-positive. ESBL_M-test bør derfor utføres uansett resultat ved ESBL_A-testing.

NordicAST brytningspunkttabell v. 7.1

FENOTYPISKE METODER FOR PÅVISNING AV ESBL_{M-C}

Basert på synergi mellom cephamyciner/3. gen. cephalosporiner og kloxacillin/borsyre

Kombinasjons gradient-test:



» Cefotetan/cefotetan+kloxacillin
» Cefoxitin/cefoxitin+kloxacillin

» Positiv test:

- ✓ Ratio ≥8
- ✓ Fantomsone

Kombinasjons tabletter:

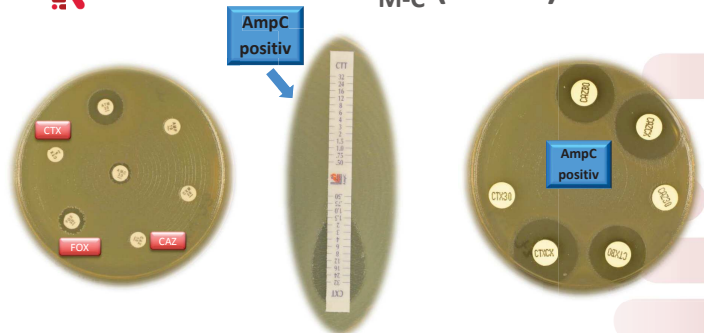


» Ceftazidim/ceftazidim+borsyre
» Ceftazidim/ceftazidim+kloxacillin
» Cefotaxime/cefotaxime+borsyre
» Cefotaxime/cefotaxime+kloxacillin

» Positiv test:

- ✓ Ratio ≥5 (1 kombinasjon nok!)

EKSEMPEL ESBL_{M-C} (*E. coli*)



» ESBL_{M-C} PCR: negativ → kromosomal AmpC

KAN MAN FENOTYPISK SKILLE MELLOM ESBL_{M-C} OG KROMOSOMAL AmpC?

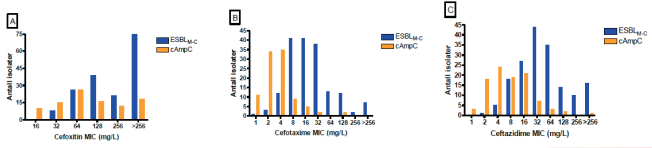


Table 1 Occurrence of multidrug resistance among isolates with putative chromosomal and plasmid-acquired AmpC

Resistance to GEN, CIP, and TSU (MDR) ^a	No. of putative chromosomal AmpC	MDR among putative chromosomal AmpC (%)	No. of plasmid-acquired AmpC	MDR among plasmid-acquired AmpC (%)
Resistance to 2/3	224	47 (21.0 %)	154	48 (31.1 %) ^b
Resistance to 3/3	224	16 (7.1 %)	154	16 (10.4 %)

^a GEN gentamicin, CIP ciprofloxacin, TSU trimethoprim-sulfamethoxazole, MDR multidrug resistance (resistance to either two or three out of the three antibiotics)

^b Statistically significant higher proportion of MDR compared to putative chromosomal AmpC ($p=0.04$)

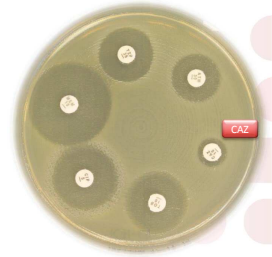
Samuelsen Ø. AmpC rapport K-res 2013 (www.unn.no/kres); Edquist P. Eur. J. Clin. Microbiol. Infect. Dis. 2013

EKSEMPEL ESBL_A & ESBL_{M-C} (*E. coli*)



ESBL_A

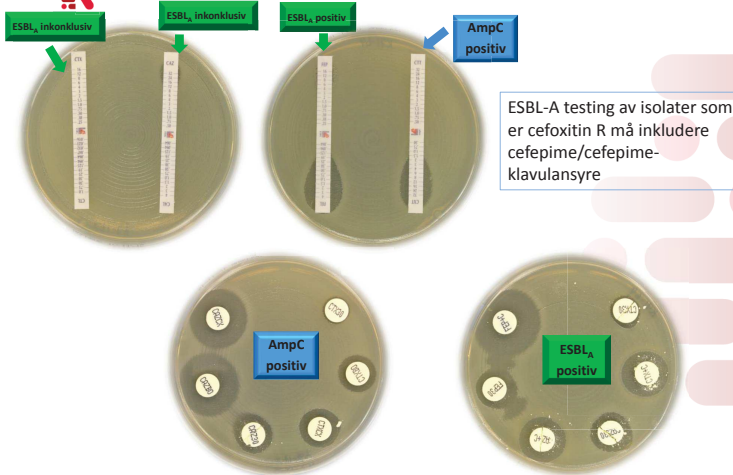
Cefotaksim R/ceftazidim R¹ eller cefepodioxim R



ESBL_{M-C}

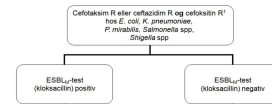
Cefotaksim R eller ceftazidim R og cefoksitin R¹ hos *E. coli*, *K. pneumoniae*, *P. mirabilis*, *Salmonella* spp., *Shigella* spp

EKSEMPEL ESBL_A & ESBL_{M-C} (*E. coli*)



LITEN NB! ROSCO AmpC kit

Enterobacteriaceae ALGORITME FOR PÅVISNING AV PLASMIDMEDIERT AmpC (ESBL_{M-C})



- 6/10 ESBL_{M-C}-negative *K. pneumoniae* falsk positiv med CAZ-BO
- 2/9 ESBL_{M-C}-positive (DHA) *K. pneumoniae* kun positiv med CAZ-BO

ESBL (ekstendert spektrum β-laktamase)



β-laktamgruppe	ESBL _A	ESBL _{M-C}
Penicilliner (Ampicillin, Piperacillin)	✓	✓
3. gen. cefalosporiner (Cefotaxime, Cefazidim)	✓	✓
4. gen. cefalosporiner (Cefepime)	✓*	-
Cephamyrciner (Cefoxitin, Cefotetan)	-	✓
Monobaktamer (Aztreonam)	✓*	✓
Karbaenemer (Meropenem, Imipenem, Ertapenem)	-	-
β-laktamase inhibitorer	ESBL _A	ESBL _{M-C}
Klavulansyre, Tazobaktam, Sulbactam, Avibactam	✓	-
Borsyre	-	✓
Kloxacillin	-	✓
Metall-kelatører (EDTA/DPA)	-	-

*variabel

Alltid unntak!! Eks: ACC (ESBL_{M-C}): Begrenset/ingen aktivitet mot cephamyciner (cefoxitin)

OPPSUMMERING ESBL_A/ESBL_{M-C}

ESBL (ekstendert spektrum β-laktamase)



➢ ESBL_A: hemmes av klavulansyre



➢ ESBL_A + ESBL_{M-C} (AmpC): Cefepime/cefepime+klavulansyre

➢ ESBL_{M-C}: hemmes av borsyre/kloxacillin



➢ Fenotypiske metoder skiller ikke mellom ESBL_{M-C} og kromosomal AmpC



OPPSUMMERING ESBL_A/ESBL_{M-C}

- ***K. oxytoca*, *P. vulgaris*, *C. koseri*, *C. sedlakii*, *C. farmeri*, *S. fonticola*.....:**
 - ✓ Kromosomale β-laktamaser – noen er ESBL_A - oftest lavgradig uttrykt
 - ✓ Test kun for ESBL_A hvis ceftazidime R
 - ✓ Hyperproduksjon → falsk positive ESBL_A tester:
 - Cefotaxime/cefotaxime-klavulansyre
 - Cefepime/cefepime-klavulansyre

- **"Arter med kromosomal klasse C β-laktamase": (*Enterobacter* spp., *C. freundii*, *Morganella* spp., *Serratia* spp. (untatt *fonticola*), *Providencia* spp., *Hafnia* spp.):**
 - ✓ Induserbar kromosomal AmpC
 - ✓ Klavulansyre-synergi med ceftazidim/cefotaxime kan bli maskert
 - ✓ Inkluder cefepime/cefepime-klavulansyre

- Falsk positive resultat – cefepime/cefepime-klavulansyre:
 - ✓ OXA-1 produserende *E. coli*

- Falsk positive resultat:
 - ✓ SHV-1, TEM-1, OXA-1 hyperprodusenter

- Fenotypiske tester utviklet og evaluert i hovedsak på *E. coli*/*K. pneumoniae*
- Inkonklusive tester er ikke negative!

