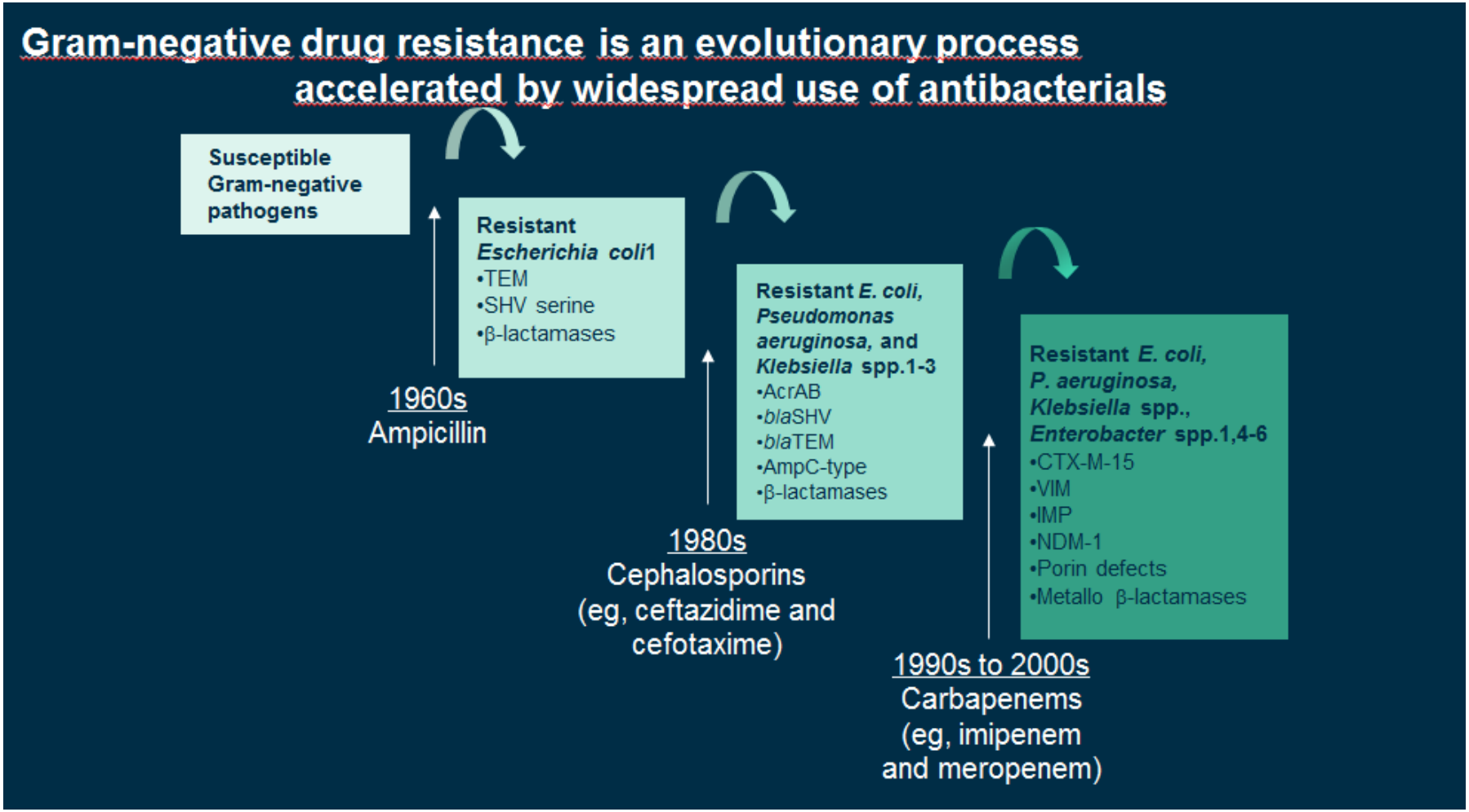
MSD eucan

ZERBAXA’t
(Ceftolozane/Tazobactam)
tutvustav koosolek
Madriid 16.05.2016

Kaisa Kirs
18.05.2016

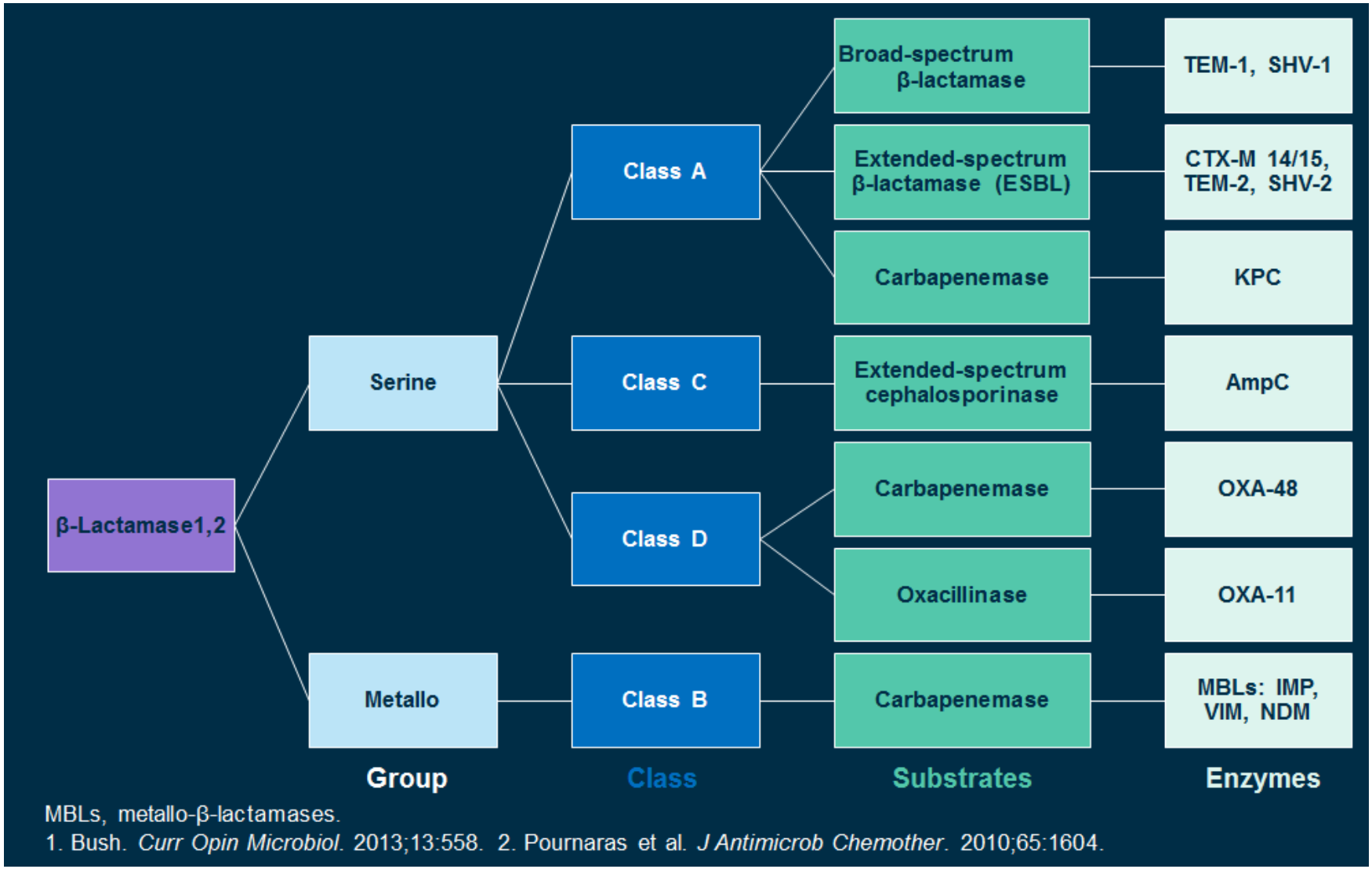
2003-2011 turule 3 uut gramnegatiivsetesse toimivat antibiootikumi(doripeneem,tigetsükliin ,tsefaroliin.)

Evolution of Gram-negative Pathogens Has Caused Widespread Drug Resistance



What Is a β-Lactamase?

Nomenclature Includes Multiple Classes and Enzymes

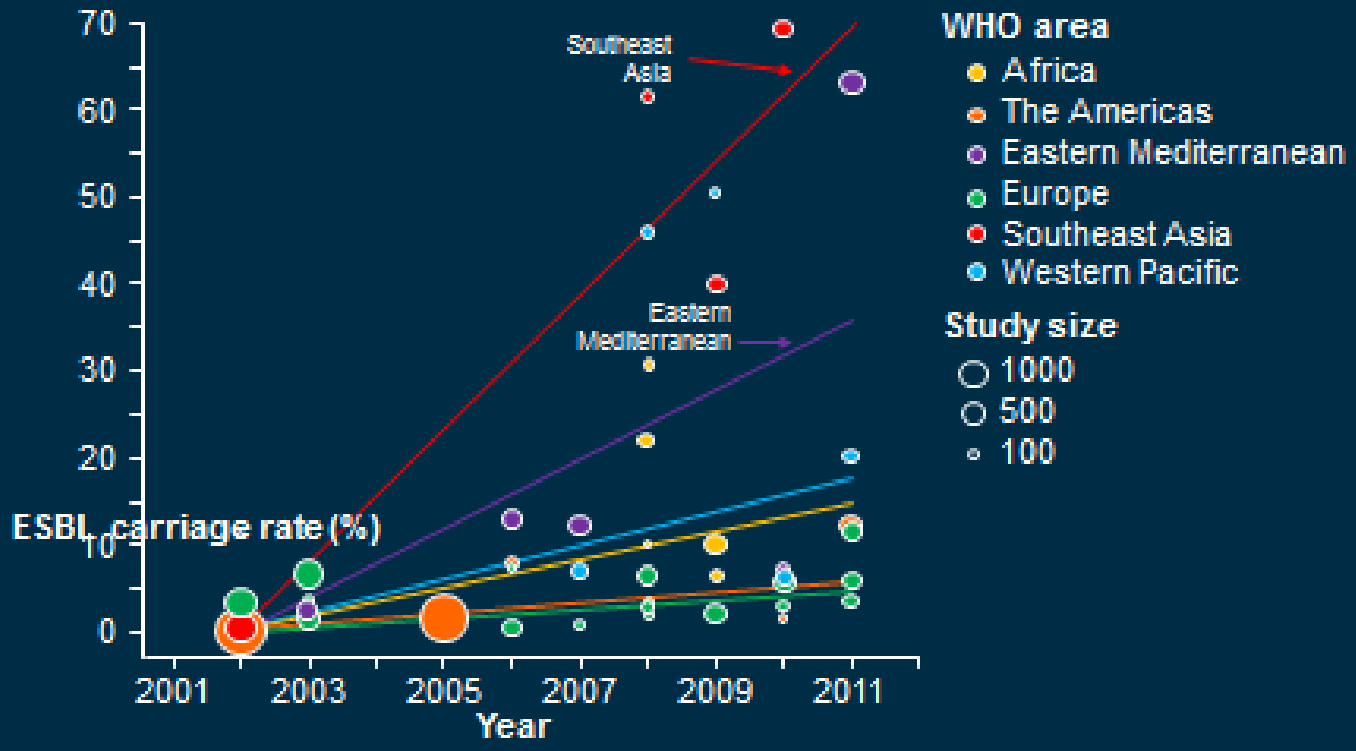


MBLs, metallo-β-lactamases.

1. Bush. *Curr Opin Microbiol*. 2013;13:558. 2. Pournaras et al. *J Antimicrob Chemother*. 2010;65:1604.

GL

Global Trends in Human Carriage of ESBLs



Each bubble area is proportional to the size of the corresponding study. The lines represent evolution of extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae carriage rates over time for each geographical area, by a weighted linear regression model using the values in the literature from 2002 to 2011.

Woerther et al. *Clin Microbiol Rev.* 2013;26:744-58.

US

US Prevalence of ESBL+ Enterobacteriaceae (2012)

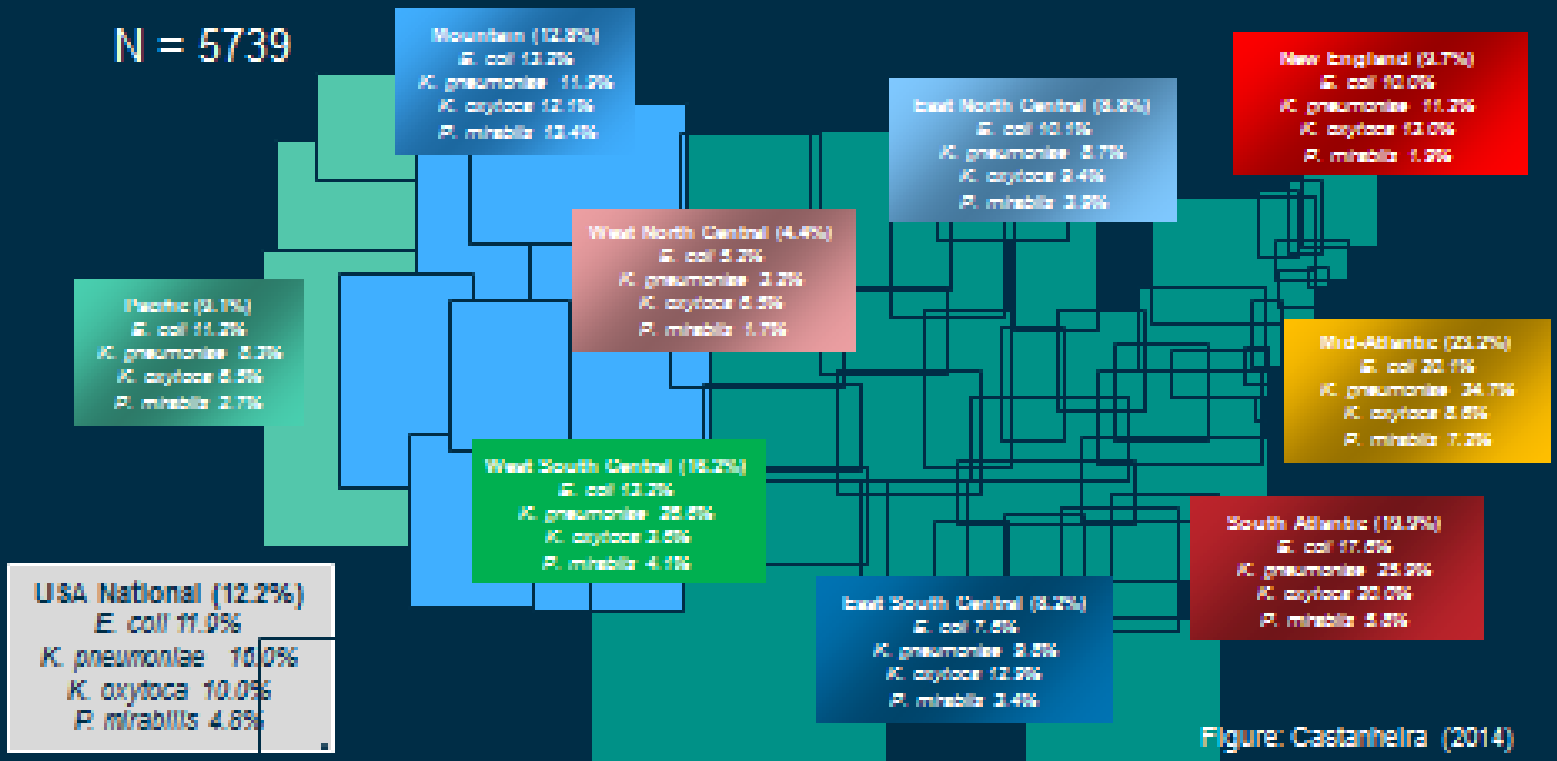


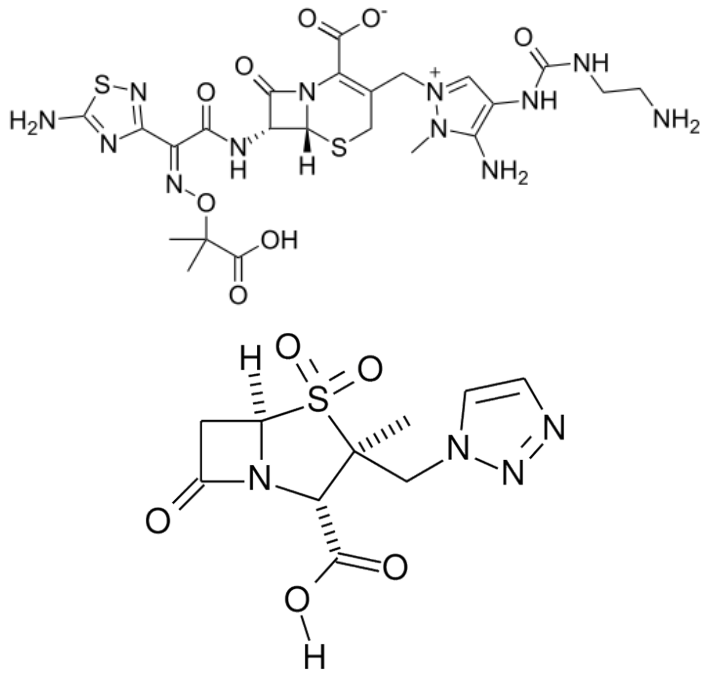
Figure: Castanheira (2014)

ESBLs include CTX-M-15, SHV, KPC, CTX-M-14, CMY-2, FOX, TEM, DHA

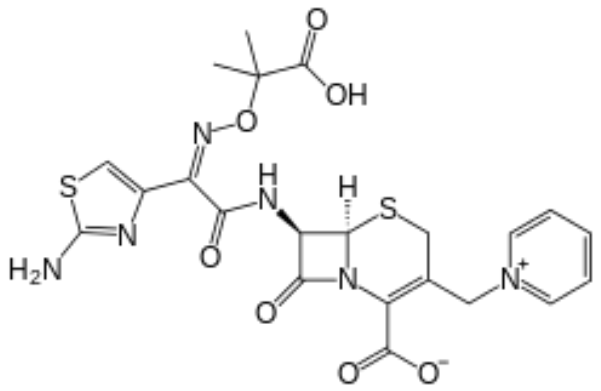
E. coli, *Escherichia coli*; ESBL, extended-spectrum β-lactamase; *K. pneumoniae*, *Klebsiella pneumoniae*; KPC, *K. pneumoniae* carbapenemase; *K. oxytoca*, *Klebsiella oxytoca*; *P. mirabilis*, *Proteus mirabilis*.

Castanheira et al. *Antimicrob Agents Chemother.* 2014;58:833-7.

CEFTOLOZANE +tazobactam. CEFTAZIDIME



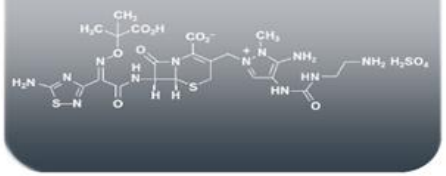
Ceftolozane is a 5th generation cephalosporin antibiotic. Novel, cephalosporin combined with a well-established β-lactamase inhibitor tazobactam.



Ceftazidime is a 3rd generation cephalosporin.

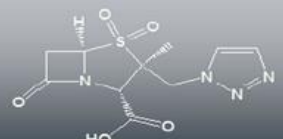
ZERBAXA™(Ceftolozane/Tazobactam [MSD]): Overview

Ceftolozane



- Exerts bactericidal activity
  - Binds important penicillin-binding proteins[1]
  - Inhibits cell wall synthesis, which leads to cell death[1]

Tazobactam



- Irreversible inhibitor of some β-lactamases[1]
  - These include many extended spectrum β-lactamases and cephalosporinases[1]

Ceftolozane/tazobactam retains in-vitro activity against select ESBL-producing Enterobacteriaceae

1. Zhanel GG et al. *Drugs* 2014;74:1.

ESBL = extended-spectrum β-lactamase; MSD = Merck Sharpe & Dohme.

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In-vitro activity of ZERBAXA™

ZERBAXA™ Efficacy

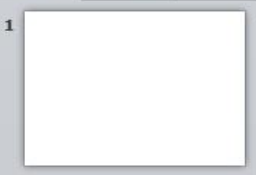
- *Staphylococcus aureus*, *Enterococcus faecalis*, and *E. faecium* are not susceptible to ZERBAXA™[1]
- Efficacy of ZERBAXA™ has ben demonstrated in clinical studies against the following pathogens:

Acute Pyelonephritis, Complicated Urinary Tract Infections[2]		
Gram-Negative Bacteria		
Escherichia coli	*Klebsiella pneumoniae*	*Proteus mirabilis*

Complicated Intra-Abdominal Infections[2]		
Gram-Negative Bacteria		Gram-Positive Bacteria
Enterobacter cloacae	*Klebsiella pneumoniae*	*Streptococcus anginosus*
Escherichia coli	*Proteus mirabilis*	*Streptococcus constellatus*
Klebsiella oxytoca	*Pseudomonas aeruginosa*	*Streptococcus salivarius*

1. ZERBAXA™ [Summary of Product Characteristics]. Kenilworth, NJ, USA: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003772/WC500194595.pdf. Accessed December 11, 2015. **2.** Sader HS et al. *J Infect* 2014;69:266–277.

Click to add notes






What Makes ZERBAXA™ Different? Activity Against *Pseudomonas aeruginosa*

- In a study of *P. aeruginosa* hospital isolates, AmpC derepression and OprD loss were the most common mutation-driven resistance mechanisms detected
- OprD loss was present in all carbapenem-resistant isolates

Resistance Mechanisms	OprD Loss	β-lactamase Enzyme	Efflux Pump	Efflux Pump
	OprD	AmpC	MexXY	MexAB
ZERBAXA™	●	●	●	●
Meropenem	◐	●	○	◐

○ No activity ◐ Partial activity ● Inhibitory activity

- ZERBAXA™ has a spectrum of activity against *P. aeruginosa and P. aeruginosa* strains with certain resistance mechanisms (loss of outer membrane porin [OprD], chromosomal AmpC, upregulation of efflux pumps [MexXY, MexAB])

Castanheira M et al. *Antimicrob Agents Chemother* 2014;58:6844–6850.
OprD = outer membrane porin.

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Click to add notes

Zerbaxa efektiivsus *in vitro*:

Kõhuõõne tüsistunud infektsioonid

- Gramnegatiivsed bakterid
- *Enterobacter cloacae*
- *Escherichia coli*
- *Klebsiella oxytoca*
- *Klebsiella pneumoniae*
- *Proteus mirabilis*
- *Pseudomonas aeruginosa*
- Grampositiivsed bakterid
- *Streptococcus anginosus*
- *Streptococcus constellatus*
- *Streptococcus salivarius*

Kuseteede tüsistunud infektsioonid, sh püelonefriit

- Gramnegatiivsed bakterid
- *Escherichia coli*
- *Klebsiella pneumoniae*
- *Proteus mirabilis*

Kliinilist efektiivsust järgmiste patogeenide suhtes ei ole tõestatud, kuid *in vitro* uuringud näitavad, et need on Zerbaxa suhtes tundlikud omandatud resistentsusemehhanismide puudumisel:

- *Citrobacter freundii*
- *Citrobacter koseri*
- *Enterobacter aerogenes*
- *Enterobacter cloacae*
- *Morganella morganii*
- *Proteus vulgaris*
- *Serratia liquefaciens*
- *Serratia marcescens*

In vitro andmete kohaselt ei ole tseftolosaani/tasobaktaami suhtes tundlikud järgmised liigid:

- *Staphylococcus aureus*
- *Enterococcus faecalis*
- *Enterococcus faecium*

Zerbaxa näidustused:

- Kõhuõõne tüsistunud infektsioonid
- Äge püelonefriit
- Kuseteede tüsistunud infektsioonid
- 3 astme kliiniline uuring nosokomiaalsete pneumooniate raviks on pooleli.

Zerbaxa intravenoosne annus olenevalt infektsiooni tüübist patsientidel kreatiniini kliirensiga > 50 ml/min

Infektsiooni tüüp	Annus	Sagedus	Infusiooni kestus	Ravi kestus
Kõhuõõne tüsistunud infektsioon*	1 g tseftolosaani / 0,5 g tasobaktaami	Iga 8 tunni järel	1 tund	4...14 päeva
Kuseteede tüsistunud infektsioon, äge püelonefriit	1 g tseftolosaani / 0,5 g tasobaktaami	Iga 8 tunni järel	1 tund	7 päeva

Anaeroobsete patogeenide esinemise kahtluse korral kasutada koos metronidasooliga.

Farmatseutiline teave

- Viaalis 1g tseftolosaani,500 mg tazobaktaami
- Pakendis on 10 viaali.
- Pärast manustamiskõlblikuks muutmist on ravimi kasutusaegne keemilis-füüsikaline stabiilsus tõestatud 4 päeva jooksul temperatuuril 2...8 °C.
- Ravim on valgustundlik ning seda tuleb kaitsta valguse eest, kui seda ei säilitata originaalpakendis.
- Hoida külmkapis (2 °C...8 °C)

Enterobacteriacae

Cephalosporins1	MIC break point (mg/ L)	Disk cont ent (µg)	Zone diame ter break point (mm)		
S ≤	R >	S ≥	R <		
Ceftolozane-tazobactam	13	13	30-10	23	23

Pseudomonas spp.

Cephalosporins	**MIC breakpoint (mg/L)**	**Disk content (µg)**	**Zone diameter breakpoint (mm)**		
S ≤	**R >**	**S ≥**	**R <**		
Ceftolozane-tazobactam, *P. aeruginosa*	43	43	**30-10**	IP	IP

Overall Microbiology Summary

- Ceftolozane has potent activity against drug-resistant *Pseudomonas aeruginosa* because it is relatively stable against hydrolysis by the AmpC enzymes of *P. aeruginosa*, and is also little affected by efflux and porin resistance mechanisms
- High potency for *P. aeruginosa*1,2
  - –MIC50/90 = 0.5/2 mg/L (US)1 and 0.5/1 mg/L (Canada)2
  - –In vitro activity against strains that are resistant to carbapenems, cephalosporins, fluoroquinolones, and/or aminoglycosides, including the majority of multidrug-resistant isolates1,2
- Tazobactam is a potent inhibitor of most class A and some C β-lactamases, broadening coverage to include common ESBL-producing *Escherichia coli, Klebsiella pneumoniae,* and other Enterobacteriaceae1,3
  - –Ceftolozane/tazobactam ESBL+ *E. coli:* MIC50/90 = 0.5/4 mg/L (US)1
- No activity against KPC3 or MBL-producing bacteria4
- Minimal activity against *Acinetobacter*4
- Activity against select Gram-positive bacteria, such as *some Streptococcus sp.*4
- Activity against select anaerobic bacteria, such as *Bacteroides fragilis*5
- Lower propensity for resistance selection in *P. aeruginosa* than comparators6
- Potent concentration-independent *Pseudomonas* biofilm bactericidal activity7

1. Farrell et al. *Antimicrob Agents Chemother.* 2013;57:6305-10. 2. Walkty et al. *Antimicrob Agents Chemother.* 2013;57:5707-9. 3. Livermore et al. *J Antimicrob Chemother.* 2010;65:1972-4. 4. Data on file, Cubist Pharmaceuticals. 5. Snydman et al. *Antimicrob Agents Chemother.* 2014;58:1218-23. 6. Cabot et al. *Antimicrob Agents Chemother.* 2014;58:3091-9. 7. Riera et al. *J Antimicrob Chemother.* 2010;65:1399-404.

- Eesti Infektsioonhaiguste Selts ja Eesti Anestesioloogide Selts taotlevad täiesti uut teenuskoodi Gramnegatiivsete resistentsete bakterite (MDR sh. ESBL) poolt põhjustatud infektsiooni raviks, mida saaks kohaldada kinnitatud või tõenäolise resistentse GNB poolt põhjustatud infektsiooni korral ja konsiiliumi otsuse alusel.

- Taotluse kontekstis ei ole kriitiline mitte konkreetne haiguse diagnoos, vaid hoopis tavapärasele ravile eeldatavalt mitte alluva multiresistentse tekitaja olemasolu ja seetõttu ei sobi kasutamiseks olemasolev sepsise kood.

- Eesmärk on võimaldada mitte ainult olemasolevate või kohe turule jõudva, vaid ka võimalike kaugemas tulevikus tulevate ravimite kasutamist vajadusel ka Eesti haiglates.

	Gramnegatiivsete resistentsete bakterite (MDR sh. ESBL) poolt põhjustatud infektsiooni ravi – üks ravipäev tseftolosaani/tasobaktaami või tseftasidiimi/avibaktaamiga või kolistiini pluss meropeneemiga või fosfomütsiiniga.
	Uus kood
	Kinnitatud või tõenäolise resistentse GNB poolt põhjustatud infektsiooni korral. Konsiiliumi otsuse alusel (raviarst ja infektsioonikontrolli teenistuse arst)

Kasutusvaldkonnad

- MDR Pseudomonas aeruginosa
- ESBL pos.E.coli ja Kl.pneumoniae
- Empiirilise ravi soovitus meie tingimustes kahtlane.
- Kromosomaalse AmpC ga enterobakterite kliiniline mõju ebakindel,in vitro toimib.

Tänan kuulamast!