β-λακταμικά αντιβιοτικά για νοσοκομειακή χρήση

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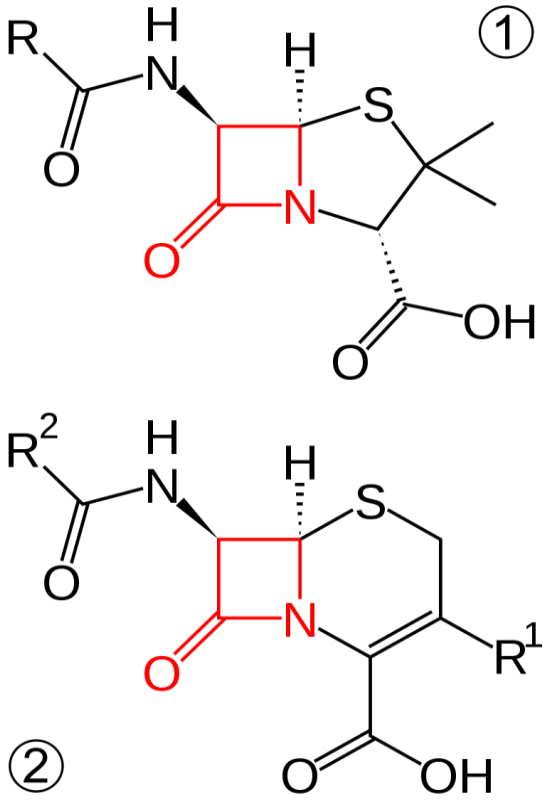
Ειδικός Παθολόγος - Λοιμωξιολόγος

- β-lactam antibiotics (beta-lactam antibiotics) are antibiotics that contain a beta-lactam ring in their molecular structure.
- This includes penicillin derivatives (penams), cephalosporins (cephems), monobactams, carbapenems[1] and carbacephems.
- Most β-lactam antibiotics work by inhibiting cell wall biosynthesis in the bacterial organism and are the most widely used group of antibiotics.
- Until 2003, when measured by sales, more than half of all commercially available antibiotics in use were β-lactam compounds.
- The first β-lactam antibiotic discovered, penicillin, was isolated from a rare variant of Penicillium notatum (since renamed Penicillium chrysogenum).
- [Picture]

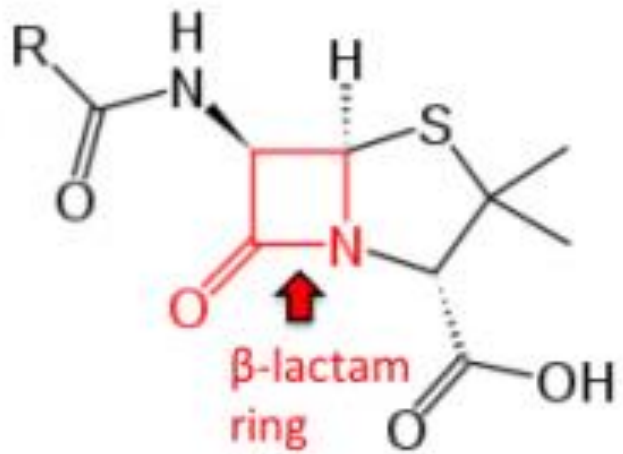
- By definition, all β-lactam antibiotics have a β-lactam ring in their structure.

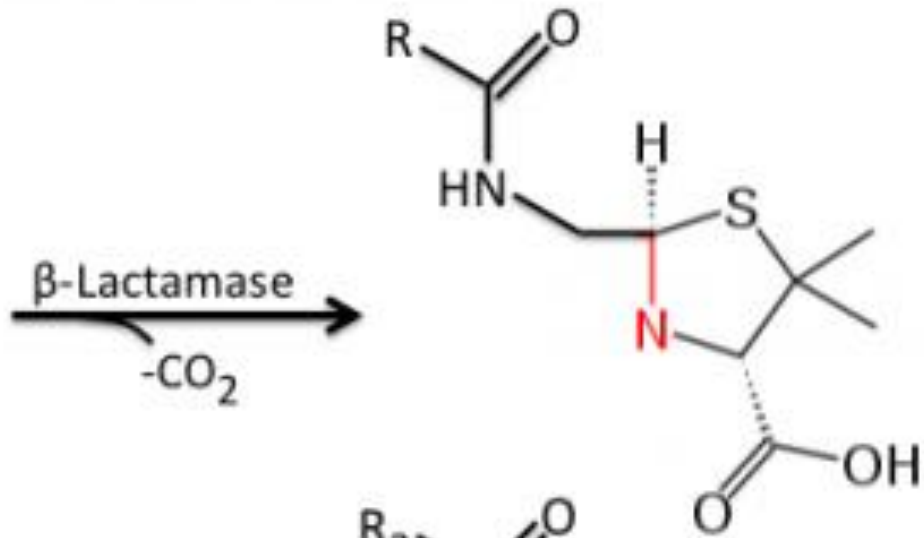


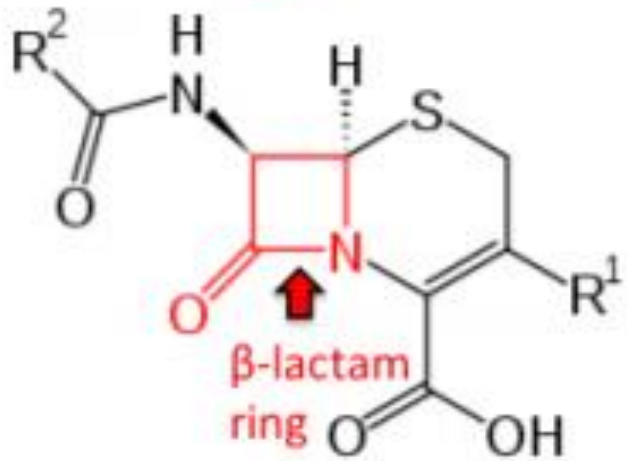
Skeletal formulae of the basic structures of penicillin (1)
and
cephalosporin (2) antibiotics,
highlighting the beta-lactam ring (red).

Bacteria often develop resistance to β-lactam antibiotics by synthesizing a β-lactamase, an enzyme that attacks the β-lactam ring.

Penicillin







Cephalosporin

inactive metabolites

- Bacteria often develop resistance to β-lactam antibiotics by synthesizing a β-lactamase, an enzyme that attacks the β-lactam ring.

- To overcome this resistance, β-lactam antibiotics can be given with β-lactamase inhibitors such as clavulanic acid.[6]

Modes of resistance

- The effectiveness of these antibiotics relies on their ability to reach the PBP intact and their ability to bind to the PBP.

- Hence, there are two main modes of bacterial resistance to β-lactams:

I. Enzymatic hydrolysis of the β-lactam ring

II. Possession of altered penicillin-binding proteins

I. Enzymatic hydrolysis of the β-lactam ring

- If the bacterium produces the enzyme β-lactamase or the enzyme penicillinase, the enzyme will hydrolyse the β-lactam ring of the antibiotic, rendering the antibiotic ineffective.[16]

(An example of such an enzyme is New Delhi metallo-beta-lactamase 1, discovered in 2009.)

- The genes encoding these enzymes may be inherently present on the bacterial chromosome

or

may be acquired via plasmid transfer (plasmid-mediated resistance),

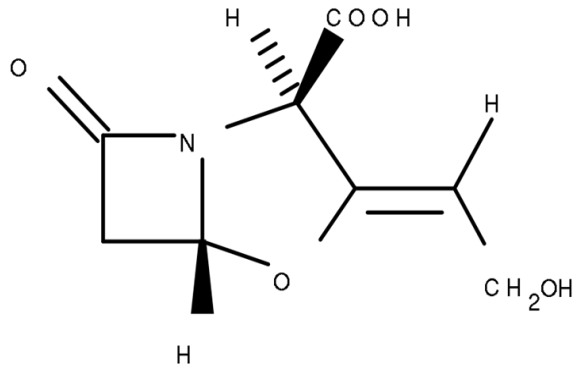
And, β-lactamase gene expression may be induced by exposure to β-lactams.

- The production of a β-lactamase by a bacterium does not necessarily rule out all treatment options with β-lactam antibiotics.

In some instances, β-lactam antibiotics may be co-administered with a β-lactamase inhibitor.

For example, Augmentin (FGP) is made of amoxicillin (a β-lactam antibiotic) and clavulanic acid (a β-lactamase inhibitor).

The clavulanic acid is designed to overwhelm all β-lactamase enzymes, and effectively serve as an antagonist so that the amoxicillin is not affected by the β-lactamase enzymes.



Clavulanic acid

- Other β-lactamase inhibitors such as boronic acids are being studied in which they irreversibly bind to the active site of β-lactamases.

- This is a benefit over clavulanic acid and similar beta-lactam competitors, because they cannot be hydrolysed, and therefore rendered useless.

- Extensive research is currently being done to develop tailored boronic acids to target different isozymes of beta-lactamases.[17]

- However,
  in all cases where infection with β-lactamase-producing bacteria is suspected,

  the choice of a suitable β-lactam antibiotic should be carefully considered prior to treatment.

- In particular,
  choosing appropriate β-lactam antibiotic therapy is of utmost importance against organisms which harbor some level of β-lactamase expression.

  In this case, failure to use the most appropriate β-lactam antibiotic therapy at the onset of treatment could result in selection for bacteria with higher levels of β-lactamase expression, thereby making further efforts with other β-lactam antibiotics more difficult.[18]

II. Possession of altered penicillin-binding proteins (PBPs)

- As a response to the use of β-lactams to control bacterial infections, some bacteria have evolved penicillin binding proteins with novel structures.

- β-lactam antibiotics cannot bind as effectively to these altered PBPs, and, as a result, the β-lactams are less effective at disrupting cell wall synthesis.

- Notable examples of this mode of resistance include methicillin-resistant Staphylococcus aureus (MRSA)[19] and penicillin-resistant Streptococcus pneumoniae.

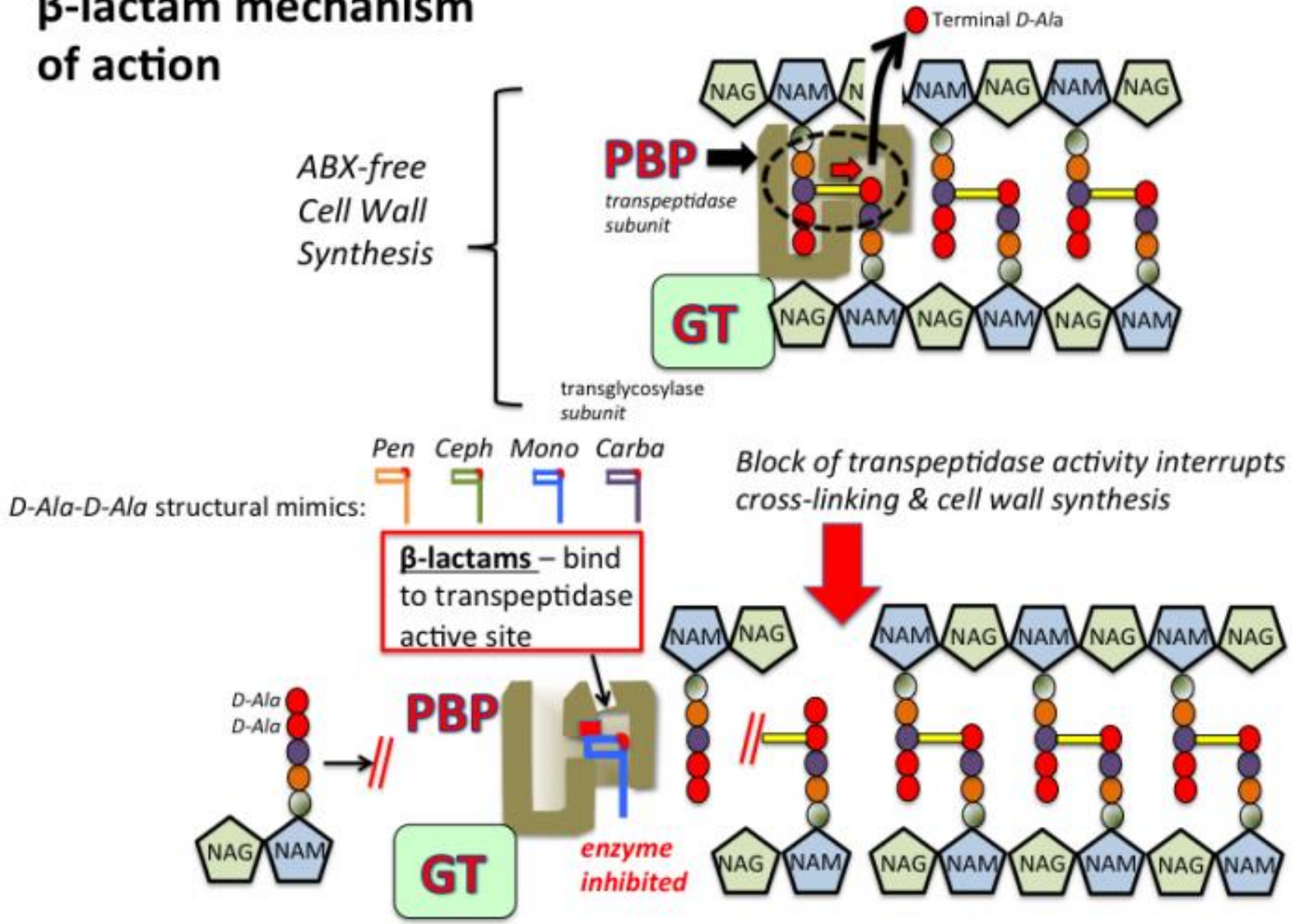
- Altered PBPs do not necessarily rule out all treatment options with β-lactam antibiotics.

Mechanism of Action

- **Peptidoglycan or murein is a vital constituent of the bacterial cell wall that provides mechanical stability to it.** It is an extremely conserved **constituent of both the gram-positive and gram-negative envelopes.** Nevertheless, peptidoglycan is a thick structure in gram-positive bacteria (≥10 layers), while it is thin (one or two layers) in gram-negative ones. Concerning its structure, peptidoglycan is composed of glycan chains made of N-acetylglucosamine and N-acetylmuramic acid disaccharide subunits; the N-acetylmuramic part is linked to highly conserved pentapeptide or tetrapeptide stems (l-alanine–d-isoglutamine–l-lysine–d-alanine–[d-alanine].

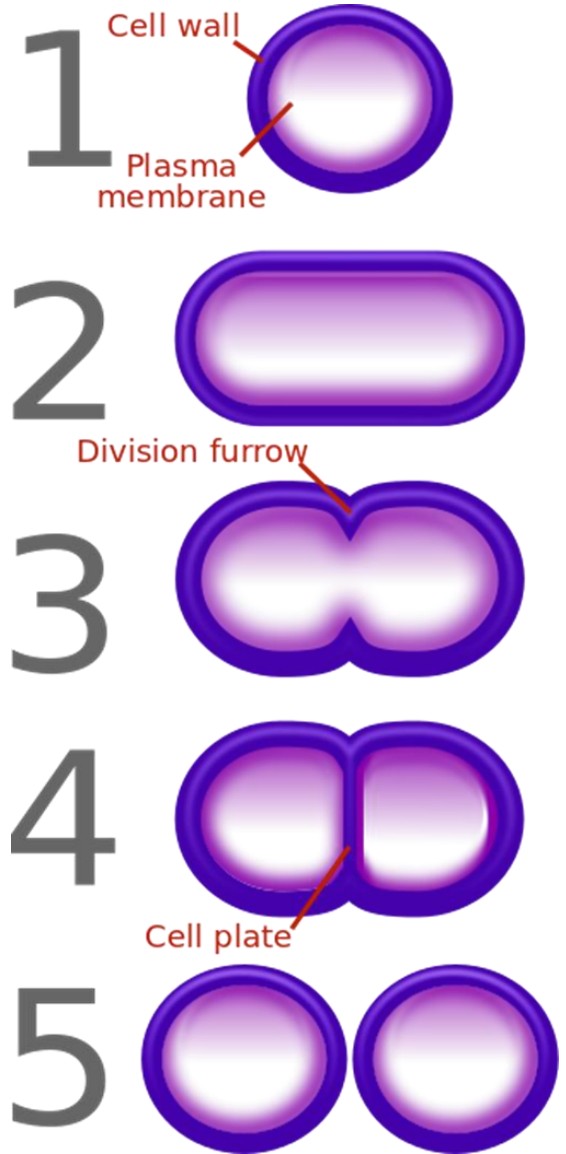
- The **beta-lactam antibiotics inhibit the last step in peptidoglycan synthesis** by acylating the transpeptidase involved in cross-linking peptides to form peptidoglycan. The **targets for the actions of beta-lactam antibiotics are** known as **penicillin-binding proteins (PBPs)**. **This binding**, in turn, **interrupts** the **terminal transpeptidation process** and **induces loss of viability and lysis**, also through autolytic processes within the bacterial cell.[2]

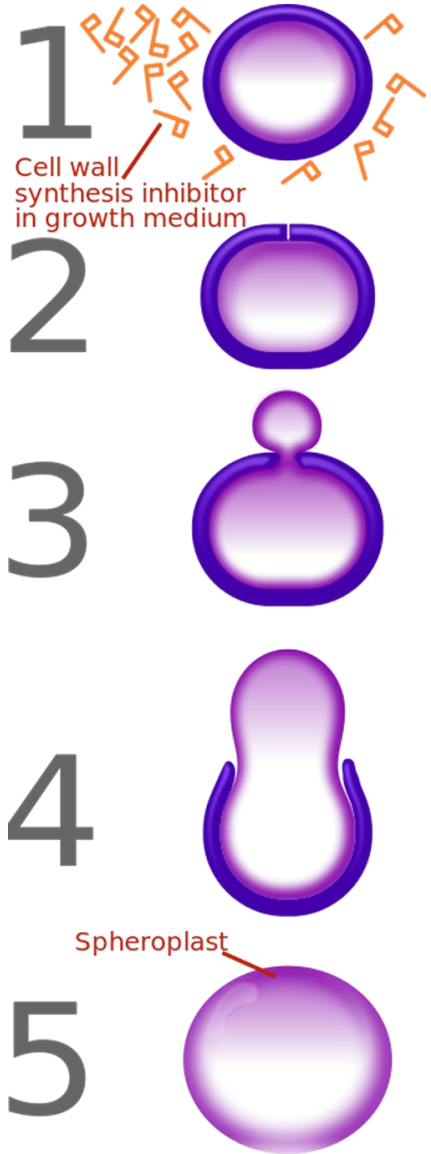
β-lactam mechanism of action



http://tmedweb.tulane.edu/pharmwiki/doku.php/betalactam_pharm

β-lactam antibiotics bind to PBPs (penicillin binding proteins), and, as a result, the β-lactams are disrupting cell wall synthesis. In the absence of β-lactam antibiotics (left), the cell wall plays an important role in bacterial reproduction. Bacteria attempting to grow and divide in the presence of β-lactam antibiotics (right) fail to do so, and instead shed their cell walls, forming osmotically fragile spheroplasts.





Nomenclature

- β-lactams are classified according to their core ring structures.[20]

- **β-lactams fused to saturated five-membered rings:**
- β-lactams containing thiazolidine rings are named **penams.**
- β-lactams containing pyrrolidine rings are named **carbapenams.**
- β-lactams fused to oxazolidine rings are named **oxapenams or clavams.**

- **β-lactams fused to unsaturated five-membered rings:**
- β-lactams containing 2,3-dihydrothiazole rings are named **penems.**
- β-lactams containing 2,3-dihydro-1H-pyrrole rings are named **carbapenems.**

- **β-lactams fused to unsaturated six-membered rings:**
- β-lactams containing 3,6-dihydro-2H-1,3-thiazine rings are named **cephems.**
- β-lactams containing 1,2,3,4-tetrahydropyridine rings are named **carbacephems.**
- β-lactams containing 3,6-dihydro-2H-1,3-oxazine rings are named **oxacephems.**

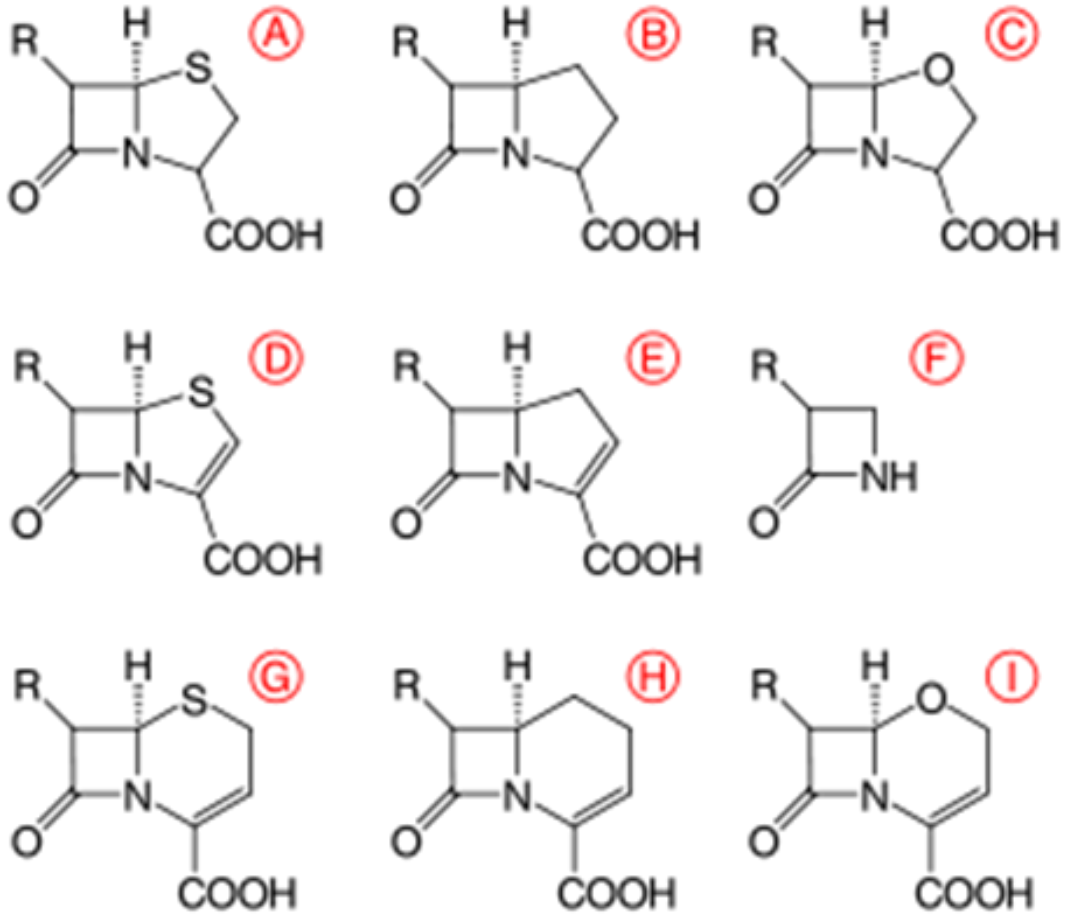
- β-lactams not fused to any other ring are named **monobactams.**

The β-lactam core structures.

(A) A penam. (B) A carbapenam. (C) An oxapenam.

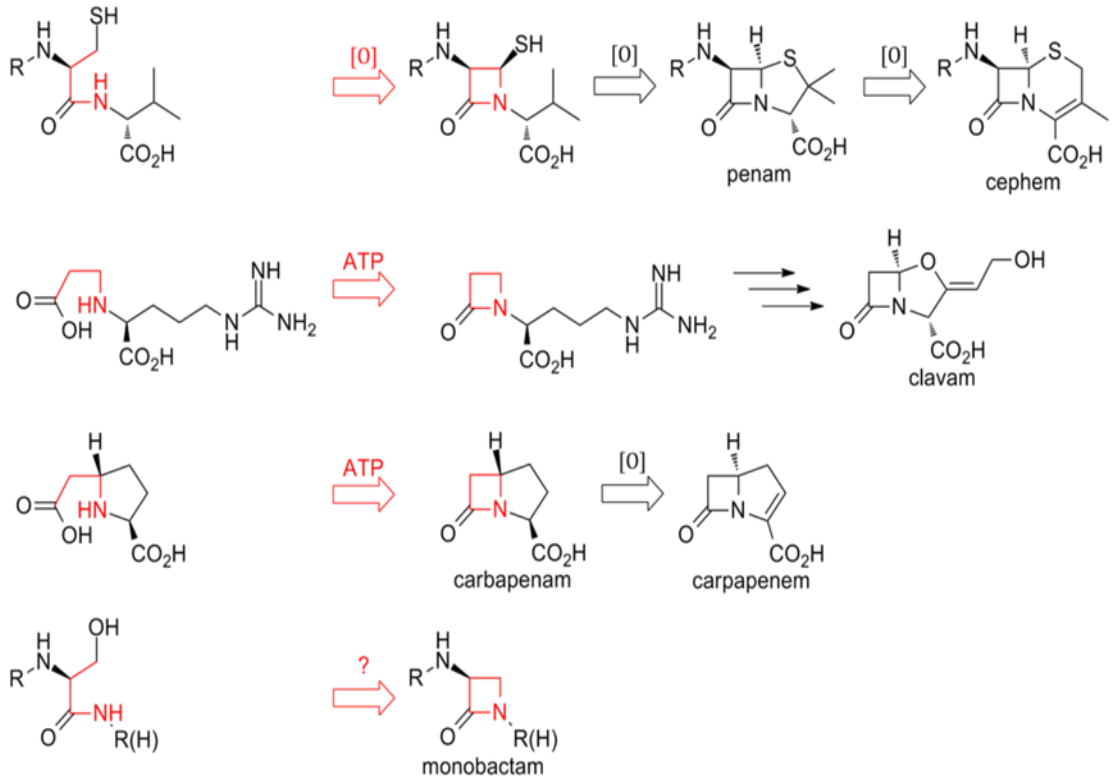
(B) (D) A penem. (E) A carbapenem. (F) A monobactam.

(C) (G) A cephem. (H) A carbacephem. (I) An oxacephem



- This figure outlines the different methods of β-lactam closure among the various classes of β-lactam compounds.
- Penams and cephems are cyclized oxidatively (first row);
- clavams and carbapenems are closed by ATP-utilizing amidation (second and third row); and
- some monobactams may be closed by a third(?) method (fourth row).

- First row
- Second row
- Third row
- Fourth row



Beta-lactam antibiotics are one of the **most commonly prescribed drug classes with numerous clinical indications**.

- Their advent starting from the 30s of the twentieth century drastically changed the scenario of the fight against bacterial infectious diseases.

- Nowadays, it has been calculated that the annual expenditure for these antibiotics amounts to approx $15 billion of USD and it makes up **65% of the total antibiotics market.**

- Their use, however, clashes with the **worrying phenomenon of antimicrobial resistance remains**, which represents a global health issue.

- From a **biochemical point of view**, these drugs have a common feature, which is the 3-carbon and 1-nitrogen ring (**beta-lactam ring**) that is **highly reactive**. This class includes:

- **Penicillins.** These antibiotics (most of which end in the suffix -cillin) contain a nucleus of 6-animopenicillanic acid (lactam plus thiazolidine) ring and other ringside chains. The group includes natural penicillins, beta-lactamase-resistant agents, aminopenicillins, carboxypenicillins, and ureidopenicillins.
- **Cephalosporins.** They contain a 7-aminocephalosporanic acid nucleus and side-chain containing 3,6-dihydro-2 H-1,3- thiazane rings. Cephalosporins are traditionally divided into five classes or generations, although acceptance for this terminology is not universal.
- **Carbapenems.** Their defining structure is a carbapenem coupled to a beta-lactam ring that confers protection against most beta-lactamases, although resistance to these compounds is a significant issue and occurs mainly among gram-negative pathogens (e.g., Klebsiella pneumoniae, Pseudomonas aeruginosa, and Acinetobacter baumannii) which produce different classes of beta-lactamases termed as carbapenemase.
- **Monobactams.** The beta-lactam ring stands alone and not fused to another ring.

ΕΝΔΕΙΞΕΙΣ ΣΗΜΕΡΑ ΓΙΑ ΧΟΡΗΓΗΣΗ β-ΛΑΚΤΑΜΙΚΩΝ ΑΝΤΙΒΙΟΤΙΚΩΝ ΣΕ ΝΟΣΟΚΟΜΕΙΑΚΟ ΠΕΡΙΒΑΛΛΟΝ

The indications for using the beta-lactam antibiotics are many and vary according to the subclass considered[4]*

*Οι ενδοφλέβιες μορφές των σκευασμάτων αφορούν κυρίως ενδονοσοκομειακή χρήση ενώ οι από του στόματος χορηγούμενες μορφές των σκευασμάτων αφορούν κυρίως εξωνοσοκομειακή χρήση

Penicillins

- Natural penicillins [penicillin G (IV), penicillin V (PO)] are used to treat selected gram-positive and gram-negative infections:

- Penicillin susceptible Streptococcus pneumonia and meningitis
- Streptococcal pharyngitis
- Endocarditis
- Skin and soft tissue infections
- Neisseria meningitides infections
- Syphilis

Oxacillin (IV),

Nafcillin (IV),

Dicloxacillin (PO),

by definition beta-lactamase resistant agents, are active against gram-positive organisms.

Despite the occurrence of widespread resistance among staphylococci, they remain antibiotics of choice in managing methicillin-susceptible staphylococci (MSSA):

- Skin and soft tissue infections (MSSA)
- Serious infections due to MSSA

Aminopenicillins

- These antibiotics have activity against gram-positive and gram-negative bacteria (e.g., many Enterobacteriaceae) and, anaerobic organisms when used together with beta-lactamase inhibitors.

- Ampicillin (PO/IV),
- Amoxicillin (PO):

- Upper respiratory tract infections (sinusitis, pharyngitis, otitis media)
- Enterococcus faecalis infections
- Listeria infections

Carboxypenicillins and ureidopenicillins

Ticarcillin (carboxypenicillin) and

Piperacillin (ureidopenicillin)

- have **activity against** aminopenicillin-resistant gram-negative bacilli (**Pseudomonas aeruginosa**).

- Are commonly combined with beta-lactamase inhibitors (broader spectrum to cover Pseudomonas aeruginosa and anaerobes)

Cephalosporins

First-generation cephalosporins

Cefazolin(IV),
Cephalexin (PO),
Cefadroxil (PO)

- Skin and soft tissue infections serious infections due to MSSA

- Perioperative surgical prophylaxis

Second-generation cephalosporins

Cefuroxime (IV/PO),

Cefoxitin (IV),

Cefotetan (IV),

Cefaclor (PO),

Cefprozil (PO).

- Upper respiratory tract infections (sinusitis, otitis media)
- Cefoxitin, cefotetan-gynecologic infections,
- Perioperative surgical prophylaxis

Third-generation cephalosporins

- Cefotaxime (IV),
- Ceftriaxone (IV),
- Cefpodoxime (PO),
- Cefixime (PO),
- Cefdinir (PO),
- Cefditoren (PO),
- Ceftibuten (PO)

- Community-acquired pneumonia, meningitis
- Urinary tract infections
- Streptococcal endocarditis
- Gonorrhea
- Severe Lyme disease.

Anti-pseudomonal Cephalosporins

Ceftazidime (IV),

Ceftazidime/avibactam* (IV), **[also been described as "fifth-generation"]**

Cefepime (IV) [**Fourth-generation**],

Ceftolozane/tazobactam* (IV) [also been described as **"fifth-generation"**]

- Nosocomial infections-pneumonia

- Meningitis

Complicated Intra-abdominal Infections (cIAI)

[ceftolozane plus beta-lactamase inhibitor]

Complicated Urinary Tract Infections (cUTI)

[ceftolozane plus beta-lactamase inhibitor]

Carbapenems

Imipenem/cilastatin (IV),

Meropenem (IV),

Doripenem (IV)

- Nosocomial infections-pneumonia, intra-abdominal infections, urinary tract infections
- Meningitis (especially meropenem)

AND for

Ertapenem (IV): (no cover for Pseudomonas spp.)

- Community-acquired infections
- Nosocomial infections.

Monobactams

Aztreonam (IV).

It is **effective only against aerobic gram-negative organisms** but shows no activity against gram-positive bacteria or anaerobes.

- Nosocomial infections, e.g., pneumonia
- Urinary tract infections

Αντιμικροβιακά έναντι Gram θετικών (νεότερα κυρίως για MRSA, VRE)

- **Β-λακτάμες**
  - **Κεφταρολίνη (ceftaroline)**
  - **Κεφτομπιπρόλη (ceftobiprole)**
- Κινολόνες
  - Delafloxacin
- Τετρακυκλίνες
  - Omadacycline
  - Eravacycline
- Δαπτομυκίνη
- Τιγκεκυκλίνη
- Λινεζολίδη
- Τεντιζολίδη (Tedizolid)
- Νταλμπαβανσίνη (Dalbavancin)
- Οριταβανσίνη (Oritavancin)

Anti-Methicillin-resistant Staphylococcus aureus (MRSA) cephalosporins

Ceftaroline (IV),

ceftobiprole (IV)

[They are both also been described as **"fifth-generation"**]

- Community-acquired pneumonia
- Hospital-acquired pneumonia (excluding ventilator-acquired pneumonia?)
- Skin and soft tissue infection

Ceftaroline fosamil (Zinforo)

Ceftaroline fosamil acetic acid solvate monohydrate equivalent to

600 mg ceftaroline fosamil

Therapeutic indications

Zinforo is indicated for the treatment of the following infections in neonates, infants, children, adolescents and adults:

Complicated skin and soft tissue infections (cSSTI)

Community-acquired pneumonia (CAP)

Ceftaroline has high affinity for PBP2a of methicillin-resistant Staphylococcus aureus (MRSA) and PBP2x of penicillin non-susceptible Streptococcus pneumoniae (PNSP).

- Ceftaroline is **not active against** strains of **Enterobacterales** producing extended-spectrum betalactamases (**ESBLs**) from the TEM, SHV or CTX-M families, serine carbapenemases (such as **KPC**), class B metallo-beta-lactamases (**MBL**) or class C (**AmpC**) cephalosporinases.

- The recommended **duration of treatment are 5-14 days for cSSTI and 5-7 days for CAP**

Special warnings and precautions for use

- Hypersensitivity reactions
- Rash: common frequency
- Clostridium difficile-associated diarrhoea
- Patients with pre-existing seizure disorder
- Direct antiglobulin test (Coombs test) seroconversion and potential risk of haemolytic anaemia
- Pregnancy: limited data

- **Dosage in adults with normal renal function, creatinine clearance (CrCL)> 50 mL/min**

Standard dose

- Complicated skin and soft tissue infections (**cSSTI**)

  AND

- Community-acquired pneumonia (**CAP**)

  600 mg IV over 1 hour/every 12 hours

  [For treatment of S. aureus for which the ceftaroline MIC is ≤ 1 mg/L, the standard dose is recommended]

High dose

- cSSTI confirmed or suspected to be caused by S. aureus with an MIC = 2 mg/L or 4 mg/L to ceftaroline

  600 mg IV over 2 hours/every 8 hours

Renal impairment:

The dose should be adjusted when creatinine clearance (CrCL) is ≤ 50 mL/min

Hepatic impairment:

No dosage adjustment is considered necessary in patients with hepatic impairment

Clinical efficacy against specific pathogens

- Efficacy has been demonstrated in clinical studies against the pathogens listed under each indication that were susceptible to ceftaroline in vitro.

Complicated skin and soft tissue infections

Gram-positive micro-organisms

- Staphylococcus aureus (including methicillin-resistant strains)
- Streptococcus pyogenes
- Streptococcus agalactiae
- Streptococcus anginosus group (includes S. anginosus, S. intermedius, and S. constellatus)
- Streptococcus dysgalactiae

Gram-negative micro-organisms

- Escherichia coli
- Klebsiella pneumoniae
- Klebsiella oxytoca
- Morganella morganii

Community-acquired pneumonia

- No cases of CAP due to MRSA were enrolled into the studies. The available clinical data cannot substantiate efficacy against penicillin non-susceptible strains of S. pneumoniae.

Gram-positive micro-organisms

- Streptococcus pneumoniae
- Staphylococcus aureus (methicillin-susceptible strains only)

- Gram-negative micro-organisms
- Escherichia coli
- Haemophilus influenzae
- Haemophilus parainfluenzae
- Klebsiella pneumoniae

Anaerobic micro-organisms

Gram-positive micro-organisms

- Peptostreptococcus spp.

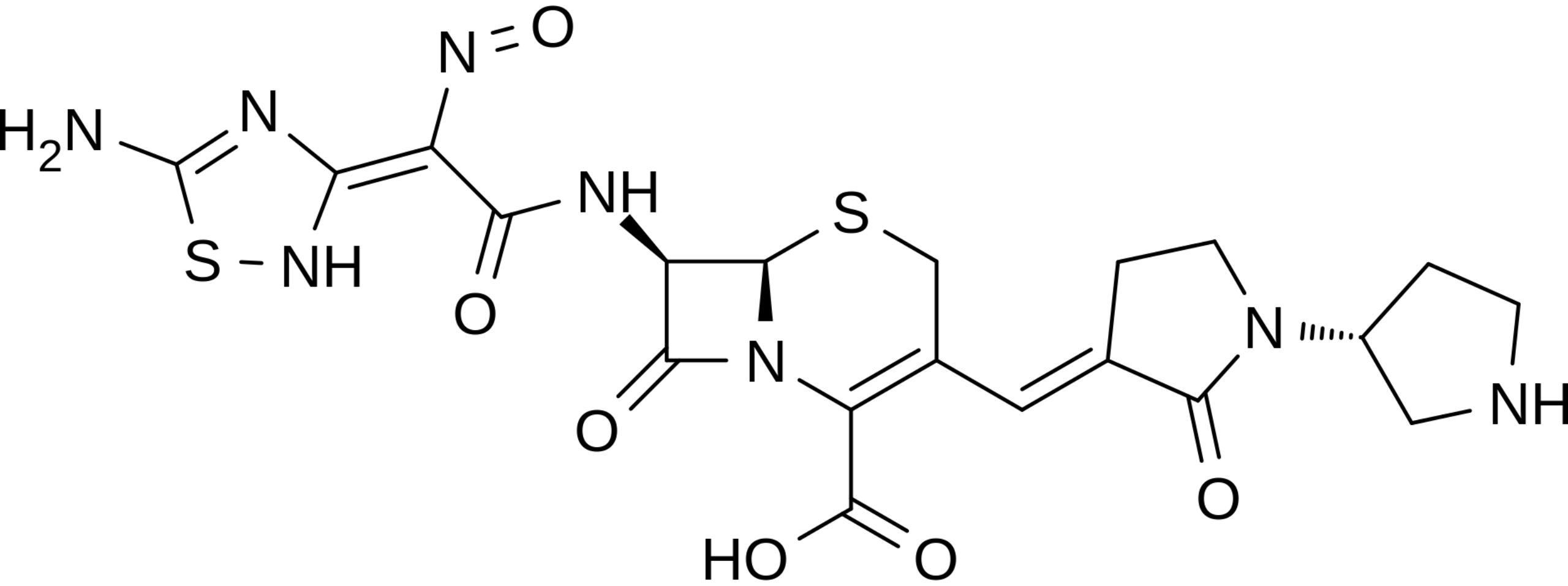
Gram-negative micro-organisms

- Fusobacterium spp.

- In vitro data indicate that the following species are **not susceptible to ceftaroline**:
- Chlamydophila spp.
- Legionella spp.
- Mycoplasma spp.
- Proteus spp.
- Pseudomonas aeruginosa

Ceftobiprole

https://www.medicines.org.uk/emc/product/9164#gref



Ceftobiprole (Zevtera/Mabelio)

A fifth-generation cephalosporin for the treatment of hospital-acquired pneumonia (excluding ventilator-associated pneumonia) and community-acquired pneumonia.

The efficacy of ceftobiprole has been demonstrated in two large randomized, double-blind, phase 3 clinical trials in patients with hospital-acquired and community-acquired pneumonia.

Ceftobiprole was non-inferior to ceftazidime plus linezolid in the treatment of hospital-acquired pneumonia (excluding ventilator-acquired pneumonia) and non-inferior to ceftriaxone with or without linezolid in the treatment of community-acquired pneumonia.

- Ceftobiprole is the active moiety of the prodrug ceftobiprole medocaril and is available for intravenous treatment only. The recommended dose is 500 mg as 2-hour infusion every 8 hours. It is mainly excreted renally. Dose adjustment is required for patients with moderate or severe renal impairment and for patients with end-stage renal disease, but no dose adjustment is needed by gender, ethnicity or age, in severely obese patients or in patients with hepatic impairment.

- Ceftobiprole has been approved for the treatment of adult patients with hospital acquired pneumonia (excluding ventilator-acquired pneumonia) and community-acquired pneumonia in 12 European countries, Canada and Switzerland.

- It exhibits tight binding to several different PBPs of Gram-positive and Gram-negative pathogens, and a most notable feature is the ability to inhibit also the PBPs that are resistant or poorly susceptible to conventional β-lactams, including PBP2a of methicillin-resistant Staphylococcus aureus (MRSA) and PBP2x of penicillin-resistant pneumococci (PRP).

Exhibits broad spectrum of antimicrobial activity which covers staphylococci (including methicillin-resistant strains of S. aureus (MRSA) and of coagulase-negative staphylococci CoNS)), streptococci (including PRP strains), Haemophilus influenzae, Moraxella catarrhalis, most members of the order Enterobacterales, and also P. aeruginosa and Enterococcus faecalis.

Ceftobiprole has reduced or no activity against Enterococcus faecium, Acinetobacter baumannii, Burkholderia cepacia complex, Stenotrophomonas maltophilia, Proteus vulgaris, most Gram-negative anaerobes (e. g. Bacteroides fragilis group and Prevotella spp.), and strains of Enterobacterales producing acquired ESBLs or carbapenemases.

The activity against methicillin-resistant staphylococci and PRP, which is outstanding compared to that of conventional β-lactams, has led to classification of ceftobiprole among the fifth generation of cephalosporins [11].

No clinical breakpoints are yet available for CoNS, streptococci other than pneumococci, E. faecalis, H. influenzae, M. catarrhalis, and P. aeruginosa.

- Therapeutic indications
- Zevtera is indicated for the treatment of the following infections in adults:

- - Hospital-acquired pneumonia (HAP), excluding ventilator-associated pneumonia (VAP)

- - Community-acquired pneumonia (CAP)

- Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Ceftobiprole is administered intravenously at the dosage of 500 mg q8h infused over 2 hours.

Dosage adjustments are needed in patients with renal impairment (500 mg q12h over 2 h, 250 mg q12h over 2 h, 250 q24h over 2 h in presence of CLCr 30–50 mL/min, <30 mL/min and end stage renal disease or intermittent hemodialysis, respectively) [32].

Renal impairment:

creatinine clearance [CLCR] 50 to 80 mL/min, no dosage adjustment is necessary. In patients with moderate renal impairment (CLCR 30 to < 50 mL/min), the recommended dose of Zevtera is 500 mg administered every 12 hours as a 2-hour intravenous infusion. In patients with severe renal impairment (CLCR < 30 mL/min), the recommended dose of Zevtera is 250 mg administered every 12 hours as a 2-hour intravenous infusion.

Hepatic impairment

There is no experience in patients with hepatic impairment.

Contraindications

- Hypersensitivity to the cephalosporin class of antibacterials.
- Immediate and severe hypersensitivity (e.g. anaphylactic reaction) to any other type of beta-lactam antibacterial agent (e.g. penicillins or carbapenems).
- Pregnancy
- There are no adequate and well-controlled studies

Mechanisms of Resistance

- Ceftobiprole is inactive against strains of **Enterobacteriaceae** that express Ambler class A β-lactamases, especially TEM, SHV and CTX-M type extended-spectrum β-lactamases (ESBL) and the KPC-type carbapenemases, Ambler class B β-lactamases and Ambler class D β-lactamases, especially ESBL variants and carbapenemases (OXA-48). Ceftobiprole is also inactive against strains that have high levels of expression of Ambler class C β-lactamases.

- Ceftobiprole is inactive against strains of **P. aeruginosa** that express enzymes belonging to Ambler class A (e.g., PSE-1), Ambler class B (e.g., IMP-1, VIM-1, VIM-2) and Ambler class D (e.g., OXA-10). It is also inactive against isolates that have acquired mutations in regulatory genes leading to de-repressed levels of expression of the chromosomal Ambler class C β-lactamase, or over-expression of the Mex XY efflux pump.

- Ceftobiprole is inactive against strains of **Acinetobacter spp.** that express enzymes belonging to Ambler class A (e.g., VEB-1), Ambler class B (e.g., IMP-1, IMP-4) Ambler class D (e.g., OXA-25, OXA-26), or that have de-repressed levels of expression of the chromosomal Ambler class C β-lactamase.

Clinical efficacy against specific pathogens

- Efficacy has been demonstrated in clinical studies against the following pathogens in patients with HAP (not including VAP) and CAP that were susceptible to ceftobiprole in vitro:

- Staphylococcus aureus (including MRSA)

- Streptococcus pneumoniae (including MDRSP)

- Escherichia coli

- Klebsiella pneumoniae

Clinical efficacy has not been established against the following pathogens, although in vitro studies suggest that they would often be susceptible to ceftobiprole in the absence of an acquired mechanism of resistance:

- Acinetobacter spp.
- Citrobacter spp.
- Enterobacter spp.
- Haemophilus influenzae
- Klebsiella oxytoca
- Moraxella catarrhalis
- Morganella morganii
- Proteus mirabilis
- Providencia spp.
- Pseudomonas spp.
- Serratia spp.
- In vitro data indicate that the following species are not susceptible to ceftobiprole:
- Chlamydophila (Chlamydia) pneumoniae
- Burkholderia cepacia complex
- Mycoplasma pneumoniae
- Mycobacteria
- Norcardia spp.
- Stenotrophomonas maltophilia

BRITISH NATIONAL FORMULARY

BNF March-September 2022

INDICATIONS V.1

1. Ceftolozane / Tazobactam

- Complicated Intra Abdominal Infection
- Complicated UTI/Acute Pyelonephritis
- Hospital Acquired Pneumonia (HAP)/Ventilator Associated Pneumonia (VAP)

2. Ceftazidime / Avibactam

- Complicated Intra Abdominal Infection
- Complicated UTI / Pyelonephritis
- Hospital Acquired Pneumonia (HAP)/Ventilator Associated Pneumonia (VAP)
- Infections due to Gram negative bacteria with limited treatment option

V.1

3. Ceftaroline Fosamil

- Community Acquired Pneumonia (CAP)
- Complicated Skin Infections / Complicated Soft Tissue Infections

4. Ceftobiprole

- Hospital Acquired Pneumonia (excluding VAP)
- Community Acquired Pneumonia (CAP)

V.1

4. Meropenem/Vaborbactam

- Complicated UTIs including pyelonephritis
- Complicated Intra Abdominal Infections
- Hospital Acquired Pneumonia (HAP) / Ventilator Associated Pneumonia (VAP)
- Bacteremia (occurring in association with or suspected to be associated with the licensed indications)
- Aerobic Gram negative Infections (in patients with limited treatment options – administered on expert advice)

- 5. Imipenem/cilastatin / Relebactam
- Aerobic Gram negative Infections (in patients with limited treatment options – administered on expert advice)

V.1

7. Cefiderocol

- Aerobic Gram negative Infections (in patients with limited treatment options – administered on expert advice)

REMEMBER THE

ISSUE OF RESISTANCE

PERTAINING TO β-LACTAM ANTIBIOTICS

AND

THE UTILIZATION OF

B-LACTAMASE INHIBITORS

&

BETTER PBP BINDING OF β-LACTAM ANTIBIOTICS

&

Time of serum concentration above the MIC (T > MIC)

Mechanism of Resistance for β-lactam antibiotics

- Resistance to beta-lactams is an alarming and growing phenomenon and, in turn, a public health challenge. It concerns above all Streptococcus pneumoniae and individual gram-negative bacilli such as Pseudomonas aeruginosa. With emerging resistance for antibiotics, it makes sense to look into mechanisms of resistance as it can help to decide which drugs to prescribe in different scenarios and ways to overcome the same. Although bacterial resistance to beta-lactams mostly expresses through the production of beta-lactamases, other mechanisms are involved.

Following are the mechanisms of resistance[3]:

- **Inactivation by the production of beta-lactamases**
- **Decreased penetration to the target site** (e.g., the resistance of Pseudomonas aeruginosa
- **Alteration of target site PBPs** (e.g., penicillin resistance in pneumococci)
- **Efflux from the periplasmic space through specific pumping mechanisms**

Remember:

Beta-lactams are antibiotics that have a beta-lactam ring nucleus.

All beta-lactams bind to and inactivate enzymes required for bacterial cell wall synthesis.

Beta-lactamases are enzymes produced by bacteria that break open the beta-lactam ring, inactivating the beta-lactam antibiotic.

Some beta-lactamases are **encoded on** mobile genetic elements (eg, **plasmids**); **others** are encoded **on chromosomes**.

There are numerous **different types of beta-lactamases**.

They are **not all active against all beta-lactam antibiotics** and so are broadly **classified into** several **main groups based on their affinity for particular beta-lactams:**

- **Penicillinases:** Narrow-spectrum penicillins.
  Penicillinase-resistant penicillins: oxacillin, cloxacillin, dicloxacillin, methicillin, and nafcillin.
  Aminopenicillins: ampicillin and amoxicillin.
  Carboxypenicillins: carbenicillin and ticarcillin.

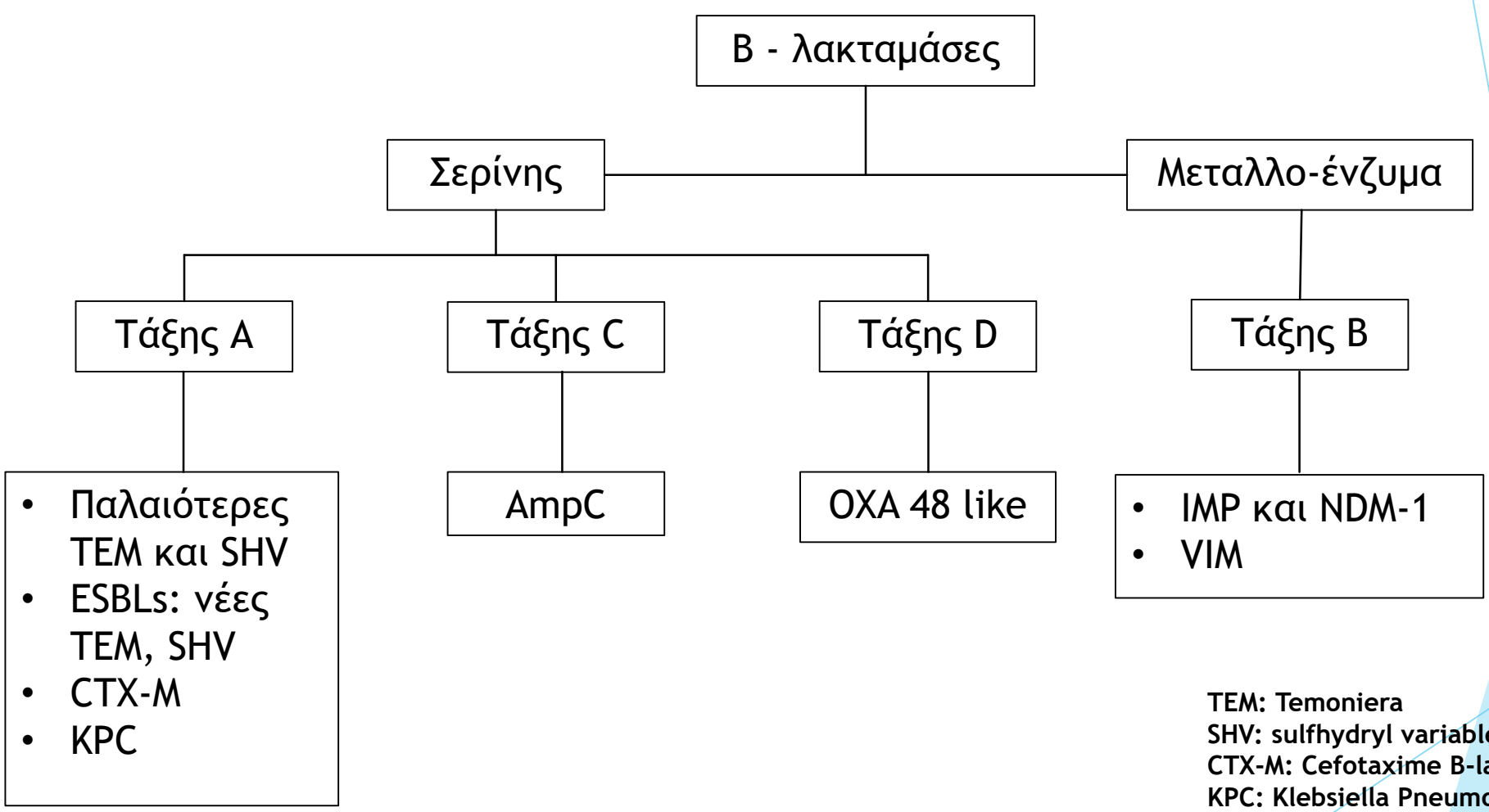
- **Extended-spectrum beta-lactamases:** Extended-spectrum penicillins (eg, piperacillin), most cephalosporins, monobactams

- **AmpC:** Cephalosporins, cephamycins, monobactams, penicillins

- **Metallo-beta-lactamases:** Carbapenems plus all other beta-lactams, **except** the monobactam **aztreonam** (note, <u>these enzymes are not inhibited by beta-lactamase inhibitors</u>)

- **Serine carbapenemases:** Carbapenems plus all other beta-lactams

Ταξινόμηση κατά Ambler



TEM: Temoniera
SHV: sulfhydryl variable
CTX-M: Cefotaxime B-lactamase
KPC: Klebsiella Pneumoniae Carvapenemase
IMP: Imipenemase type carvapenemase
NDM-1: New Delhi metallo-b-lactamase
VIM: verona integron-encoded metallo-β-lactamase

- **Penicillinases** are narrow-spectrum enzymes produced by a variety of organisms including staphylococci such as Staphylococcus aureus.

- **Extended-spectrum beta-lactamases (ESBLs)** refer to a variety of plasmid-carried beta-lactamases produced by some Klebsiella species, Escherichia coli, and other Enterobacteriaceae.

- **AmpC beta-lactamases** are generally chromosomally encoded and commonly produced by Enterobacter, Serratia, Citrobacter, Providencia, Morganella, and Pseudomonas aeruginosa. AmpC production is variable and inducible by beta-lactam exposure, so some of these organisms may appear to be falsely susceptible to 3rd-generation cephalosporins by minimum inhibitory concentration (MIC) testing.

- **Metallo-beta-lactamases** can be chromosomally encoded in some organisms, such as Stenotrophomonas maltophilia, or can be acquired as can occur with a variety of gram-negative organisms including Klebsiella, Pseudomonas, and Acinetobacter.

- **Serine carbapenemases**, such as plasmid-mediated Klebsiella pneumoniae carbapenemase (KPC), are produced most often by K. pneumoniae but have also been reported among other Enterobacteriaceae.

Beta-lactamase inhibitors

- **Beta-lactamase inhibitors are drugs that block the activity of certain beta-lactamases and are thus sometimes combined with beta-lactam antibiotics.** Examples include:

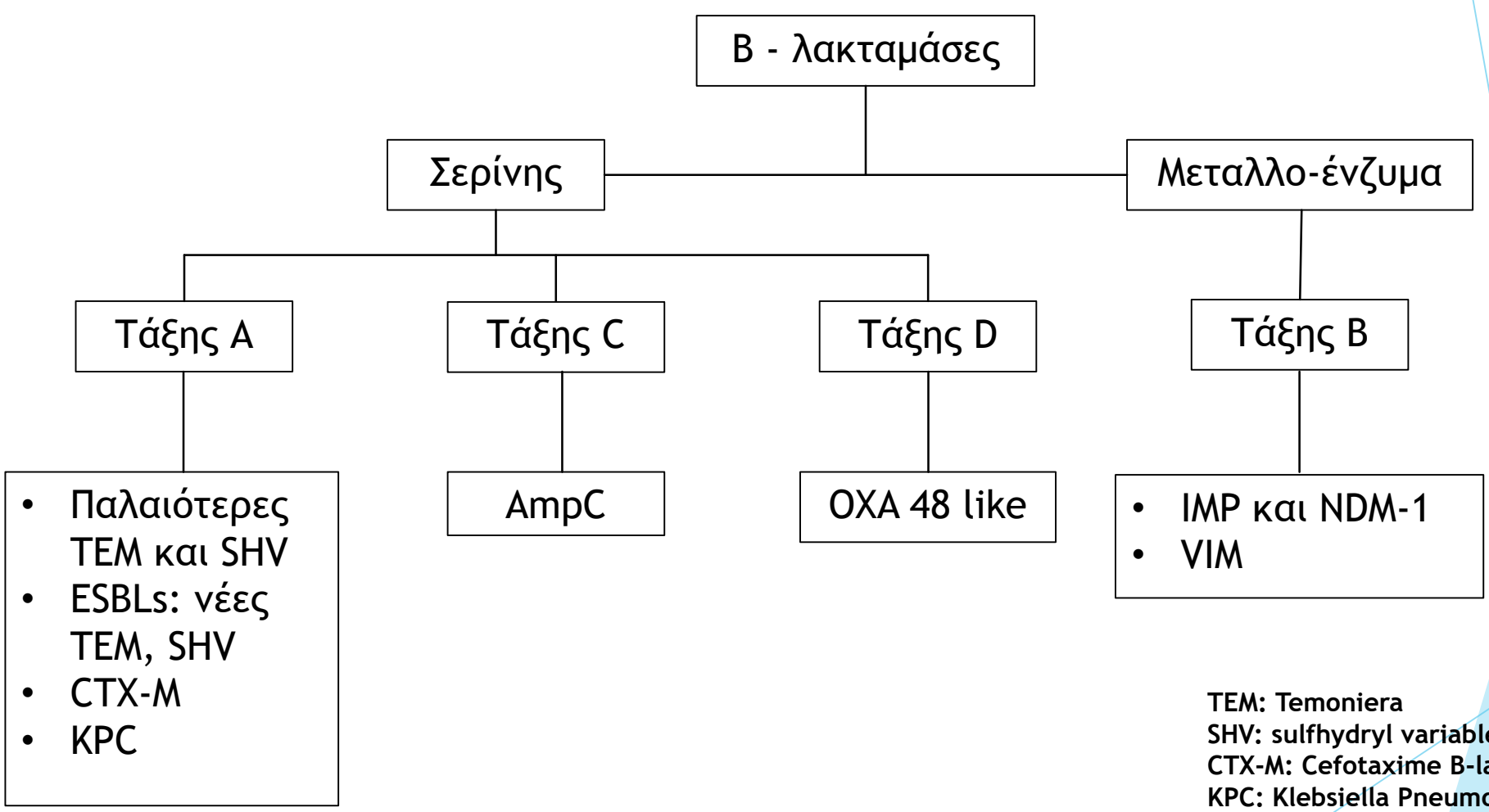
- **Clavulanate, sulbactam, tazobactam:** These drugs block penicillinases but not AmpC or carbapenemases. They also block some ESBLs in vitro, but most combinations that include these drugs are not reliable against ESBL producers clinically.

- **Avibactam, relebactam, vaborbactam:** These drugs block ESBLs, most serine carbapenemases including KPC, and AmpC but not the metallo-beta-lactamases.

- **Avibactam:** This drug also blocks some OXA carbapenemases.

- There are **no currently available beta-lactamase inhibitors active against metallo-beta-lactamases (MBLs), such as NDM-1 (New Delhi MBL-1), VIMs (Verona integron–encoded MBLs), and IMP (imipenem)-types**, which can inactivate all beta-lactam antibiotics **except for aztreonam**. However, many strains that produce MBLs also produce other beta-lactamases that can hydrolyze aztreonam.

Ταξινόμηση κατά Ambler



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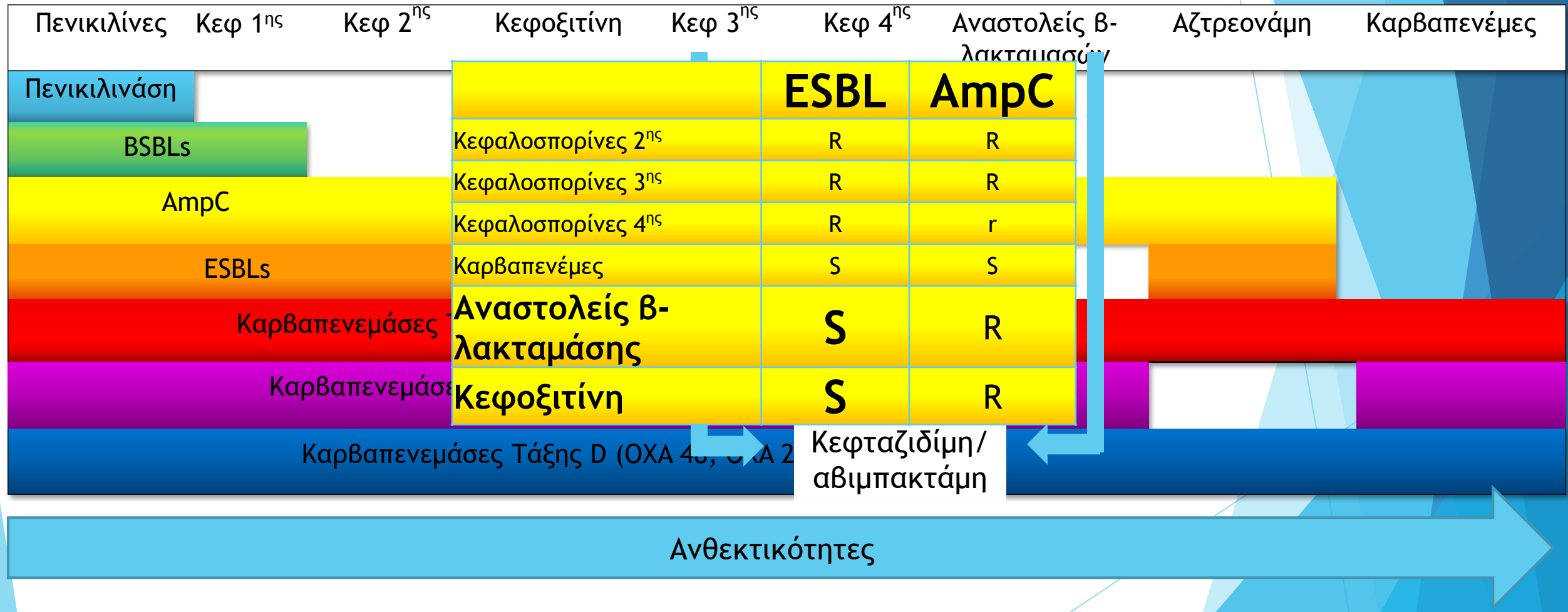
Συνοπτικά



	ESBL	AmpC
Κεφαλοσπορίνες 2ης	R	R
Κεφαλοσπορίνες 3ης	R	R
Κεφαλοσπορίνες 4ης	R	r
Καρβαπενέμες	S	S
Αναστολείς β-λακταμάσης	**S**	R
Κεφοξιτίνη	**S**	R

Coronell-Rodríguez W, Arteta-Acosta C, Dueñas-Castell C. Interpretive Reading of the Antibiogram: A Tool for Clinical Practice. InSepsis 2018 (pp. 95-115). Springer, New York, NY.

Beta-lactamase inhibitors.

- They work primarily by **inactivating serine beta-lactamases**, which are enzymes that hydrolyze and inactivate the beta-lactam ring (especially in gram-negative bacteria).

- These agents include the **first-generation beta-lactamase inhibitors**:

- clavulanic acid,
- sulbactam, and
- tazobactam) and,

- the **newer beta-lactamase inhibitors**:

- avibactam and
- vaborbactam

that are active against carbapenemase such as Klebsiella pneumoniae carbapenemase (KPC).

Aminopenicillins/beta-lactamase inhibitors (first-generation beta-lactamase inhibitors)

- **amoxicillin/clavulanate (IV/PO),**
- **ampicillin-sulbactam (IV/PO)**

The combinations have activity against many Gram-positive and Gram-negative bacteria **except** Pseudomonas aeruginosa.

- Upper respiratory tract infections (sinusitis, otitis media)
- Community acquired pneumonia (CAP)
- Intra-abdominal infections

- **Piperacillin/tazobactam (IV)**
- The combination has activity against many Gram-positive and Gram-negative bacteria including Pseudomonas aeruginosa.

- Pelvic inflammatory disease,
- Intra-abdominal infection,
- Pneumonia,
- Cellulitis, and
- Sepsis

Νεότερα αντιμικροβιακά για Gram-αρνητικά παθογόνα

- Νεότερες κινολόνες
  - Delafloxacin
  - Finafloxacin
- Νεότερες τετρακυκλίνες
  - Omadacycline
  - Eravacycline
- **Συνδυασμοί β-λακταμικών με νέους ανταγωνιστές**
  - **Ceftolozane-tazobactam**
  - **Ceftazidime-avibactam**
  - **Meropenem-varbobactam**
  - **Imipenem-cilastatin/relabactam**
- **Νεότερες κεφαλοσπορίνες**
  - **Cefiderocol**
- Νεότερες αμινογλυκοσίδες
  - Plazomicin
- Παλαιότερα αντιμικροβιακά που έγιναν νέα
  - Fosfomysin
  - Colistin

- Because the emergence of antimicrobial resistance has become a progressively great concern,

  new beta-lactam, and beta-lactamase inhibitor combinations:
- (ceftolozane/tazobactam,
- ceftazidime/avibactam,
- meropenem/vaborbactam,
- imipenem/cilastatin/relebactam,
- aztreonam/avibactam),
- siderophore-conjugated cephalosporins (cefiderocol), and
- siderophore-conjugated monobactams

have been developed and represent options for the management of complicated infections, especially in intensive care unit.

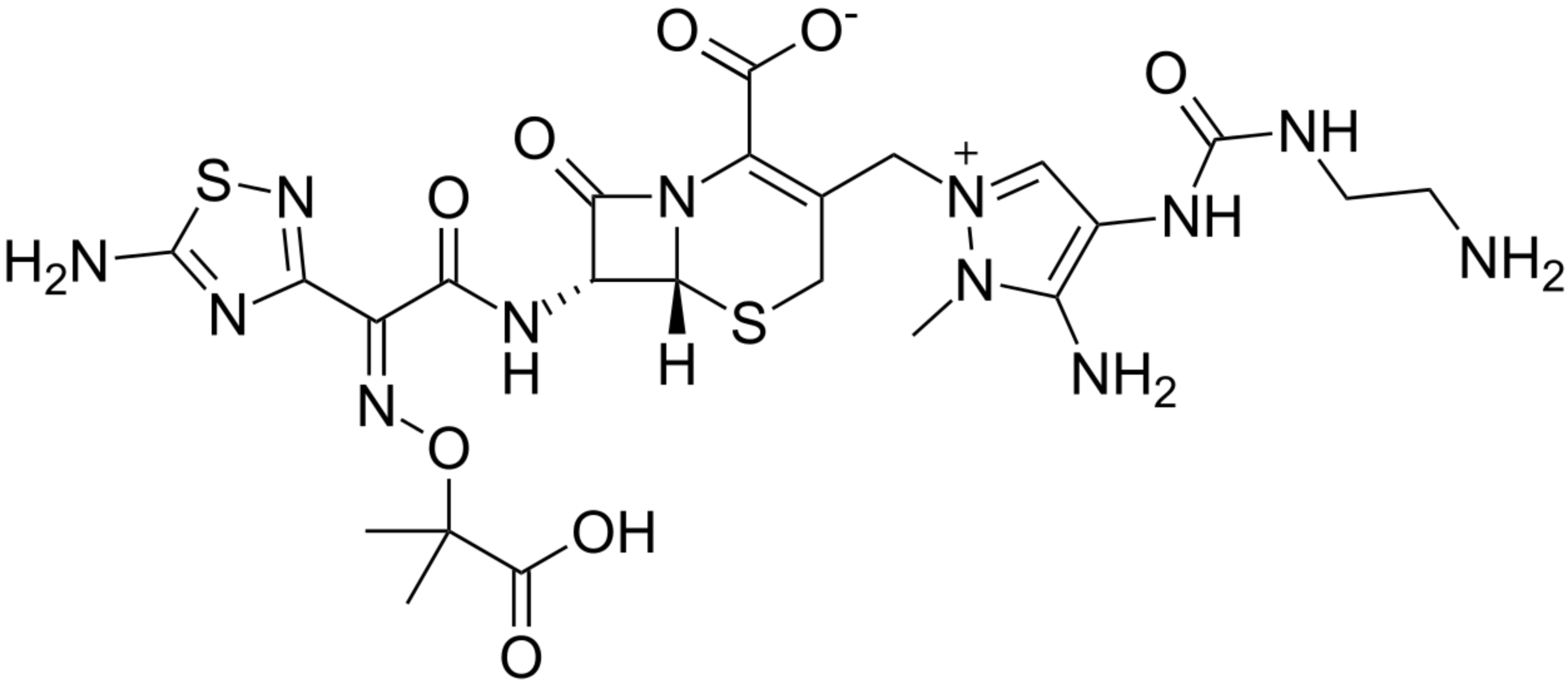
Νέοι συνδυασμοί β-λακταμικών με αναστολείς καρβαπενεμασών

Είδος	Φάση
Ceftazidime – Avibactam	Approved in 2015 in USA and in 2016 in Europe
Meropenem – Vaborbactam	Approved in 2017 in USA
Aztreonam – Avibactam	Phase 3
Imipenem/cilastatin – Relebactam	Phase 3
Ceftaroline fosamil – Avibactam	Phase 2
Cefepime - Zidebactam*	Phase 2
Meropenem - Nacubactam	Phase 1

*** Activity against Enterobacteriaceae and *P. aeruginosa* producing ESBL, KPC, AmpC and MBL**

Karaiskos I, et al. Expert Opin Drug Metab Toxicol. 2019 Feb;15(2):133-149

Ceftolozane - tazobactam



Ceftolozane/tazobactam

- Dosage Forms & Strengths
- powder for reconstitution, IV
- 1.5g/vial (ie, 1.5g = 1g ceftolozone plus 0.5g tazobactam)
- Dose is based on the sum of the ingredients

Complicated Intra-abdominal Infections

- Indicated for use in combination with metronidazole for complicated intra-abdominal infections (cIAI) cause by **Enterobacter cloacae, Escherichia coli, Klebsiella oxytoca, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, Bacteroides fragilis, Streptococcus anginosus, Streptococcus constellatus, and Streptococcus salivarius**

- 1.5 g IV q8hr x 4-14 days

Complicated Urinary Tract Infections

- Indicated for complicated urinary tract infections (cUTI), including pyelonephritis, caused by **Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, and Pseudomonas aeruginosa**

- 1.5 g IV q8hr x 7 days

Bacterial Pneumonia

- Indicated for treatment of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP) caused by the following susceptible Gram-negative microorganisms: **Enterobacter cloacae, Escherichia coli, Haemophilus influenzae, Klebsiella oxytoca, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, and Serratia marcescens**

- 3 g IV q8hr x8-14 days

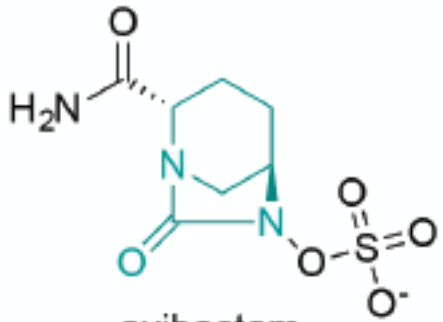
Dosage Modifications for Ceftolozane/tazobactam

- Hepatic impairment: No dosage adjustment required

- Renal impairment: YES

Ceftazidime-avibactam

- Ευρύ αντιμικροβιακό φάσμα
  - κυρίως Gram (-) & *Pseudomonas aeruginosa*
  - Δραστικότητα έναντι σε μικροβια με τους παρακάτω μηχανισμούς αντοχής
    - ESBLs
    - KPC
    - OXA-48 (τα περισσότερα στελέχη)
    - AmpC
    - Απώλεια πορινών + ESBL ή Ampc

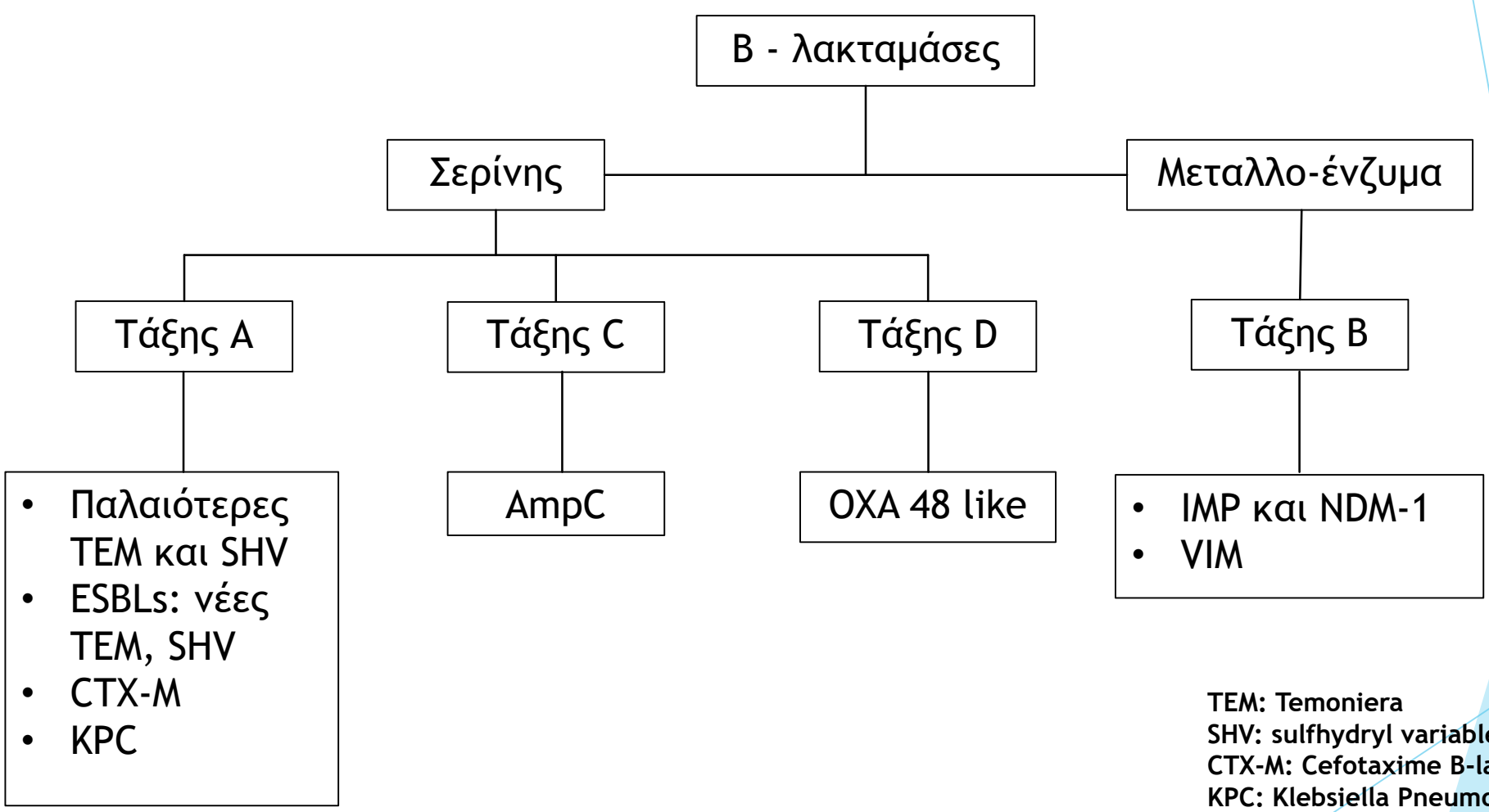


avibactam

- **Δεν είναι δραστική έναντι μικροβιών που παράγουν μεταλλο-β-λακταμασες (NDM, VIM)**
- **Δεν είναι δραστική έναντι του *Acinetobacter spp***

JAC 2016;71
AAC 2011;55

Ταξινόμηση κατά Ambler



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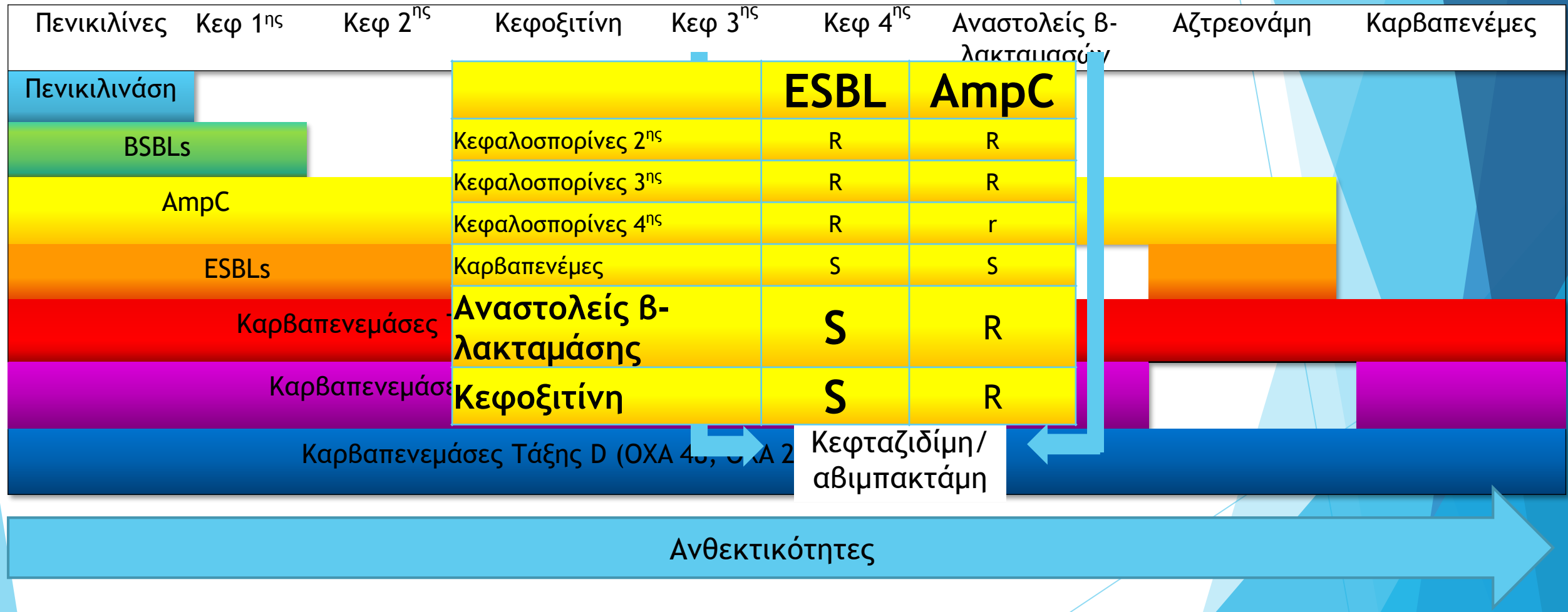


	ESBL	AmpC
Κεφαλοσπορίνες 2ης	R	R
Κεφαλοσπορίνες 3ης	R	R
Κεφαλοσπορίνες 4ης	R	r
Καρβαπενέμες	S	S
Αναστολείς β-λακταμάσης	**S**	R
Κεφοξιτίνη	**S**	R

Coronell-Rodríguez W, Arteta-Acosta C, Dueñas-Castell C. Interpretive Reading of the Antibiogram: A Tool for Clinical Practice. InSepsis 2018 (pp. 95-115). Springer, New York, NY.

Ceftazidime-avibactam

- Κατηγορία:
  - Avibactam: νέος αναστολέας β-λακταμασών
- Χορήγηση:
  - Ενδοφλέβια (2+0.5=2.5gr q8hrs, σε 2ωρη έγχυση
  - Καλά επίπεδα σε πνεύμονα και ΕΝΥ
- **Ένδειξη:**
  - **Επιπλεγμένες ενδοκοιλιακές λοιμώξεις, επιπλεγμένες λοιμώξεις ουροποιητικού, νοσοκομειακή πνευμονία (συμπεριλαμβανομένης και της VAP**)
  - Λοιμώξεις από Gram(-) με περιορισμένες θεραπευτικές επιλογές (EMEA)

Ceftazidime-avibactam

- Έγκριση:
  - FDA:Ναι EMEA: Ναι
- Ανεπιθύμητες ενέργειες
  - Θετική άμεση Coombs χωρίς αιμόλυση: 3.2-20.8%
- Προσοχή στην ανάπτυξη αντοχής
- Μείωσε την MIC στη μεροπενέμη και στην ιμιπενέμη in-vitro (όταν δοκιμάστηκαν σε συνδυασμό)

Gaibani P et al. IJID 2017;65

Clinical Infectious Diseases
MAJOR ARTICLE

Colistin Versus Ceftazidime-Avibactam in the Treatment of Infections Due to Carbapenem-Resistant Enterobacteriaceae

- Προοπτική πολυκεντρική μελέτη παρατήρησης
- 38 ασθενείς έλαβαν ceftazidime-avibactam Vs 99 έλαβαν colistin
- Οι πιο συχνές λοιμώξεις ήταν η βακτηριαιμίες και οι λοιμώξεις αναπνευστικού
- Οι περισσότεροι ασθενείς έλαβαν και άλλα αντιμικροβιακά έναντι ανθεκτικών στην καρβαπενέμη εντεροβακτηριακών
- Η ενδονοσοκομειακή θνητότητα 30 ημέρες μετά την έναρξη της αγωγής ήταν 9% για CAZ-AVI Vs 32% για COL (p=0.001)

Van Duin et al. CID 2018;66

Meropenem-Varbobactam

- Ευρύ αντιμικροβιακό φάσμα
  - Δραστικότητα έναντι σε εντεροβακτηριακά με τους παρακάτω μηχανισμούς αντοχής
    - ESBLs
    - KPC
    - AmpC
- Δεν είναι δραστική έναντι μικροβιών που παράγουν μεταλλο-β-λακταμασες (MBL/NDM, VIM) ή OXA-48
- Δράση έναντι *Acinetobacter spp, Pseudomonas aeruginosa* όπως η μεροπενέμη

Meropenem-Varbobactam

- Κατηγορία:
  - Νέος αναστολέας β-λακταμασών + μεροπενέμη
- Χορήγηση: 4gr κάθε 8 ώρες (3ωρη έγχυση)
- Ένδειξη:
  - Επιπλεγμένες λοιμώξεις ουροποιητικού (FDA)
  - EMEA: θετική εισήγηση για
    - Επιπλεγμένες ενδοκοιλιακές λοιμώξεις, επιπλεγμένες λοιμώξεις ουροποιητικού, νοσοκομειακή πνευμονία (συμπεριλαμβανομένης και της VAP)
    - Λοιμώξεις από Gram(-) με περιορισμένες θεραπευτικές επιλογές (EMEA)
- Ανεπιθύμητες ενέργειες
  - Επιληπτικοί σπασμοί
  - Μειώνει τη συγκέντρωση βαλπροϊκού νατρίου

Relebactam
Imipenem-cilastatin + relebactam

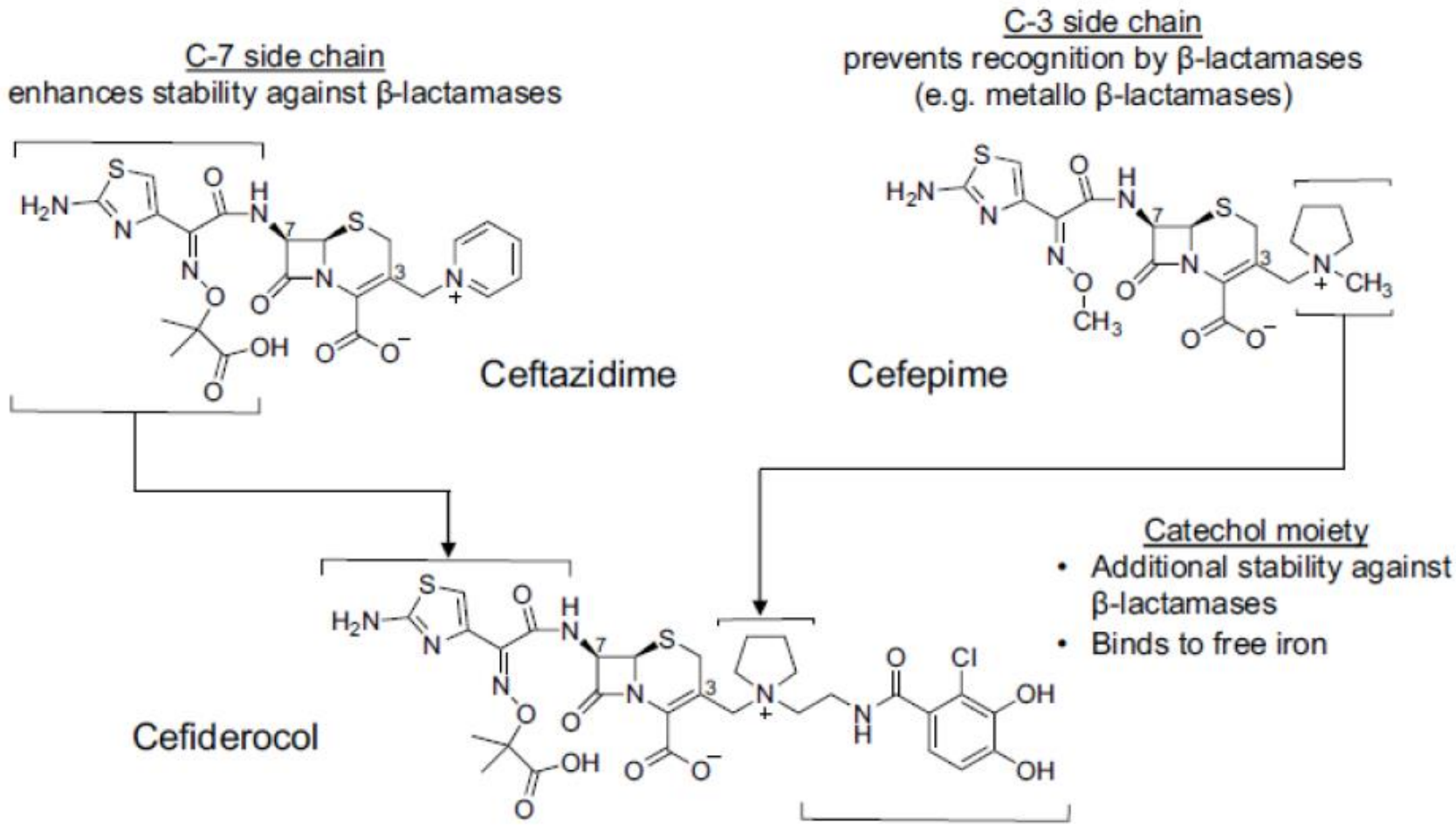
- Χορήγηση
  - Ενδοφλεβίως: 500/500mg +250mg, μισή ώρα έγχυση
- Αντιμικροβιακό φάσμα
  - Δραστικότητα έναντι εντεροβακτηριακών με τους παρακάτω μηχανισμούς αντοχής
    - ESBLs, KPC, AmpC
  - Αμφιλεγόμενη για OXA-48
  - Δεν είναι δραστική έναντι μικροβιών που παράγουν μεταλλο-β-λακταμασες (MBL/NDM, VIM)
  - Δεν είναι δραστική έναντι *Acinetobacter spp*
- Έγκριση FDA
  - Επιπλεγμένες ενδοκοιλιακές λοιμώξεις, επιπλεγμένες λοιμώξεις ουροποιητικού, όπου υπαρχουν περιορισμένες θεραπευτικές επιλογές

Aztreonam-Avibactam

Αντιμικροβιακό φάσμα

- Δραστικότητα έναντι εντεροβακτηριακών με τους παρακάτω μηχανισμούς αντοχής
    - ESBLs
    - KPC
    - AmpC
    - OXA-48
    - MBL
- Δράστικότητα έναντι *Acinetobacter spp, Pseudomonas aeruginosa* όπως η αζτεροναμη (περιορισμένη)
- Μελέτες φάσης III. Δεν υπάρχει έγκριση ακόμα

Cefiderocol



Cefiderocol

- Αποτελεσματική είσοδος στα κύτταρα
  - Χρησιμοποιεί μεταφορείς Fe
- Δραστικότητα στις καρβαπενεμάσες
- Δραστικότητα στα πολυανθεκτικά gram-αρνητικά:
  - Εντεροβακτηριακών που παράγουν KPC, VIM
  - Ψευδομονάδας που παράγει MBL
  - Stenotrophomonas maltophilia
  - A. baumannii που παράγει OXA-type β-λακταμάσες
- Έγκριση FDA για επιπλεγμένες λοιμώξεις ουροποιητικού (σε μικρόβια που έχουν ευαισθησία και υπάρχουν περιορισμένες ή καμία εναλλακτική θεραπευτική επιλογή)

Bassetti M et al Front. Med. 2019
www.FDA.gov

CONTINUOUS INFUSION OF β-LACTAM ANTIBIOTICS

Because beta-lactam antibiotics demonstrate a time-dependent effect on bacterial eradication (the duration that the pathogen is exposed to the antibiotic is crucial for bacterial eradication), their continuous infusions may have advantages over standard intermittent bolus dosing.

This therapeutic approach is particularly effective especially when pathogens present higher minimum inhibitory concentrations (MIC).

Thus, the time that free drug concentrations remain above the MIC (fT>MIC) becomes a better predictor of killing.

Most authors agree that T> MIC has to be at least 40- 50% of the dosing interval to achieve clinical effectiveness.

Maximum killing is seen when T> MIC is at least 60–70%.

- (https://academic.oup.com/jac/article/43/4/523/750673
- https://www.sciencedirect.com/science/article/pii/S0149291804900513?casa_token=hGqojpHhpmEAAAAA:65OnWoj_sulOTdmF8k1VbWcid-28MiyMbLZnXNAMlq9wQHp28LS2AG0Z_2FUd_TaGKzs_d7-
- https://journals.sagepub.com/doi/abs/10.1345/aph.1g467)

- Note:

Drug stability conditions –

: Instability of meropenem when kept at 37°C, but improved stability if: (i) the temperature is kept at ≤25°C; and (ii) solutions of ≤4 g/100 mL are used.

THANK YOU