

Novel Beta Lactam Antibiotics for the Management of Pediatric Gram-Negative Infections Resistant to Multi Drugs.

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Abstract:

Infections due to carbapenem-resistant Enterobacteriales (CRE) are increasingly prevalent in children and are associated with poor clinical issues, especially in critically ill cases. New beta lactam antibiotics, including ceftolozane-tazobactam, ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, and cefiderocol, have been released in recent times to face the arising challenge of multidrug-resistant (MDR) Gram-negative bacteria. Nevertheless, several new agents warrant pediatric suggestions approved by the Food and Drug Administration (FDA) and the European Medicine Agency (EMA), leading to uncertain pediatric-specific treatment strategies and uncertain dosing rules in the pediatric population. In this narrative review we have epitomized the available clinical and pharmacological data, current limitations and unborn prospects of new beta lactam antibiotics in the pediatric population.

Keywords: Children, multidrug resistance, pediatric, gram-negative bacterial infection, Safety and efficacy, dose, adverse effects.

Introduction:

Beta lactam antibiotics:

It is the antibiotics which contain beta lactam ring in their chemical structure. They act by inhibiting bacterial cell wall. Beta lactam antibiotics indicated for treatment and prevention of bacterial infection.

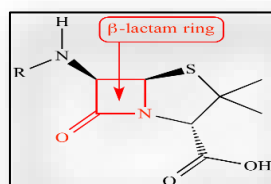
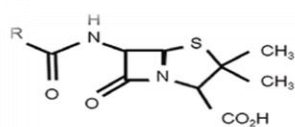


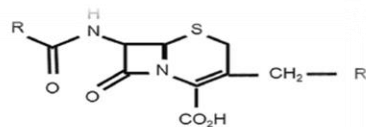
Figure: Beta lactam ring

They include

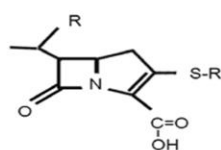
1. Penicillin derivative
2. Cephalosporin derivative
3. Carbapenems derivative
4. Monobactams derivative [1]



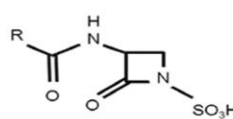
Penicillins



Cephalosporins



Carbapenems



Monobactams

Novel antibiotics:

The goal of novel antibiotics is to close the knowledge gap between fundamental science and the industry's ongoing drug development efforts. They work on creating strategies for efficiently treating infections resistant to several drugs and screening novel agents.

The drug contains the active moieties that have not been previously approved by the FDA as single ingredients or as part of combination products.

- **Need of development of novel beta lactam antibiotics:**

1. In the current situation a significant global concern to the our health society is the spread of the multi-drug resistance (MDR) gram negative bacteria such as extended spectrum beta lactamase (ESBL) produced by the various bacterial species such as Escherichia Coli, Pseudomonas Aeruginosa, Staphylococcus Aureus etc. for the treatment of these bacterial infection the antibiotics therapy gives less significant outcomes so the WHO arrange the program to overcome these problems they introduce the novel beta lactam antibiotics. [2-4]

2. Drug-resistant illnesses pose a major risk to people's health today. Every year, illnesses that are resistant to current medications cause hundreds of thousands of deaths. Modern medicine depends on the development of novel antibiotics that can eradicate microorganisms that are resistant to existing ones. [2]

3. Beta lactam antibiotics can be tailored to target and combat the unique characteristics of gram-negative infections, such as their outer membrane structure and efflux pumps.

4. Advancements in technology and research have paved the way for innovative strategies in identifying and developing potent beta lactam antibiotics with enhanced activity against multidrug resistant gram-negative pathogen. [3]

- **Safety and efficacy of novel beta lactam antibiotics:**

1. **Preclinical studies and in vitro efficacy:**

Novel beta lactam antibiotics shows promising results in preclinical studies, demonstrating potent activity against multi-drug resistant gram-negative infections.

2. **Clinical trials and outcomes in pediatric patients:**

Early phase clinical trials have shown favorable outcomes, indicating the potential of these antibiotics in treating multidrug resistance gram-negative infections in children. [3-6]

- **Challenges in implementation:**

1. **Regulatory Hurdles and Approval Process:**

The development and approval of novel antibiotics face regulatory challenges due to safety and efficacy requirements, stringent clinical trial protocols, and complex approval processes.

2. **Cost Considerations and Market Access Challenges:**

The high costs associated with drug development and commercialization, coupled with market access challenges, often pose hurdles to the availability and affordability of novel beta lactam antibiotics. [7-8]

- **Future Directions**

1. **Potential Impact of Novel Beta Lactam Antibiotics on Infection Management:**

The introduction of novel beta lactam antibiotics holds the potential to revolutionize the treatment of multidrug resistance gram-negative infections in children, improving patient outcomes and reducing the burden on healthcare systems.

2. **Need for Continued Research and Development:**

Addressing the challenge of multidrug resistance requires ongoing research and development efforts to stay ahead of evolving gram-negative pathogens and overcome potential emerging resistance mechanisms.

Classification of antibiotic resistant bacteria:

In 2017, the world health organization (WHO) has classified antibiotic resistant bacteria according to their priority as critical, high and medium

Priority 1: CRITICAL

- Acinetobacter baumannii: carbapenem-resistant
- Pseudomonas aeruginosa: carbapenem-resistant
- Enterobacteriaceae: carbapenem-resistant, ESBL-producing

Priority 2: HIGH

- Enterococcus faecium: vancomycin-resistant
- Staphylococcus aureus: methicillin-resistant, vancomycin-intermediate and resistant
- Helicobacter pylori: clarithromycin-resistant
- Campylobacter spp: fluoroquinolone-resistant
- Salmonellae: fluoroquinolone-resistant
- Neisseria gonorrhoeae: cephalosporin-resistant, fluoroquinolone-resistant

Priority 3: MEDIUM

- Streptococcus pneumoniae: penicillin-non-susceptible
- Hemophilus influenzae: ampicillin-resistant

- Shigella spp.: fluoroquinolone-resistant [5]

These gram-negative bacteria cause various infections in children as

- Pneumonia
- Typhoid fever
- Urinary tract infections
- Wound or surgical site infection
- Blood stream infections
- Tularemia
- Cat scratch disease
- Meningitis
- Shigellosis
- Brucellosis
- Cholera
- Plague
- Pertussis

➤ **Novel beta lactam antibiotics for the treatment of multidrug resistance gram negative infection in children**

1. Ceftolozane-tazobactam
2. Amoxicillin and clavunate
3. Ceftobiprole
4. Ceftazidime-avibactam
5. Cefiderocol
6. Meropenem-vaborbactam
7. Imipenem/Cilastatin/Relebactam [1-12]

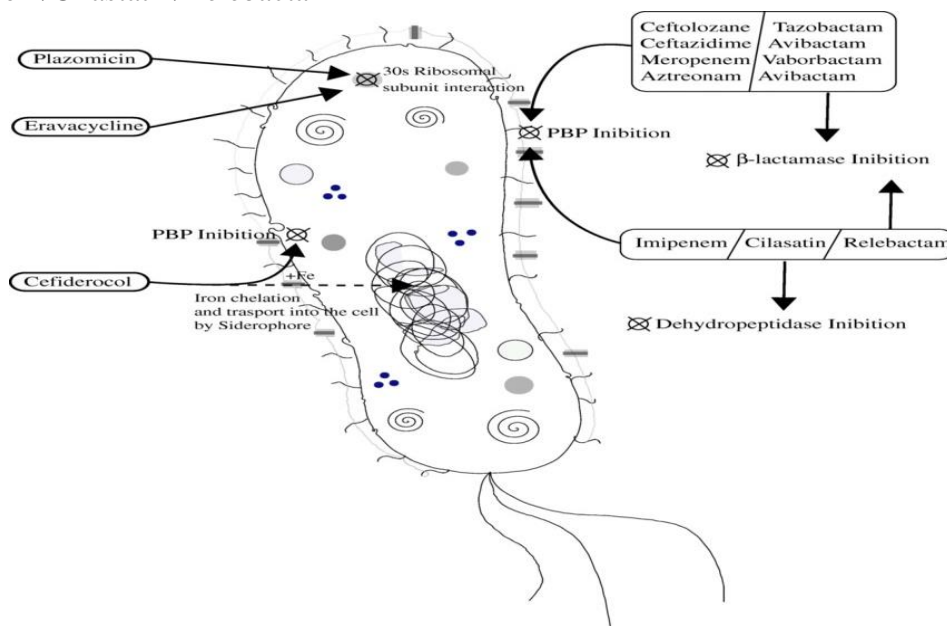
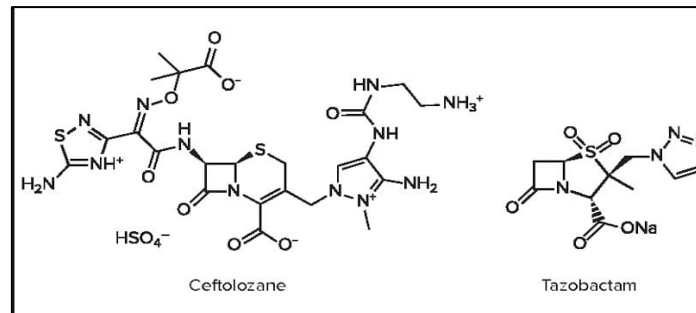


Figure: mechanism action of novel antibiotics



1) Ceftolozane + Tazobactam

Class: Ceftolozane - 5th generation cephalosporin

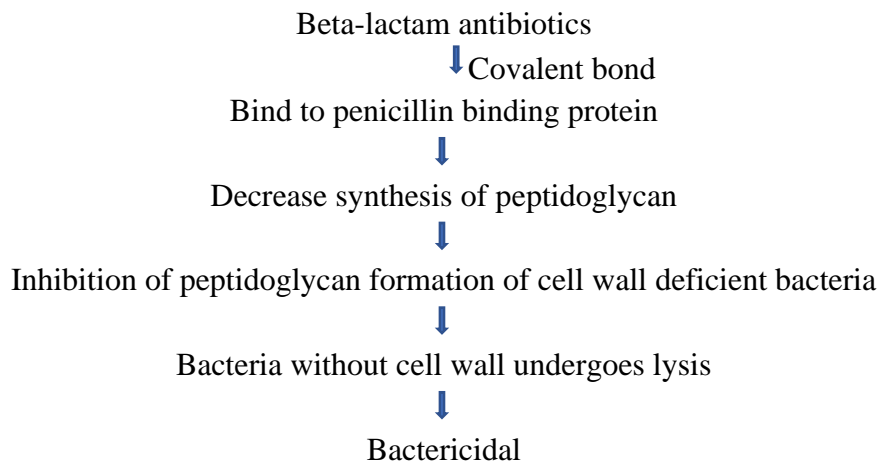
Tazobactam – beta- lactamase inhibitor

It is a beta lactam and beta lactamase inhibitor (BLBLI) combination

- **Mechanism of action**

- **ceftolozane**

It shows similar action as beta- lactam antibiotics



It binds with the PBP3 of E coli and PBP3, PBP1a, and PBP1b of Pseudomonas aeruginosa.

2) **Tazobactam** sodium inhibits some beta-lactamase and it can bind to the chromosomal and plasmid-mediated bacterial beta-lactamases

- **Adverse drug reaction:**

- a) Increase hepatic transaminase
- b) Renal impairment
- c) Cardiac disorders: tachycardia, angina pectoris
- d) Nausea, vomiting, diarrhea.

Uses: 1) Urinary tract infection (UTI)

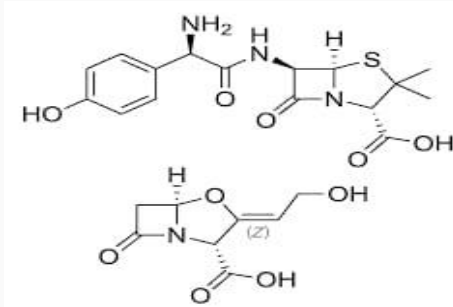
2) Pneumonia

3) Intra-abdominal infection (IAI)

- **Safety and efficacy in children:**

In pediatric patients with community-acquired UTIs, ceftolozane/tazobactam exhibited a good safety profile; rates of clinical cure and microbiologic eradication were comparable to those of meropenem. Children with cUTI now have a safe and efficient new treatment choice in ceftolozane/tazobactam, especially because antibacterial-resistant Gram-negative organisms are a problem.

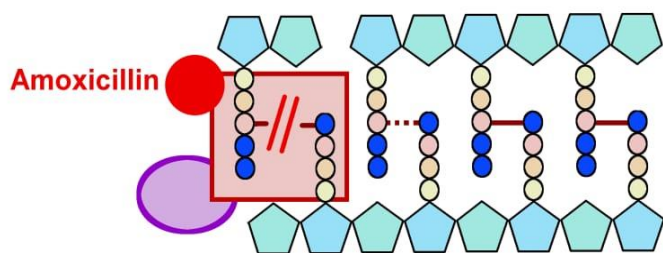
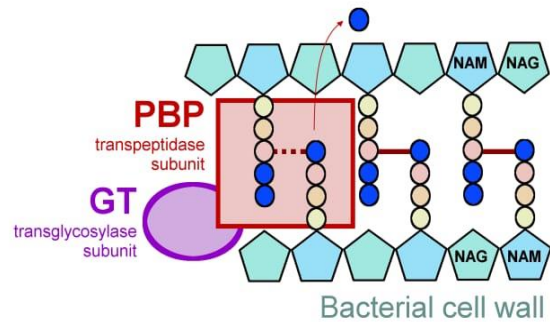
- **Pediatric dose:** IV injection and reconstitution powder 1g ceftolozane plus 0.5g tazobactam equals 1.5g/vial. Dose according to the total weight of all ingredients [13,14]
- **Clinical study data:** A phase 2 randomized clinical trial Researchers found that treating children with complicated UTIs with ceftolozane/tazobactam was a safe and successful option, as they reported in The Pediatric Infectious Disease Journal. Since last year, the FDA has approved ceftolozane/tazobactam for the treatment of complicated intra-abdominal infections (cIAI) in children as well as complicated UTIs (cUTI), which include pyelonephritis.[32]



2) Amoxicillin and clavulanate:

Amoxicillin treats bacterial infection by inhibiting bacterial cell wall growth

- 1 Amoxicillin binds to the transpeptidase's active site
- 2 Amoxicillin blocks transpeptidase's activity
- 3 Amoxicillin interrupts bacterial cross-linking and cell wall synthesis



Class: Amoxicillin-Penicillin Antibiotics

Clavulanate- beta- lactamase inhibitor

- **Mechanism of action of Amoxicillin:**
- **Mechanism action of clavulanate:**

It binds with serine residue in beta lactamase and create highly active complex. This complex bind with amino acid of beta lactamase and permanently inactivate beta lactamase enzyme and gives complete protection against resistance pathogen.

- **Mechanism action of Amoxicillin+ clavulanate:**

Amoxicillin is a member of the class of medications referred to as penicillin-like antibiotics. Clavulanate

acid belongs to a group of drugs known as beta-lactamase inhibitors. It works by preventing amoxicillin from being broken down by bacteria.^[15]

- **Indication and restriction:**

Amoxicillin with clavulanic acid should be reserved for infections due to bacteria that produce beta-lactamase enzymes including some strains of *Escherichia coli*, *Haemophiles influenzae* and *Klebsiella* species. It has good anaerobic cover.

Oral: Unrestricted (green) antibiotic

This is not a restricted agent. Follow standard ChAMP guidelines where appropriate

IV: monitored antibiotic (orange)

1. All prescriptions (both inpatient and outpatient) must be documented with the standard approved indication if the use is in line with it. This information must be sent to ChAMP.
2. The ChAMP team will assess whether the order satisfies the ChAMP Standard Indications or whether continued therapy is necessary.
3. Prior to prescribing, a phone authorization from ChAMP is required if the use is not for a commonly accepted indication.

- **Contraindication:**

1. Hypersensitivity
2. Cholestatic jaundice
3. Hepatic dysfunction

- **Dosage and dosage regimen:**

Neonates: for oral dosing. For IV dosing in premature neonates, please consult Infectious Diseases or Clinical Microbiology.

The oral dosages are relevant to the Duo 400® and Duo Forte preparations, and all doses are expressed and need to be administered as the amoxicillin component.

IV: Change to oral route when possible

1. Birth weight <4 kg and up to 3 months: 25 mg/kg/dose Twelve hourly
2. Birth weight ≥4 kg and term up to 3 months: 25 mg/kg/dose Eight hours a day
3. <40 kg and ≥3 months: IV 25 mg/kg in dosage (up to 1 gram maximum) 8 hours each day. In cases of severe infections, the dosage may be raised to six hourly.
4. Over 40 kg: IV 1g every 8 hours; in cases of severe infection, up to 1g every 6 hours. You can use up to 2g every 6–8 hours.

- **Safety and efficacy in children:**

Amoxicillin and clavulanate potassium powder oral suspension 600 mg/42.9 mg per 5 mL in infants under 3 months of age has not been proven to be safe or effective. For the treatment of acute otitis media in infants and children aged three months to twelve, the safety and effectiveness of amoxicillin and clavulanate potassium oral suspension 600 mg/42.9 mg per 5 mL have been established.^[16]

- **Clinical trials data:**

139 (6.5%) of the 2135 kids with respiratory complaints who underwent enrollment screening also had ABS. Out of the 58 patients who were enrolled, 56 were assigned at random. The average age was thirty-six months. Six patients (11%) had nonpersistent symptoms when they first arrived, compared to fifty (89%) who had persistent symptoms. The illness was categorized as mild in 24 children (43%) and as severe in the remaining 32 children (57%). Of the 28 kids who took the antibiotic, 14 (or 50%) had full recovery, 4 (or 14%) had partial recovery. Compared to children receiving a placebo, those receiving the antibiotic had a higher chance of being cured (50% vs. 14%, number needed to treat = 3) and a lower chance of treatment failure (14% vs. 68%).

3) Ceftriaxone:



Class: Cephalosporin

- **Mechanism of action:** the binding of Ceftriaxone to PBPs interferes with cell wall synthesis, inhibiting cell growth and ultimately leading to bacterial cell death.^[17]
- **Adverse drug reaction:**
 - a) Gastrointestinal effect (nausea, vomiting, diarrhea)
 - b) Dysgeusia (sense of distorted taste)
 - c) Headache
 - d) infusion site reaction.

Uses:

- a) Community acquired pneumonia
- b) Hospital acquired pneumonia.

- **Safety and efficacy:**

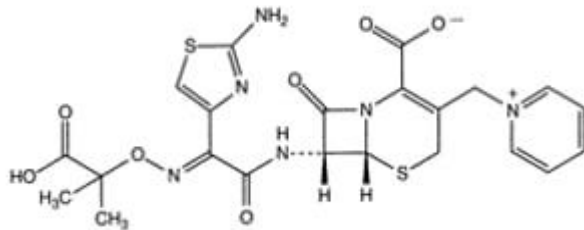
Ceftriaxone is a compelling option for the treatment of infections in children due to its wide range of activity and shown safety profile.^[18]

- **Clinical trial data:**

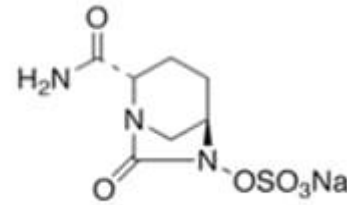
In total, 138 patients were randomly assigned to receive either a SoC cephalosporin (n = 44) or ceftriaxone (n = 94). For the ceftriaxone group, the median time to oral switch was 6.0 days, while for the SoC cephalosporin group, it was 8.0 days. Adverse events and treatment-related adverse events were reported by 18.2% and 0% of patients treated with SoC cephalosporins and 20.2% and 8.5% of patients treated with ceftriaxone during IV therapy. Clinical cure rates at the test-of-cure visit were 90.4% and 97.7% (between-group difference, -7.3%; 95% confidence interval, -15.7% to 3.6%), respectively. Early clinical response rates at day 4 in the intention-to-treat population were 95.7% and 93.2% (between-group difference, 2.6%; 95% confidence interval, -5.5% to 14.7%) in the ceftriaxone and comparator groups.^[33]

4) Cefazolin sodium:

**Class: Ceftazidime-3rd generation cephalosporin
Avibactam- beta- lactamase inhibitor**



Ceftazidime



Avibactam

- Mechanism Of Action:** Avycaz contains ceftazidime, a third-generation cephalosporin that exhibits activity against specific gram-positive and gram-negative bacteria in vitro. Ceftazidime binds to important penicillin-binding proteins to exert its bactericidal effect. Ceftazidime is protected from degradation by the non-beta-lactam beta-lactamase inhibitor avibactam, which also inactivates certain beta-lactamases. Ceftazidime has a longer half-life and takes longer to start working in the body thanks to avibactam. Both in vitro and in clinical infections, Avycaz exhibits activity against a wide range of bacteria.^[19]

- Dosage Regimen:**

Every eight hours for three months to less than six months: 50 mg/kg IV

6 months to less than 18 years: 62.5 mg/kg IV every 8 hours

Maximum dose: 2.5 g/dose

Duration of therapy: 7 to 14 days^[20]

- Side Effects:**

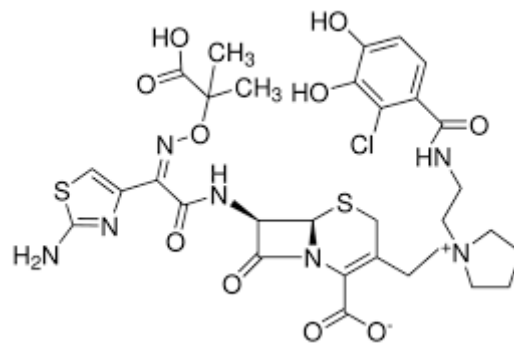
- Headache
- Dizziness
- Vomiting
- Nausea
- Abdominal Pain

- Safety and Efficacy:** safety and Efficacy data of ceftazidime and avibactam not established in children^[21-22]

- Clinical trial data:**

95 kids in all got at least one IV study dosage (of ceftazidime–avibactam, n = 67; of cefepime, n = 28). Escherichia coli accounted for the majority of baseline Gram-negative uropathogens (92.2%). In the ceftazidime–avibactam and cefepime groups, adverse events (AEs) affected 53.7% and 53.6% of patients, respectively. 11.9% of ceftazidime–avibactam and 7.1% of cefepime patients experienced serious adverse events. One significant AE that was linked to the drug ceftazidime–avibactam group was reported. Favorable clinical response rates >95% were noted for both groups in the microbiologic intent-to-treat analysis set at the end of IV, and these rates remained 88.9% (ceftazidime–avibactam) and 82.6% (cefepime) at the test-of-cure. At the test-of-cure, the favorable per-patient microbiologic response was 60.9% for cefepime and 79.6% for ceftazidime–avibactam^[34]

5)Cefiderocol:



Class: Cephalosporin

• **Mechanism of action:**

Cefiderocol acts by attaching itself to penicillin-binding proteins (PBPs), inhibiting the production of the bacterial cell wall, and eventually killing the bacterium. Cefiderocol can enter bacterial cells by passive diffusion through porins, just like other β -lactam antibiotics. ^[23] Cefiderocol has a chlorocatechol group, which sets it apart from other β -lactams and enables it to chelate iron. Cefiderocol can enter bacterial cells actively once it is bound to ferric iron via iron channels in the outer cell membrane, such as those represented by the PiuA gene in *P. aeruginosa* and the cirA and fiu genes in *E. coli*. Once inside the cell, cefiderocol binds to PBP3 with high affinity and inhibits it, stopping the pentapeptide bridge from being used to link peptidoglycan layers together. Though less potent than PBP3, PBP1a, 1b, 2, and 4 are also bound and inhibited by cefiderocol, and as a result, they are anticipated to have a smaller impact on the antibacterial action of the compound. ^[24]

• **Side effects:**

- a) Sign of allergic reaction (hives, difficult breathing, swelling in face or throat)
- b) Severe skin reaction (fever, sore throat, burning eyes, skin pain)
- c) Tremor
- d) Cough, rashes, itching ^[25]

• **Indication:**

- a) Complicated urinary tract infection
- b) Nosocomial pneumonia
- c) Pyelonephritis
- d) Ventilator associated bacterial pneumonia

• **Dosage regimen:** 60mg/kg every 8 hours used.

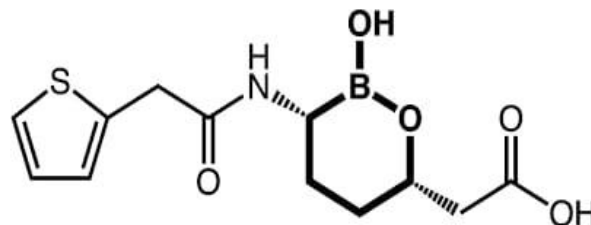
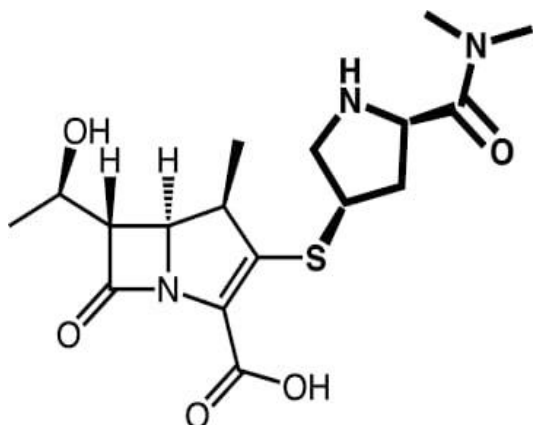
• **Safety and efficacy:** safety efficacy of Cefiderocol was not established in children. ^[26]

• **Clinical trial data:** Cefiderocol's effectiveness against several pathogens on the WHO bacterial priority pathogens list, along with its favorable resistance and cross-resistance profile and the fact that clinical trials involving children are still underway, led to its inclusion in the PADO priority list of the WHO. The purpose of this brief is to give an overview of the features of cefiderocol, as well as current and upcoming pediatric studies (including those involving neonates) and efforts to guarantee timely access for everyone who needs it. Additionally, it suggests treatments that funders and researchers should give top priority for both its development and, more generally, for the much-needed antibiotics for children ^[35]

6) Meropenem-vaborbactam:

Class: Meropenem: carbapenem antibiotic,

Vaborbactam: Beta lactamase inhibitor



Meropenem

Vaborbactam

- **Mechanism of action:** Meropenem, a carbapenem antibacterial agent, disrupts bacterial cell-wall synthesis by inhibiting penicillin-binding proteins causing cell death. Vaborbactam is a non-suicidal beta-lactamase inhibitor of boronic acid that lacks antibacterial properties. It stops meropenem from hydrolyzing when beta-lactamases, like KPCs, are present ^[27]

- **Indication:** Treatment of complicated urinary tract infections (cUTI), including pyelonephritis, Susceptible Caused by Escherichia coli, Klebsiella Pneumoniae, and Enterobacter Cloacae species complex in patients >18 years of age.

- **Contraindications:**

Hypersensitivity Meropenem, vaborbactam, other carbapenems or beta-lactamase inhibitors, or any component of the formulation; patients who have demonstrated anaphylactic reactions to beta-lactam antibacterial agents.

- **Adverse Effect:** Phlebitis, headache, hypokalemia, diarrhea, nausea, increased serum AST/ALT, hypersensitivity, infusion site reaction, fever.

- **Dose:** The safety and efficacy of meropenem/vaborbactam in children and adolescents younger than 18 years of age have not yet been established. No data are available. ^[28]

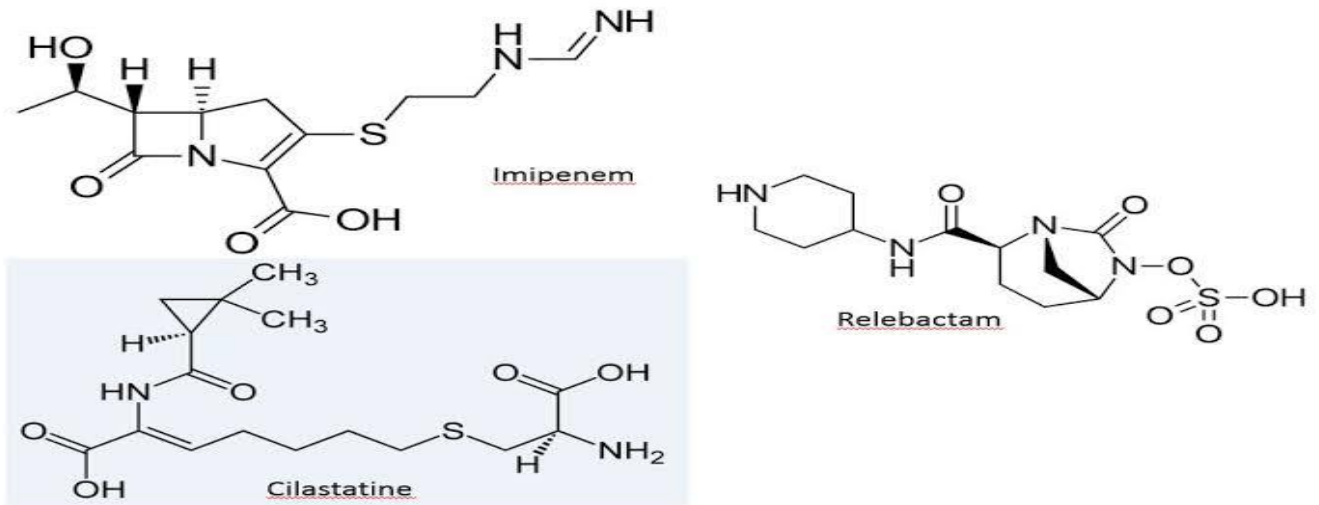
- **Clinical trials data:**

Pediatric experiences with meropenem/vaborbactam are currently limited to case reports, and there are no available PK safety or efficacy data. ^[36]

6) Imipenem/Cilastatin/Relebactam:

Class: Imipenem- Carbapenem antibiotics, Cilastatin: Dehydropeptidase inhibitor

Relebactam: Beta lactamase inhibitor



MECHANISM OF ACTION

Imipenem

- Carbapenem
- Bactericidal; inhibits cell wall synthesis

Cilastatin

- Renal dehydropeptidase inhibitor
- Does not have antibacterial activity; limits renal metabolism of imipenem

Relebactam

- New beta-lactamase inhibitor
- Inhibits class A carbapenemases and class C cephalosporinases
- No intrinsic antibacterial activity; protects imipenem from degradation

- **Indication:**

- Pneumonia
- Urinary tract infection
- Blood stream infection ^[29]

- **Contraindication:**

a history of severe hypersensitivity to any component, including cilastatin, imipenem, and relebactam

- **Safety and efficacy:**

<18 years: Safety and efficacy not established ^[30]

Clinical study data: The plasma PK/PD targets for imipenem and relebactam were exceeded; imipenem, cilastatin, and relebactam single doses were well tolerated and did not pose any significant safety risks. These findings guided the dose selection of imipenem, cilastatin, and relebactam for additional pediatric clinical assessment. ^[30]

- **Conclusion:**

The development of novel beta lactam antibiotics for children with multi-drug resistance is an Encouraging advancement in pediatric healthcare. These antibiotics hold promise in addressing the Challenges posed by resistant pathogens. Future research should focus on optimizing dosing regimens,

evaluating long-term safety, and exploring combination therapies to combat multi-drug resistance effectively. By harnessing the potential of novel beta lactam antibiotics, healthcare providers can achieve improved treatment outcomes for multidrug resistance gram negative infections in children, reducing morbidity and mortality rates. Novel beta lactam antibiotics offer hope in combating multidrug resistance gram-negative infections in children. By addressing the limitations of current treatment options and leveraging innovative drug discovery approaches, these antibiotics have the potential to significantly impact infection management. Continued research and development are essential to ensure our ability to tackle emerging challenges in the field of therapy antimicrobial therapy.

• **Abbreviation's:**

1. CRE- carbapenem- resistant Enterobacter
2. MDR-Multidrug resistance
3. FDA-Food and drug administration
4. PBP: Penicillin binding protein
5. ChAMP. - Children's Antimicrobial Management Program
6. IV-Intravenously
7. UTI- Urinary tract infection
8. IAI- intra-abdominal infection

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