

Novel Antibiotics Approved by the FDA (2022–2025): Mechanisms, Applications, and Clinical Relevance

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ABSTRACT

Antimicrobial resistance (AMR) is a growing global health crisis, emphasizing the urgent need for new antibiotics. Despite high costs and long development timelines, several novel antibiotics were approved by the U.S. Food and Drug Administration (FDA) between 2022 and 2025. This review summarizes the antibiotic discovery process, the FDA approval pipeline, and highlights key novel agents including Voquezna, Xacduro, Orlynvah, Zevtera, Exblifep, and Blujepa. These therapies employ diverse strategies to achieve selective toxicity, such as inhibition of bacterial cell wall synthesis, β -lactamase activity, and DNA replication, as well as modulation of host-pathogen environments, while limiting damage to host tissues. This review highlights their mechanisms of action, approved clinical indications, and safety profiles, and evaluates their clinical relevance in treatment of infections caused by multidrug-resistant pathogens. Lastly, we discuss the implications of these recent approvals for the future of antibiotic development and emphasize the continued need for sustained investment and innovation to address the growing AMR crisis.

Keywords: Antimicrobial resistance (AMR), FDA approval, Drug development, Antibiotic development, Artificial intelligence (AI)

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INTRODUCTION – THE URGENT NEED FOR NOVEL ANTIBIOTICS:

Antimicrobial resistance (AMR) is a major global health problem that makes antibiotics less effective against infections. Almost every variant of human pathogenic bacteria has developed resistance to or become less susceptible to current antibiotic treatments (10). The excessive and improper use of antibiotics in healthcare and agriculture has contributed to the rapid emergence and spread of antibiotic-resistant bacteria (54). According to the CDC, the U.S. experiences over 2.8 million antimicrobial-resistant infections each year, leading to over 35,000 deaths (3). Globally, antibiotic-resistant bacteria are responsible for over 700,000 deaths annually (11). Without major advances in antibiotic development, deaths from resistant infections could reach 10 million annually by 2050 (5).

Epidemiological studies show that antibiotic resistance places a major economic burden, causing around 11 million extra hospital stays and more than \$20 billion in additional healthcare and social costs each year in Europe and the United States (15), (20). Therefore, reducing the unnecessary use of antibiotics is crucial for preserving the effectiveness of existing drugs, while strengthening research and development of new medications is also essential to address the growing problem of antibiotic resistance (10).

The rise in bacterial resistance calls for global cooperation among governments, pharmaceutical companies, biotech firms, and academic institutions to develop new antibacterial drugs (24). In this effort, researchers are focusing on creating novel, powerful, long-lasting, and broad-spectrum antimicrobial agents from diverse sources (8), (16). While antibiotic development has slowed, there have still been notable advancements, such as the discovery of new antibiotics, the revival of older treatments, and the creation of new semi-synthetic forms (24).

MODERN ANTIBIOTIC DISCOVERY:

Worldwide, groups of scientists are taking different approaches for finding antibiotic compounds. One approach involves evaluating bacteria for their ability to make antimicrobial compounds. A recent paper identified a *Streptomyces thinghirensis* strain called MSA1 with antibacterial properties against multiple significant bacterial pathogens (21). This was done through screening bacterial isolates for their ability to inhibit the growth of prevalent pathogens like *S. aureus* and *P. aeruginosa*. They then went on to optimize the conditions that

would cause MSA1 to produce the antimicrobial compound and assessed the necessary concentrations to inhibit growth of various pathogens. The group did not identify what this compound was chemically.

Another approach identifies chemical compounds directly through *in silico* screening. A recent paper evaluated potential small molecule drug targets for LcpA_{SA}, which is a member of the LysR-CpsA-Psr (LCP) family of enzymes in *S. aureus* (27). This protein is part of the cell membrane and essential for the synthesis of the cell wall (56). The LCP family of enzymes have potential to be a strong therapeutic target. The researchers virtually screened libraries of chemical compounds to look at compounds that had strong binding affinity for LcpA_{SA} and that could act as inhibitors (27). Through further screening they identified seven compounds that bound effectively. These compounds also possessed characteristics that would make them effective drugs. The study did not test the compounds *in vitro* or *in vivo*.

Despite research like the examples above, conventional antibiotic development has significantly slowed in recent decades due to the high financial burden, lengthy timelines averaging over a decade, and low success rates of candidate molecules (20). In response, artificial intelligence (AI) technologies, particularly machine learning (ML) and deep learning (DL), have emerged as powerful tools to revitalize the antibiotic discovery pipeline (20), (29). Various AI approaches have demonstrated significant potential in accelerating the identification of novel antimicrobial agents. For example, ML combined with high-throughput Fourier-transform infrared spectroscopy successfully predicted antibiotic mechanisms of action and potency, while random forest models were used to assess phenotypic changes and predict antibacterial activity (50), (71). Deep learning and neural networks identified halicin, a compound with potent activity against drug-resistant pathogens (62). Similarly, ML algorithms have been used to identify β -lactamase inhibitors, predict and classify bacteriocins, and design bacteriocin-derived peptides with significant antimicrobial activity (45), (56), (71). These applications underscore the versatility and efficiency of AI in reducing the time, cost, and uncertainty associated with early-stage antibiotic development, offering a promising path forward in addressing the growing crisis of antimicrobial resistance (15).

From these examples, it is clear that there are many technologies and techniques that can be applied to discovering novel antibiotics, which must undergo rigorous testing before FDA approval for human use.

DRUG DEVELOPMENT AND APPROVAL BY THE FDA:

Developing a drug and getting it to market is costly. On average, this process can cost around \$800 million, covering expenses related to research, development, and clinical trials (14). Turning a promising antibiotic into a product that patients can use is a long and difficult process, often taking over ten years from discovery to final approval (14). The process begins with discovery and preclinical studies assessing antimicrobial activity, toxicity, and pharmacokinetics, followed by phased clinical trials to evaluate safety and efficacy in humans. Phase I trials focus on safety and dosing in healthy volunteers, phase II trials assess preliminary efficacy and optimal dosing in patients, and phase III trials confirm clinical effectiveness and monitor adverse effects in larger patient populations (66).

If clinical trials are successful, the drug sponsor submits a New Drug Application (NDA) to the FDA, initiating a comprehensive review process that typically takes one to two years. During this period, the FDA evaluates the drug's safety, clinical efficacy, manufacturing quality, pharmacokinetics, and benefit-risk profile, as well as compliance with Good Manufacturing Practices (GMP) and labeling requirements (41), (66). Following approval, post-marketing (Phase IV) studies continue to monitor long-term safety, effectiveness, and the emergence of rare adverse events (63).

Together, this regulatory framework shapes which antibiotic candidates ultimately reach clinical use and provides important context for understanding the limited number of antibiotics approved each year.

REVIEW OBJECTIVES:

The rigorous research, development, and testing process required for FDA approval is necessary to ensure that only safe and effective drugs can be used for treating patients. With the high cost of developing drugs, pharmaceutical companies tend to place resources that will result in the most profits. For this reason, novel antibiotics are not as high priority as drugs that would be used long-term. This results in low amounts of antibiotics that are FDA approved each year compared to other drug types. This review aims to discuss antibiotic treatments that have not been previously approved in the United States. At the same time, we aim to bring awareness to the critical need for the development of novel antibiotics.

NOVEL ANTIBIOTICS APPROVED BETWEEN 2022-2025

VOQUEZNA AS A COMBINATION TREATMENT FOR *H. PYLORI*

Voquezna Triple Pak contains three drugs, Vonoprazan, amoxicillin, and clarithromycin to serve as a combination treatment for *Helicobacter pylori* infections in adults (42). It was approved by the FDA on May 3, 2022. Voquezna is taken orally in a capsule or tablet with 500 mg amoxicillin, 500 mg clarithromycin, and 20 mg Vonoprazan fumarate. There is also the Voquezna Dual Pak which contains only Vonoprazan and amoxicillin that was approved alongside the Triple Pak. Vonoprazan itself is not an antibiotic but is part of a combination regimen with amoxicillin only for the Dual Pak and also clarithromycin for the Triple Pak. Amoxicillin inhibits bacterial cell wall synthesis and clarithromycin binds the 50S ribosome inhibiting protein synthesis (2), (46). These antibiotics are not newly approved drugs, so we will focus on the function of Vonoprazan and how it improves the efficacy of the antibiotics it is dosed with.

Vonoprazan is part of a class of drugs known as potassium-competitive acid blockers (PCAB) and is the only member of its class currently approved for use in the United States (55). Vonoprazan is able to reversibly bind to the H⁺-K⁺-ATPase pump in the stomach (Figure 1) (36). This pump is essential for the secretion of stomach acid. When Vonoprazan binds to this pump, acid secretion is reduced because the H⁺-K⁺-ATPase enzyme is inactivated. This is beneficial for treating *H. pylori* infections.

At a gastric pH of approximately 6-7 *H. pylori* actively replicates and is susceptible to antibiotic treatment, whereas at lower pH values (approximately 3-6) the bacterium transitions into a coccoid, dormant form that is largely resistant to antimicrobial therapy (31), (32). Vonoprazan increases gastric pH by inhibiting acid secretion, which keeps *H. pylori* in its replicative, antibiotic-susceptible state and enhances the effectiveness of co-administered agents such as amoxicillin and clarithromycin (Figure 1). The selective toxicity is achieved indirectly through host gastric acid modulation, which shifts *H. pylori* into its replicative, antibiotic-susceptible state while minimizing direct toxicity to host tissues.

The traditional standard of care for *H. pylori* infection involves treatment with a proton pump inhibitor (PPI) (31). This method has lost effectiveness over time and takes about three days to effectively and stably suppress the secretion of gastric acid (69). Vonoprazan effectively blocks acid secretion within the first day of use (37). A recent meta-analysis of

Vonoprazan dual or triple regimen clinical data from multiple western and eastern countries showed that overall efficacy of 86% and 88%, respectively (7). The same study also determined that overall efficacy of treating *H. pylori* infections in treatment naïve patients was increased when using regimens with Vonoprazan compared to PPIs (87% vs 70%).

Vonoprazan is considered safe when compared to other treatments for *H. pylori* infection (69). When comparing the safety of a Vonoprazan and amoxicillin regimen to a PPI and amoxicillin regimen this study found that adverse reactions were significantly lower for the group treated with Vonoprazan and amoxicillin. Compliance for the treatment was also significantly higher for the Vonoprazan and amoxicillin treatment group.

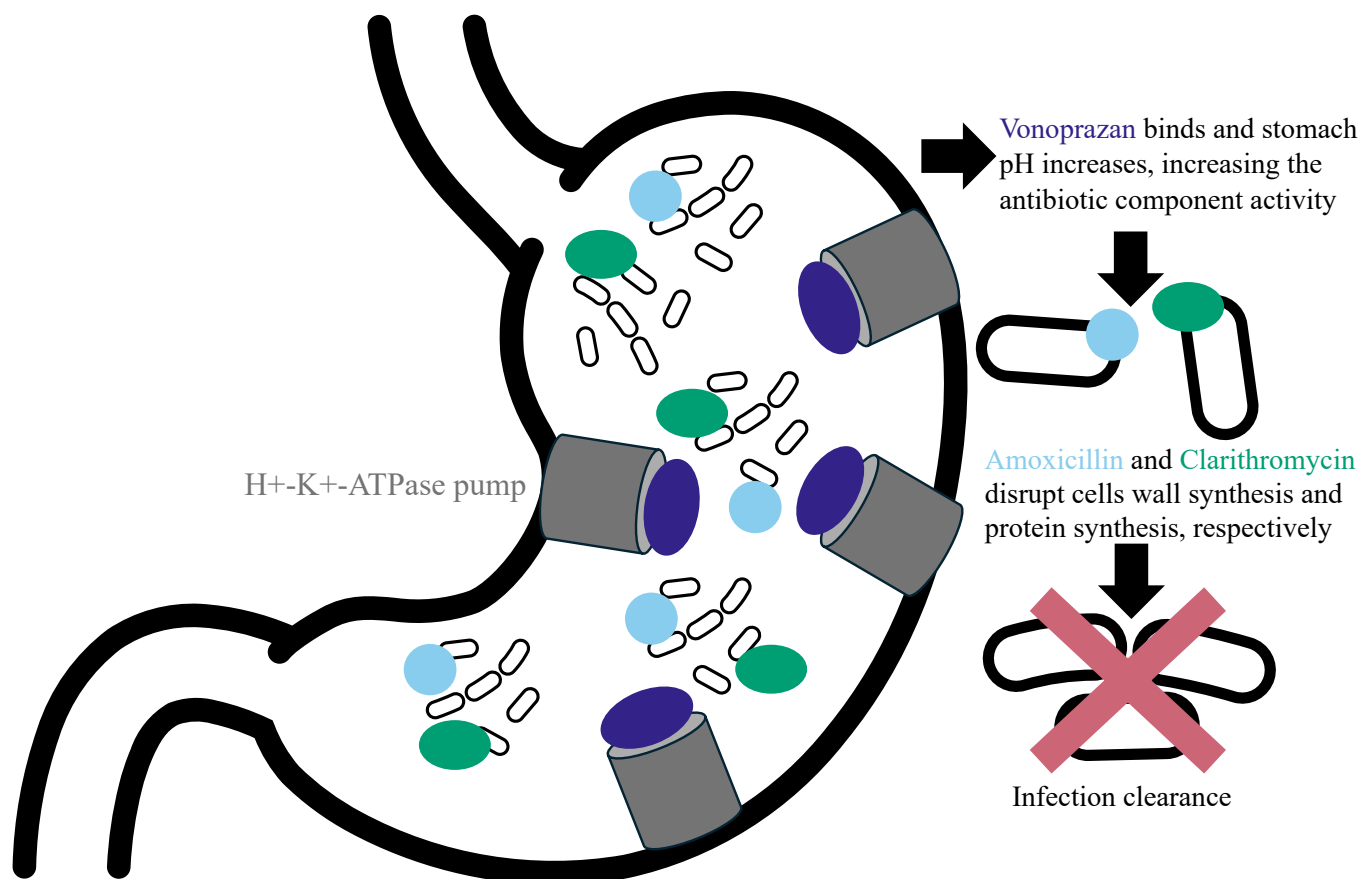
While they are considered safe, both the triple Pak and

dual Pak treatments can cause unintended side effects. The Vonoprazan-associated side effects include abdominal pain, abdominal bloating, diarrhea, headache, and dysgeusia (36). These side effects are common among antibiotic-containing treatment regimens. Upon treatment termination, these side effects are resolved. There is a current gap in our understanding of long-term adverse side effects of Vonoprazan use. In the context of its use of improving antibiotic function, long-term use should not be relevant since Voquezna is not a drug meant for long-term use.

Voquezna is an example of using new drugs to amplify the efficacy of existing antibiotics. Without the Vonoprazan component, both amoxicillin and clarithromycin would likely be less effective due to the biology of *H. pylori*. It is possible that in the future new PCABs could be developed that target

FIGURE 1

Voquezna Triple Pak mechanism of action.



Voquezna consists of Vonoprazan, amoxicillin, and clarithromycin used for the treatment of *Helicobacter pylori*. Vonoprazan is a new class of drug known as a potassium-competitive acid blocker (PCAB). Vonoprazan reversibly binds to the H⁺-K⁺-ATPase pump in the stomach. This results in a pH increase within the stomach causing *H. pylori* to be more susceptible to the well-established antibiotics, amoxicillin and clarithromycin also found within Voquezna. Amoxicillin disrupts cell wall synthesis and clarithromycin disrupts protein synthesis, clearing the *H. pylori* infection.

other cell-specific H^+-K^+ -ATPase along the GI tract that could impact the microbiota or help clear infections of the GI tract.

XACDURO AS A TREATMENT FOR PNEUMONIA CAUSED BY *ACINETOBACTER BAUMANNII-CALCOACE-TICUS* COMPLEX

Xacduro is approved for administration intravenously for the treatment of hospital- and ventilator-acquired bacterial pneumonia (42). Xacduro is a combination drug containing Sulbactam and Durlobactam. It was approved by the FDA on May 23, 2023. Xacduro is dosed over the course of three hours as 1.0 g of Sulbactam and 1.0 g of Durlobactam. While this combination is considered to have a broad spectrum of susceptible bacteria, it should only be used to treat strains of *Acinetobacter baumannii-calcoaceticus* (ABC) that are shown to be susceptible to the drug (33), (42). For non-ABC infections, use of Xacduro should be guided by susceptibility testing, as its approval and demonstrated efficacy are limited to ABC pathogen.

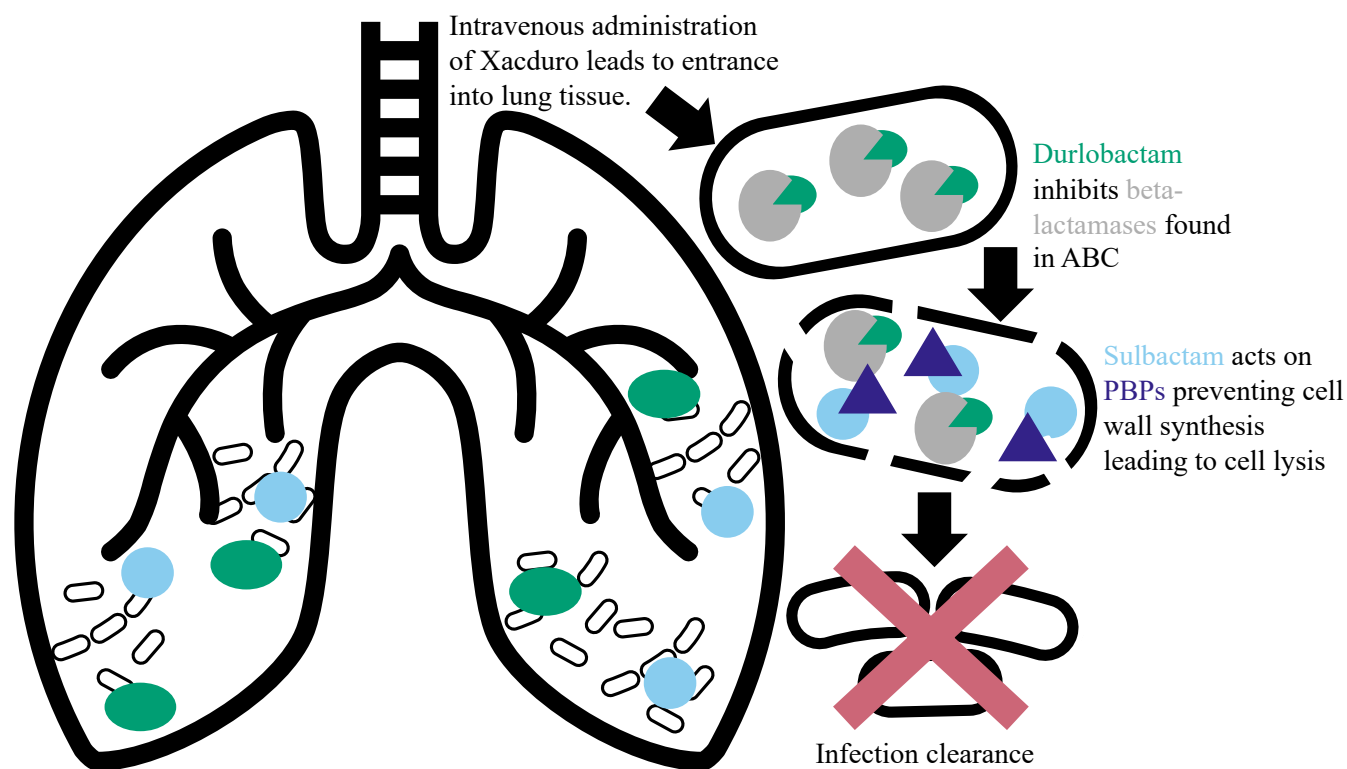
Sulbactam has been used in the past in combination with ampicillin to treat a variety of infections (9). These infections include skin and skin structure infections, intra-abdominal infections, and as an alternative treatment for gynecological infections caused by *Neisseria gonorrhoeae* or *Chlamydia trachomatis*. The other bacteria found to be susceptible to Sulbactam in combination with ampicillin include *Haemophilus influenzae*, *Escherichia coli*, *Acinetobacter*, *Klebsiella*, *Staphylococcus aureus*, *Enterobacter*, and anaerobes.

Sulbactam is a first generation β -lactam- β -lactamase inhibitor that resembles penicillin (33). It can inhibit Am- bler class A serine beta-lactamases (1), (18). This allows it to improve the function of other β -lactam antibiotics that could otherwise be degraded by β -lactamase producing pathogens. In combination with amoxicillin, Sulbactam serves as a β -lactamase inhibitor to allow for amoxicillin to be effective.

ABC was once directly susceptible to Sulbactam. Sulbactam can bind multiple penicillin-binding proteins (PBPs) found in ABC. They include PBP1a, PBP1b, and PBP3 (47).

FIGURE 2.

Xacduro mechanism of action



Xacduro is a combination of Sulbactam and Durlobactam used to treat pneumonia caused by *Acinetobacter baumannii-calcoaceticus* complex. After intravenous administration, Xacduro enters the infected lung tissue. While Durlobactam is acting as a beta-lactamase inhibitor, Sulbactam can effectively act and penicillin binding proteins (PBPs) to prevent cell wall synthesis. Cell lysis follows resulting in the clearance of the infection.

When these proteins are bound, they are unable to facilitate the synthesis of the bacterial cell wall. Treating ABC with Sulbactam as a β -lactam antibiotic is now ineffective because ABC has developed very efficient hydrolysis of Sulbactam (59). Another mode of resistance for ABC against Sulbactam are in strains that have a rare PBP3 mutation. This mutation was generated in a lab from a clinical isolate and significantly increased resistance to Sulbactam (38). Clinical isolates that contain PBP3 mutations that confer resistance to Sulbactam and Durlobactam remain rare (40). When Sulbactam is used to treat ABC infections in combination with Durlobactam, then Sulbactam regains its ability to interfere with cell wall synthesis (Figure 2).

Durlobactam is a novel diazabicyclooctane class β -lactamase inhibitor. It is considered broad spectrum because it is active against Ambler class A, C, and D serine β -lactamases, all of which are produced by ABC (33), (59). It does not inhibit class B metallo- β -lactamases, which are also found in ABC, but rarely (58), (59). Durlobactam has strong activity against Ambler class D β -lactamases which is not common in other β -lactamase inhibiting drugs (44). The Durlobactam portion of Xacduro is able to inhibit the many β -lactamases found in ABC so the Sulbactam β -lactam antibiotic can directly work towards inhibiting cell wall synthesis of ABC (Figure 2). Selective toxicity is achieved by targeting bacterial β -lactamases and penicillin-binding proteins unique to *Acinetobacter baumannii*, thereby restoring antibacterial activity while sparing mammalian cells.

The FDA prescribing information reported that 36 patients (40%) experienced serious adverse reactions when treated with Xacduro (19). Notably this was lower than the colistin (control) treatment group where 49% of patients had serious adverse reactions. The three most common adverse reactions were liver test abnormalities (19%), diarrhea (17%), and anemia (13%). Like many antibiotics, Xacduro treatment can also lead to the development of *Clostridioides difficile*-associated diarrhea and the prescribing information states to evaluate for this pathogen if diarrhea occurs during or after a Xacduro regimen.

Like Voquezna, Xacduro exemplifies the importance of developing novel drugs that can improve the efficacy of existing treatments. This highlights that there are many types of approaches for drug development and that for drugs to be effective they do not have to work alone. Simultaneously, this demonstrates the difficulty of finding a molecule that can work alone as an effective antibiotic amid the MDR crisis. Since ABC is steadily gaining new resistance traits, it is possible Xacduro will lose effectiveness against ABC in the future. This also highlights the importance of continual development

of antibiotics.

ORLYNVAH AS A TREATMENT FOR UNCOMPLICATED URINARY TRACT INFECTIONS

Orlynvah is a combination of Sulopenem etzadroxil and probenecid that is approved for oral prescription use of uncomplicated female UTIs (42). It was approved by the FDA on February 25, 2024. Sulopenem etzadroxil is an antibiotic component and probenecid is a renal tubular transport inhibitor.

Sulopenem etzadroxil is a novel ester prodrug (68). Ester prodrugs are an inactive version of a drug which can then be activated once they enter the body and are further processed. In the case of Sulopenem etzadroxil, it is hydrolyzed by intestinal esterases to make the active form, Sulopenem. Once active, Sulopenem functions as a β -lactam. The β -lactam ring of the drug alkylates the peptidoglycan-binding protein (PBP) serine residues which inhibits peptidoglycan cross linkage to form the cell wall (Figure 3) (68). This combination demonstrates selective toxicity through β -lactam-mediated inhibition of bacterial cell wall synthesis, a pathway absent in human cells, while probenecid enhances antibiotic exposure without intrinsic antibacterial activity.

Probenecid is a uricosuric agent that was originally developed to decrease the kidney's ability to clear penicillin from the body (51). It was developed in 1949 and approved by the FDA under the brand name Benemid on April 21, 1951 (42), (51). It later was approved and widely used for the treatment of gout because of its ability to decrease uric acid levels in the blood. It became the standard of care for many years until it was determined that decreasing uric acid in the blood did not necessarily improve gout symptoms. Its ability to enhance antibiotic presence in blood was revitalized in the FDA with the approval of Orlynvah. The purpose of dosing Sulopenem and probenecid together is to promote retention of Sulopenem in the blood by limiting renal tubular secretion with probenecid.

Orlynvah is prescribed for women with uncomplicated urinary tract infections caused by *E. coli*, *K. pneumoniae*, and *P. mirabilis* who do not have other oral antibiotic treatment options (42). It is not approved for the treatment of complicated urinary tract infections. Complicated urinary tract infections are those with a high risk of treatment failure such as those in immunocompromised individuals, men, and UTIs involving the kidneys (53). Complicated UTIs are often caused by bacteria that are unlikely to be susceptible to Sulopenem (42). Since Sulopenem is considered a new drug, the FDA wants to maintain its effectiveness against MDR pathogens, so it is not considered suitable for treating compli-

cated UTIs. Even in uncomplicated UTIs, Orlynvah should only be used to treat infections that are proven to be or likely to be susceptible to Sulopenem.

The FDA prescribing information provides data on the adverse reactions/side effects from taking Orlynvah. Serious adverse reactions only occurred in 6/1932 (0.3%) between two Phase 3 clinical trials (19). There were 21/1932 (1%) patients who discontinued treatment due to adverse reactions. The most commonly reported side effects were diarrhea (10%), nausea (4%), vulvovaginal mycotic infection (2%), headache (2%), vomiting (2%), and abdominal pain (1%). The prescribing information also warns about potential *Clostridioides difficile*-associated diarrhea and exacerbation of gout.

Because of its efficacy against multiple pathogens, Orlynvah is a promising and strong therapeutic option for the treatment of uncomplicated UTIs that could be reapproved

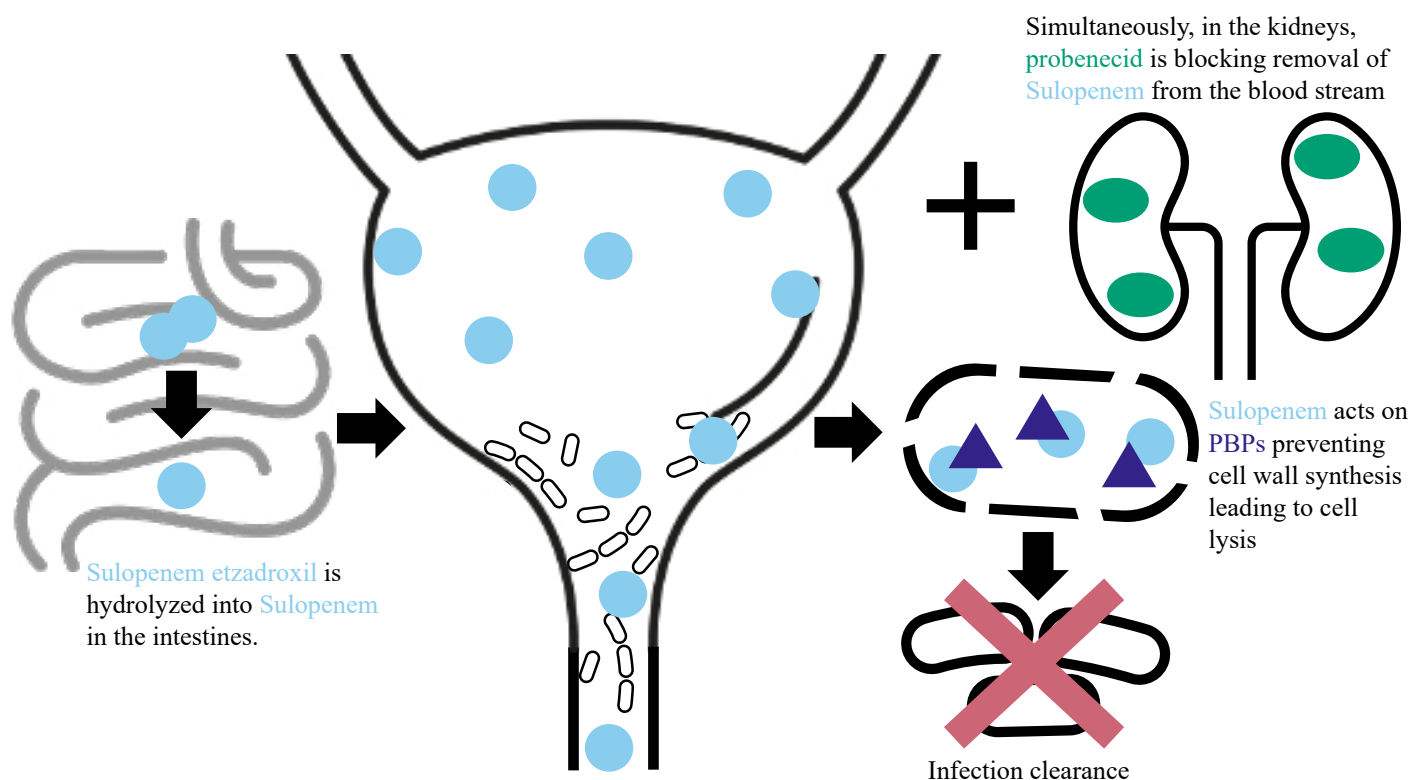
at a later date for uses in other types of infections. It is also possible that probenecid will continue to regain relevance in use with other antibiotics.

ZEVTERA AS A BROAD-SPECTRUM TREATMENT FOR LUNG AND BLOOD INFECTIONS

Zevtera, also known as Ceftobiprole medocartil, is a fifth-generation cephalosporin antibiotic and was developed to combat the increasing threat of antimicrobial resistance (23), (57). It is notable for its broad-spectrum activity against both Gram-positive and Gram-negative bacteria, including challenging pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa* (49), (70). On April 3, 2024, the U.S. Food and Drug Administration (FDA) approved Zevtera for the treatment of adults with *Staphylococcus aureus* bloodstream infections (bacteremia),

FIGURE 3.

Orlynvah mechanism of action.



Orlynvah is a combination of the antibiotic prodrug, Sulopenem etzadroxil and the renal tubular inhibitor probenecid used to treat uncomplicated UTI. Sulopenem etzadroxil is hydrolyzed into Sulopenem in the intestines. Upon circulation to the bladder, Sulopenem acts as a beta-lactam antibiotic, acting on penicillin binding proteins (PBPs) preventing cell wall synthesis and ultimately bacterial lysis. Probenecid simultaneously acts in the kidney as a renal tubular inhibitor to maintain levels of Sulopenem within the body. Image attributions: Bladder icon: Flaticon.com and Intestine icon: Flaticon.com. This figure has been designed using resources from Flaticon.com.

including those with right-sided infective endocarditis; adults with acute bacterial skin and skin structure infections (ABSSSI); and adult and pediatric patients (ages 3 months to <18 years) with community-acquired bacterial pneumonia (CABP) (22). The recommended dosing for this drug is 667 mg of Zevtera by injection. Zevtera has already been approved in several countries for the treatment of hospital-acquired pneumonia (HAP), including MRSA-associated cases, and community-acquired pneumonia (CAP), excluding ventilator-associated pneumonia (VAP) (12).

Ceftobiprole medocartil is a prodrug, meaning it becomes active only after it is converted in the body, specifically in the bloodstream (70). Once activated into Ceftobiprole, it targets penicillin-binding proteins (PBPs), which are essential for building bacterial cell walls (Figure 4). Ceftobiprole exhibits selective toxicity by preferentially binding bacterial penicillin-binding proteins, including resistance-associated PBPs such as PBP2a in MRSA, which have no counterparts in human cells. It binds strongly to PBP2a in methicillin-resistant *Staphylococcus aureus* (MRSA) and PBP2x in *Streptococcus pneumoniae* (23), (70). Besides treating lung infections, Zevtera also shows promise for managing more severe infections, such as bloodstream infections caused by *Staphylococcus aureus* (bacteremia) (26). It has also been used in cases of right-sided infective endocarditis caused by both methicillin-susceptible and methicillin-resistant strains (23). This broader use shows its value in situations where quick and effective treatment is critical.

Ceftobiprole has a wide spectrum of activity. Among Gram-positive bacteria, it works against *Staphylococcus aureus* (both MSSA and MRSA), *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and *Enterococcus faecalis* (23). It also covers Gram-negative bacteria like *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* (23). However, it is less effective against bacteria that produce extended-spectrum β -lactamases (ESBLs) or carbapenem-resistant strains, which may limit its use in those cases (23), (48).

Zevtera is generally well tolerated (64). Common adverse effects include nausea, diarrhea, vomiting, headache, rash, injection site reactions, and elevated liver enzymes (64). Patients with known severe hypersensitivity to Ceftobiprole or other cephalosporins should avoid Zevtera (22), (23). Key safety considerations include the potential for hypersensitivity reactions, central nervous system effects such as seizures, *Clostridioides difficile*-associated diarrhea, and an observed increase in mortality among patients with ventilator-associated bacterial pneumonia (22). The FDA granted Zevtera Priority Review, Fast Track, and Qualified Infectious Disease Product designations for treating *Staphylococcus aureus* bacteremia

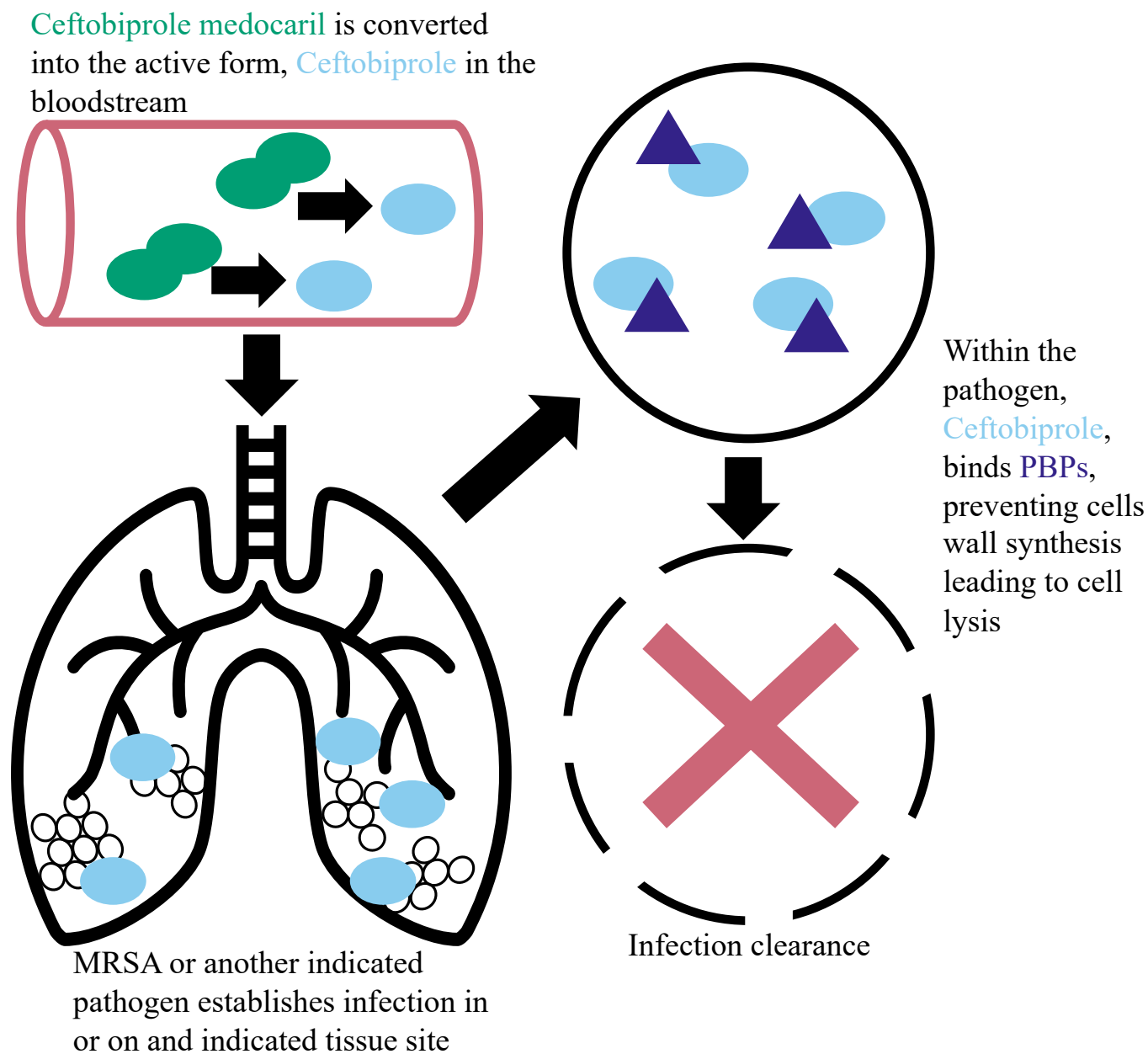
(SAB), ABSSSI, and CABP (22). These designations highlight its value in addressing urgent medical needs related to severe and drug-resistant bacterial infections.

EXBLIFEP AS A TREATMENT FOR COMPLICATED URINARY TRACT INFECTIONS

Exblifep (Cefepime/Enmetazobactam) is a novel intravenous antibiotic approved by the FDA on February 22, 2024, for the treatment of complicated urinary tract infections (cUTIs), including pyelonephritis, in adults (17). It is specifically indicated to treat these infections caused by susceptible strains of *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, and *Enterobacter cloacae* (35). This fixed-dose combination pairs cefepime, a fourth-generation cephalosporin, with Enmetazobactam, a novel β -lactamase inhibitor.

Cefepime interferes with bacterial cell wall synthesis and is effective against many Gram-negative and Gram-positive pathogens (Figure 5) (35). This includes *Pseudomonas*. It binds with PBPs and is stable against some β -lactamases. While cefepime is effective across a broad-spectrum of pathogens, its combination with Enmetazobactam is only approved for Gram-negative infections at this time. Both cefepime and Enmetazobactam are zwitterions, meaning they have a net neutral charge. This improves the ability of cefepime to penetrate the bacterial cell wall. For Enmetazobactam, being a zwitterion increases its potency as a β -lactamases inhibitor compared to other drugs in the same class. As a combination treatment, Enmetazobactam can improve the effectiveness of cefepime against isogenic *E. coli* strains of bacteria expressing class A β -lactamases and shows limited inhibition of select class D β -lactamases, while remaining inactive against class B and C β -lactamases. Selective toxicity is maintained through targeted inhibition of bacterial penicillin-binding proteins and β -lactamases, enhancing activity against Gram-negative pathogens while minimizing effects on host cellular processes.

For the treatment of susceptible pathogens, Exblifep is recommended to be dosed as 2.0 g cefepime and 0.5 g Enmetazobactam intravenously every eight hours (17). The dosing is recommended to be altered for patients with estimated glomerular filtration rates that fall outside of 60-129 mL/min. This regimen should be continued for at least seven days, but it is not recommended to go beyond 14 days. Following the regimen, patients generally tolerated Exblifep well. The most common side effects were increased transaminases (20% of patients), increased bilirubin (7%), headache (5%), infusion site reactions (5%) and diarrhea (4%).

FIGURE 4.*Zevtera mechanism of action.*

Zevtera starts as the prodrug Ceftobiprole medocaryl. Within the bloodstream it is converted into the active Ceftobiprole. This antibiotic is indicated for multiple types of infections including lung, skin, and blood infection. Within the infected tissue, Ceftobiprole, a beta-lactam antibiotic is able to bind bacterial penicillin binding proteins (PBPs). This binding prevents cell wall synthesis leading to cell lysis and infection clearance.

In a randomized clinical trial comparing Cefepime and Enmetazobactam to piperacillin and tazobactam, 79.1% of patients receiving Cefepime and Enmetazobactam cleared their infections by day 14 which was higher compared to 58.9% in the piperacillin and tazobactam group, a difference of 20.2% (34). Piperacillin in combination with tazobactam combines an extended-spectrum penicillin, piperacillin, with tazobactam, a β -lactamase inhibitor that protects piperacillin from degradation by β -lactamases. Notably, among patients with infections caused by extended-spectrum β -lactamase (ESBL)-producing pathogens, the clinical cure rate was 73.7% with Cefepime and Enmetazobactam versus 51.5% with piperacillin and tazobactam.

Currently in the EU, Cefepime/Enmetazobactam is approved to treat additional types of infections aside from complicated UTIs. If the United States is to follow in these footsteps, it is possible that Exblifep will be approved for additional uses in the future. It is also possible due to its general broad-spectrum activity Exblifep could be used off-label by

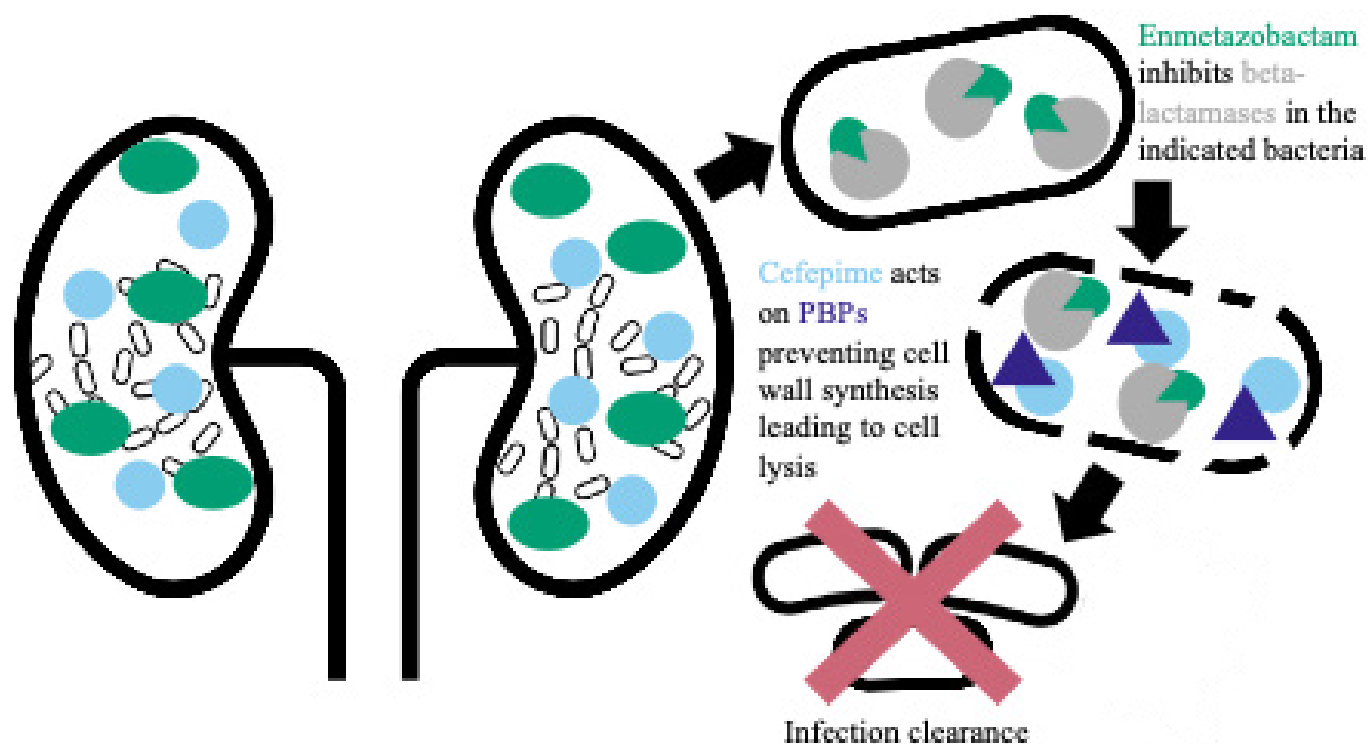
clinicians for treatment of infections not involving the urinary tract. This of course would be after careful consideration and input from specialists.

BLUJEPAS AS A TREATMENT FOR UNCOMPLICATED URINARY TRACT INFECTIONS

Blujepa is also known as Gepotidacin. It was approved on March 25, 2025, for the treatment of uncomplicated urinary tract infections (19). This drug is the first in its class of atri-azaacenaphthylenes, a kind of type IIA topoisomerase inhibitor. The inhibition of topoisomerase IIAs prohibits DNA replication leading to bacterial death (Figure 6) (52). Gepotidacin achieves selective toxicity by inhibiting bacterial DNA gyrase and topoisomerase IV, enzymes that are structurally distinct from their human counterparts, thereby limiting host toxicity. Outside of treating uncomplicated UTIs, Gepotidacin is also showing to be non-inferior to a standard ceftriaxone and azithromycin combination treatment for treating

FIGURE 5.

Exblifep mechanism of action



Exblifep is a combination of the Enmetazobactam, a beta-lactamase inhibitor and Cefepime, a beta-lactam. Exblifep is indicated for the treatment of complicated UTI. Enmetazobactam binds to beta-lactamases in the indicated pathogen allowing for Cefepime to function. Cefepime binds penicillin binding proteins (PBPs) preventing cell wall synthesis. This leads to cell lysis and infection clearance.

urogenital gonorrhea in a phase III clinical trial. Gepotidacin is administered orally as two 750 mg tablet twice daily as indicated for susceptible *Escherichia coli*, *Klebsiella pneumoniae*, *Citrobacter freundii* complex, *Staphylococcus saprophyticus*, and *Enterococcus faecalis* causing uncomplicated UTIs (19). The treatment is carried out for five days. The FDA recommends taking the regimen after a meal to reduce gastrointestinal side effects.

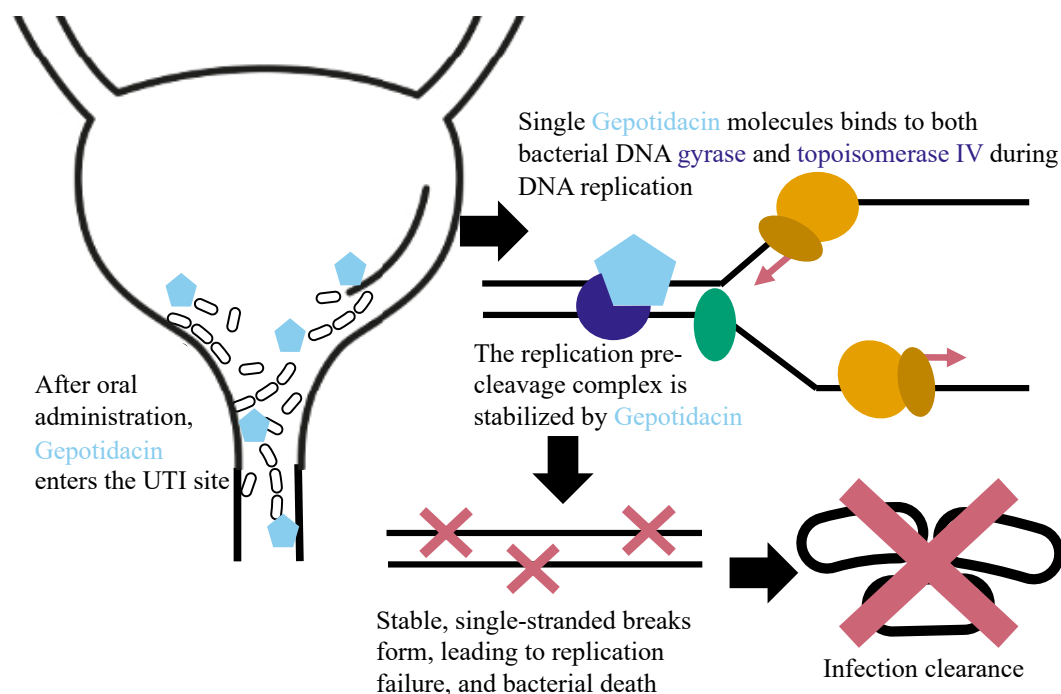
The FDA states that outside of the aforementioned clinically susceptible bacteria, there are *in vitro* data for other Gepotidacin-susceptible Gram-negative bacteria (19). They include *Citrobacter koseri*, *Klebsiella aerogenes*, *Klebsiella oxytoca*/ *Raoultella ornithinolytica*, *Morganella morganii*, *Proteus mirabilis*, and *Providencia rettgeri*. At the time of FDA approval

there was no clinical data about the effectiveness of Blujepa against these pathogens.

Blujepa is mostly well tolerated in patients (67). There were no life threatening or fatal side effects during the clinical trials leading up to its approval. The most common side effects were categorized as mild to moderate and were most commonly reported to be diarrhea (14-18%) and nausea (8-11%). Blujepa can cause QTc prolongation, a type of irregular heartbeat, and is therefore not recommended for patients with a history of these conditions or in patients with relevant cardiac diseases (19). Blujepa is also not recommended for patients with liver and kidney impairment. The use of Blujepa can also lead dysarthria, a speech disorder caused from weakness in facial muscles, due to acetylcholinesterase inhibition,

FIGURE 6.

Blujepa mechanism of action.



Blujepa is the brand name for the drug Gepotidacin. Gepotidacin targets both bacterial gyrase and bacterial topoisomerase IV. Gepotidacin stabilizes the pre-cleavage complex that forms during DNA replication. The stabilized complex prevents proper supercoiling and unwinding of DNA leading to single stranded breaks. As a result, replication fails and the pathogen dies, leading to infection clearance. Image attributions: Bladder icon: Flaticon.com. This figure has been designed using resources from Flaticon.com

TABLE 1.
FDA-approved antibiotics discussed in this review (2022-2025).

Drug(Brand)	Year	Active component(s)	Class/Primary target	Indication
Voquezna	2022 (42)	Vonoprazan*, amoxicillin, clarithromycin (42)	PCAB(acid suppression); β -lactam(cell wall); macrolide (protein synthesis) (55),(2),(46)	<i>H. pylori</i> infection (31),(32)
Xacduro	2023 (42)	Sulbactam, Durlobactam* (42)	B-lactam (PBPs); β -lactamase inhibitor (33),(1),(18)	<i>Acinetobacter baumannii</i> -calcoeticus complex infections (33)
Orlynvah	2024 (42)	Sulopenem etzadroxil*, probenecid (42)	B-lactam (cell wall); renal clearance inhibitor (68)	Uncomplicated UTIs (42)
Zevtera	2024 (22)	Ceftobiprole medocaril* (70)	B-lactam (PBPs incl. PBP2a) (23),(70)	ABSSSI, CAP (22),(12)
Exblifep	2024 (17)	Cefepime, Enmetazobactam* (17)	B-lactam (PBPs); β -lactamase inhibitor (35)	Complicated UTIs (35)
Blujepa	2025 (19)	Gepotidacin* (19)	DNA gyrase & topoisomerase IV (52)	Uncomplicated UTIs (19)

Summary of recently approved antibacterial agents, their active components, primary targets, and clinical indications. Combination therapies are presented as single entries for clarity. *Denotes a newly approved molecular entity.

as well as *Clostridioides difficile* infection, and possible hypersensitivity reactions, including anaphylaxis.

Not only does Gepotidacin inhibit topoisomerase IV, but also gyrase (Figure 6) (19). This new type of drug is an attempt at combating antibacterial resistance to fluoroquinolone antibiotics (6). While both fluoroquinolones and Gepotidacin have the same enzymatic targets, Gepotidacin binds different amino acid residues than fluoroquinolones (25), (43).

Another difference between the drug classes is that fluoroquinolones preferentially target DNA gyrase, whereas Gepotidacin targets gyrase and topoisomerase IV equally (43). By targeting these enzymes, Gepotidacin enhances the stabilization of single stranded DNA breaks over double stranded DNA breaks from supercoiled DNA (28), (43). While fluoroquinolones enhance both types of breakage, double-stranded breaks are more prevalent with this treatment. Overall, Gepotidacin’s mechanistic differences are important in overcoming treatment barriers for pathogens that have developed resistance to fluoroquinolones and could be approved for use in treating other infections in the future.

A comparative summary of the recently approved antibiotics discussed above is provided in Table 1.

FUTURE DIRECTIONS AND PROSPECTS/CONCLUSIONS

The rising threat of antimicrobial resistance (AMR) demands urgent and coordinated global action. While this review has highlighted several novel antibiotics approved by the FDA between 2022 and 2025, each offering distinct mechanisms and improved efficacy against drug-resistant pathogens, the frequency of such approvals remains limited in comparison to the magnitude of the AMR crisis. Despite notable progress, the development of novel antibiotics must become a sustained global priority, backed by policies that encourage innovation and ensure equitable access to these life-saving treatments. Addressing AMR will require not only scientific breakthroughs but also systemic changes that focus on the responsible development, approval, and widespread availability of new antimicrobial therapies.

A key priority is the establishment of sustainable antibiotic development pipelines (39). These pipelines must be designed to overcome economic and scientific hurdles that have historically limited the commercial viability of antibiotics. Incentive structures that reward long-term effectiveness over short-term sales volume, such as delinkage models, should be

more broadly implemented to align public health goals with industry priorities (61).

The role of public-private partnerships and funding initiatives cannot be overstated. Initiatives like CARB-X, GARDP, Tiny Earth, Small World Initiative, and the AMR Action Fund demonstrate the power of collaborative investment in early-stage research and clinical development (4), (13), (30), (60), (65). These partnerships reduce the risks in antibiotic R&D and provide crucial support to small biotech companies and universities, which are often leading innovation.

In the post-antibiotic era, where treatment failures become increasingly common, there is growing interest in alternative antimicrobial strategies. These include phage therapy, antimicrobial peptides, anti-virulence agents, probiotics, and microbiome-based therapies. While still in various stages of development, these alternatives offer the potential to complement or even replace traditional antibiotics, particularly for multidrug-resistant infections.

Another promising frontier is the use of machine learning (ML) and artificial intelligence (AI) in antibiotic discovery. By harnessing large datasets and predictive algorithms, ML can streamline the identification of potential drug targets, opti-

mize the screening of compounds, and even help repurpose existing drugs for new antimicrobial uses (15). Recent breakthroughs in discovering novel antibiotics using AI highlight the potential for these technologies to reinvigorate antibiotic discovery and accelerate the development of new treatments.

Despite these promising directions, there remains a critical need for urgent action at both the scientific and policy levels. Governments, global health agencies, and industry leaders must treat antibiotic resistance with the same level of urgency as other global crises. Comprehensive policy reforms, including stronger surveillance systems, stewardship programs, and streamlined regulatory pathways, are essential to support both innovation and access.

REFERENCES

1. Adnan, S., Paterson, D. L., Lipman, J., & Roberts, J. A. (2013). Ampicillin/sulbactam: its potential use in treating infections in critically ill patients. *International Journal of Antimicrobial Agents*, 42(5), 384–389. <https://doi.org/10.1016/J.IJANTIMICAG.2013.07.012>
2. Akhavan, B. J., Khanna, N. R., & Vijhani, P. (2023). Amoxicillin. *Helicobacter Pylori*, 497–506. https://doi.org/10.1007/978-981-97-0013-4_40
3. Antimicrobial Resistance Facts and Stats | Antimicrobial Resistance | CDC. (n.d.). Retrieved March 19, 2025, from <https://www.cdc.gov/antimicrobial-resistance/data-research/facts-stats/index.html>
4. Antimicrobial Resistance Research & Development - AMR Action Fund. (n.d.). Retrieved April 15, 2025, from <https://www.amractionfund.com/>
5. Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations. (n.d.).
6. Bax, B. D., Chan, P. F., Eggleston, D. S., Fosberry, A., Gentry, D. R., Gorrec, F., Giordano, I., Hann, M. M., Hennessy, A., Hibbs, M., Huang, J., Jones, E., Jones, J., Brown, K. K., Lewis, C. J., May, E. W., Saunders, M. R., Singh, O., Spitzfaden, C. E., ... Gwynn, M. N. (2010). Type IIA topoisomerase inhibition by a new class of antibacterial agents. *Nature*, 466(7309), 935–940. <https://doi.org/10.1038/NATURE09197>;SUBJMET=1290,154,22,2420,309,326,555,631;KWRD=ANTIBIOTICS,STRUCTURE-BASED+DRUG+DESIGN,TARGET+IDENTIFICATION
7. Benito, B. M., Nyssen, O. P., & Gisbert, J. P. (2024). Efficacy and Safety of Vonoprazan in Dual/Triple/Quadruple Regimens Both in First-Line and Rescue Therapy for *Helicobacter pylori* Eradication: A Systematic Review With Meta-Analysis. *Helicobacter*, 29(6). <https://doi.org/10.1111/HEL.13148>,
8. Bérdy, J. (2005). Bioactive Microbial Metabolites. *The Journal of Antibiotics* 2005 58:1, 58(1), 1–26. <https://doi.org/10.1038/ja.2005.1>
9. BV, P., & M, G. (2025). Ampicillin/Sulbactam. *Drugs of Today*, 24(3), 169–174. <https://doi.org/10.2165/00128415-199405090-00014>
10. Chu, J., Wang, Y., Zhao, B., Zhang, X. ming, Liu, K., Mao, L., & Kalamiyets, E. (2019). Isolation and identification of new antibacterial compounds from *Bacillus pumilus*. *Applied Microbiology and Biotechnology*, 103(20), 8375–8381. <https://doi.org/10.1007/S00253-019-10083-Y/FIGURES/4>
11. Church, N. A., & McKillip, J. L. (2021). Antibiotic resistance crisis: challenges and imperatives. *Biologia*, 76(5), 1535–1550. <https://doi.org/10.1007/S11756-021-00697-X/METRICS>
12. Cillóniz, C., Dominedò, C., Garcia-Vidal, C., & Torres, A. (2019). Ceftobiprole for the treatment of pneumonia. *Revista Española de Quimioterapia*, 32(Suppl 3), 17. <https://pmc.ncbi.nlm.nih.gov/articles/PMC6755349/>
13. Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X) | NIAID: National Institute of Allergy and Infectious Diseases. (n.d.). Retrieved April 15, 2025, from <https://www.niaid.nih.gov/research/carb-x>
14. Conly, J. M., & Johnston, B. L. (2005). Where are all the new antibiotics? The new antibiotic paradox. *The Canadian Journal of Infectious Diseases & Medical Microbiology*, 16(3), 159. <https://doi.org/10.1155/2005/892058>
15. David, L., Brata, A. M., Mogosan, C., Pop, C., Czako, Z., Muresan, L., Ismaiel, A., Dumitrascu, D. I., Leucuta, D. C., Stanculete, M. F., Iaru, I., & Popa, S. L. (2021). Artificial Intelligence and Antibiotic Discovery. *Antibiotics*, 10(11), 1376. <https://doi.org/10.3390/ANTIBIOTICS10111376>
16. Devi, S., Sharma, M., & Manhas, R. K. (2023). Purification and biological analysis of antimicrobial compound produced by an endophytic *Streptomyces* sp. *Scientific Reports*, 13(1), 15248. <https://doi.org/10.1038/S41598-023-41296-X>
17. Drug Trials Snapshots: EXBLIFEP | FDA. (n.d.). Retrieved April 16, 2025, from <https://www.fda.gov/drugs/drug-approvals-and-databases/drug-trials-snapshots-exblifep>
18. Drugs@FDA: FDA-Approved Drugs. (n.d.-a). Retrieved April 24, 2025, from <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm>
19. Drugs@FDA: FDA-Approved Drugs. (n.d.-b). Retrieved July 25, 2025, from <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm>

20. ECDC/EMA Joint Technical Report: The bacterial challenge: time to react. (n.d.). Retrieved April 13, 2025, from <https://www.ecdc.europa.eu/en/publications-data/ecdcema-joint-technical-report-bacterial-challenge-time-react>
21. Fathima, S. A., Arafath, A. Y., Prathiviraj, R., Hassan, S., Kiran, G. S., & Selvin, J. (2025). Bioactive Fraction of *Streptomyces thinghirensis* MSA1 Effectively Inhibits Biofilm Forming Clinically Significant AMR Pathogens. *Current Microbiology*, 82(6), 234. <https://doi.org/10.1007/S00284-025-04214-0>
22. FDA. (n.d.). FDA Approves New Antibiotic for Three Different Uses. Retrieved April 15, 2025, from <https://www.fda.gov/news-events/press-announcements/fda-approves-new-antibiotic-three-different-uses>
23. FDA (n.d.). HIGHLIGHTS OF PRESCRIBING INFORMATION. Retrieved April 14, 2025, from https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/218275s000lbl.pdf.
24. Fedorenko, V., Genilloud, O., Horbal, L., Marcone, G. L., Marinelli, F., Paitan, Y., & Ron, E. Z. (2015). Antibacterial Discovery and Development: From Gene to Product and Back. *BioMed Research International*, 2015, 591349. <https://doi.org/10.1155/2015/591349>
25. Fishman, C., Rae, J. M. C., Posobiec, L. M., Laffan, S. B., Lerman, S. A., Pearson, N., Janmohamed, S., Dumont, E., Nunn-Floyd, D., & Stanislaus, D. J. (2022). Novel Bacterial Topoisomerase Inhibitor Gepotidacin Demonstrates Absence of Fluoroquinolone-Like Arthropathy in Juvenile Rats. *Antimicrobial Agents and Chemotherapy*, 66(11). <https://doi.org/10.1128/AAC.00483-22>,
26. Gajdacs, M. (2019). The Continuing Threat of Methicillin-Resistant *Staphylococcus aureus*. *Antibiotics*, 8(2), 52. <https://doi.org/10.3390/ANTIBIOTICS8020052>
27. Ganesh, B., Banerjee, A., & Guruprasad, L. (2025). Evaluating the ability of in silico identified hit compounds to bind *Staphylococcus aureus* LcpASA using steered molecular dynamics simulations. *Molecular Diversity*. <https://doi.org/10.1007/S11030-025-11155-0>,
28. Gibson, E. G., Bax, B., Chan, P. F., & Osheroff, N. (2019). Mechanistic and Structural Basis for the Actions of the Antibacterial Gepotidacin against *Staphylococcus aureus* Gyrase. *ACS Infectious Diseases*, 5(4), 570. <https://doi.org/10.1021/ACSINFECDIS.8B00315>
29. Hamid, M. N., & Friedberg, I. (2018). Identifying antimicrobial peptides using word embedding with deep recurrent neural networks. *Bioinformatics*, 35(12), 2009. <https://doi.org/10.1093/BIOINFORMATICS/BTY937>
30. Hurley, A., Chevrette, M. G., Acharya, D. D., Lozano, G. L., Garavito, M., Heinritz, J., Balderrama, L., Beebe, M., Denhartog, M. L., Corinaldi, K., Engels, R., Gutierrez, A., Jona, O., Putnam, J. H. I., Rhodes, B., Tsang, T., Hernandez, S., Bascom-Slack, C., Blum, J. E., ... Handelsman, J. (2021). Tiny earth: A big idea for stem education and antibiotic discovery. *MBio*, 12(1), 1–7. <https://doi.org/10.1128/MBIO.03432-20>
31. Ierardi, E., Losurdo, G., Fortezza, R. F. La, Principi, M., Barone, M., & Leo, A. Di. (2019). Optimizing proton pump inhibitors in *Helicobacter pylori* treatment: Old and new tricks to improve effectiveness. *World Journal of Gastroenterology*, 25(34), 5097–5104. <https://doi.org/10.3748/WJG.V25.I34.5097>,
32. Ierardi, E., Losurdo, G., Mileti, A., Paolillo, R., Giorgio, F., Principi, M., & Di Leo, A. (2020). The puzzle of coccoid forms of *Helicobacter pylori*: Beyond basic science. *Antibiotics*, 9(6), 1–14. <https://doi.org/10.3390/ANTIBIOTICS9060293>,
33. Kabbara, W. K., Sadek, E., & Mansour, H. (2025). Sulbactam–Durlobactam: A Novel Antibiotic Combination for the Treatment of *Acinetobacter baumannii*–*Calcoaceticus* Complex (ABC) Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia. *Canadian Journal of Infectious Diseases and Medical Microbiology*, 2025(1). <https://doi.org/10.1155/CJID/2001136>,
34. Kaye, K. S., Belley, A., Barth, P., Lahlou, O., Knechtel, P., Motta, P., & Velicitat, P. (2022). Effect of Cefepime/Enmetazobactam vs Piperacillin/Tazobactam on Clinical Cure and Microbiological Eradication in Patients With Complicated Urinary Tract Infection or Acute Pyelonephritis: A Randomized Clinical Trial. *JAMA*, 328(13), 1304. <https://doi.org/10.1001/JAMA.2022.17034>
35. Keam, S. J. (2024). Cefepime/Enmetazobactam: First Approval. *Drugs*, 84(6), 737–744. <https://doi.org/10.1007/S40265-024-02035-2/METRICS>
36. Liu, L., & Nahata, M. C. (2023). Vonoprazan With Amoxicillin or Amoxicillin and Clarithromycin for the Treatment of *Helicobacter pylori* Infection. *Annals of Pharmacotherapy*, 57(10), 1185–1197. <https://doi.org/10.1177/10600280221149708>,

37. Matsumoto, H., Shiotani, A., & Graham, D. Y. (2019). Current and Future Treatment of *Helicobacter pylori* Infections. *Advances in Experimental Medicine and Biology*, 1149, 211–225. https://doi.org/10.1007/5584_2019_367,
38. McLeod, S. M., Shapiro, A. B., Moussa, S. H., Johnstone, M., McLaughlin, R. E., De Jonge, B. L. M., & Millera, A. A. (2018). Frequency and mechanism of spontaneous resistance to sulbactam combined with the novel β -lactamase inhibitor ETX2514 in clinical isolates of *Acinetobacter baumannii*. *Antimicrobial Agents and Chemotherapy*, 62(2). <https://doi.org/10.1128/AAC.01576-17>,
39. Miethke, M., Pieroni, M., Weber, T., Brönstrup, M., Hammann, P., Halby, L., Arimondo, P. B., Glaser, P., Aigle, B., Bode, H. B., Moreira, R., Li, Y., Luzhetskyy, A., Medema, M. H., Pernodet, J. L., Stadler, M., Tormo, J. R., Geniloud, O., Truman, A. W., ... Müller, R. (2021). Towards the sustainable discovery and development of new antibiotics. *Nature Reviews Chemistry* 2021 5:10, 5(10), 726–749. <https://doi.org/10.1038/s41570-021-00313-1>
40. Moussa, S. H., Shapiro, A. B., McLeod, S. M., Iyer, R., Carter, N. M., Tsai, Y. K., Kristopher Siu, L., & Miller, A. A. (2023). Molecular drivers of resistance to sulbactam-durlobactam in contemporary clinical isolates of *Acinetobacter baumannii*. *Antimicrobial Agents and Chemotherapy*, 67(11). https://doi.org/10.1128/AAC.00665-23/SUPPL_FILE/AAC.00665-23-S0002.XLSX
41. New Drug Application (NDA) | FDA. (n.d.). Retrieved April 7, 2025, from <https://www.fda.gov/drugs/types-applications/new-drug-application-nda>
42. Novel Drug Approvals for 2025 | FDA. (n.d.). Retrieved April 23, 2025, from <https://www.fda.gov/drugs/novel-drug-approvals-fda/novel-drug-approvals-2025>
43. Oviatt, A. A., Gibson, E. G., Huang, J., Mattern, K., Neuman, K. C., Chan, P. F., & Osheroff, N. (2024). Interactions between Gepotidacin and *Escherichia coli* Gyrase and Topoisomerase IV: Genetic and Biochemical Evidence for Well-Balanced Dual-Targeting. *ACS Infectious Diseases*, 10(4), 1137–1151. https://doi.org/10.1021/ACSINFEC-DIS.3C00346/ASSET/IMAGES/LARGE/ID3C00346_0011.JPEG
44. Papp-Wallace, K. M., McLeod, S. M., & Miller, A. A. (2023). Durlobactam, a Broad-Spectrum Serine β -lactamase Inhibitor, Restores Sulbactam Activity Against *Acinetobacter* Species. *Clinical Infectious Diseases*, 76(Suppl 2), S194–S201. <https://doi.org/10.1093/CID/CIAD095>,
45. Parvaiz, N., Ahmad, F., Yu, W., MacKerell, A. D., & Azam, S. S. (2021). Discovery of beta-lactamase CMY-10 inhibitors for combination therapy against multi-drug resistant Enterobacteriaceae. *PLoS ONE*, 16(1), e0244967. <https://doi.org/10.1371/JOURNAL.PONE.0244967>
46. Patel, P. H., & Hashmi, M. F. (2025). Macrolides. *StatPearls*. <https://pubmed.ncbi.nlm.nih.gov/31855339/>
47. Penwell, W. F., Shapiro, A. B., Giacobbe, R. A., Gu, R. F., Gao, N., Thresher, J., McLaughlin, R. E., Huband, M. D., DeJonge, B. L. M., Ehmann, D. E., & Miller, A. A. (2015). Molecular mechanisms of sulbactam antibacterial activity and resistance determinants in *Acinetobacter baumannii*. *Antimicrobial Agents and Chemotherapy*, 59(3), 1680–1689. <https://doi.org/10.1128/AAC.04808-14>,
48. Pfaller, M. A., Flamm, R. K., Mendes, R. E., Streit, J. M., Smart, J. I., Hamed, K. A., Duncan, L. R., & Sader, H. S. (2018). Ceftobiprole Activity against Gram-Positive and -Negative Pathogens Collected from the United States in 2006 and 2016. *Antimicrobial Agents and Chemotherapy*, 63(1), e01566-18. <https://doi.org/10.1128/AAC.01566-18>
49. Queenan, A. M., Shang, W., Kania, M., Page, M. G. P., & Bush, K. (2007). Interactions of Ceftobiprole with β -Lactamases from Molecular Classes A to D. *Antimicrobial Agents and Chemotherapy*, 51(9), 3089. <https://doi.org/10.1128/AAC.00218-07>
50. Ribeiro da Cunha, B., Fonseca, L. P., & Calado, C. R. C. (2021). Simultaneous elucidation of antibiotic mechanism of action and potency with high-throughput Fourier-transform infrared (FTIR) spectroscopy and machine learning. *Applied Microbiology and Biotechnology*, 105(3), 1269–1286. <https://doi.org/10.1007/S00253-021-11102-7/FIGURES/7>
51. Robbins, N., Koch, S. E., Tranter, M., & Rubinstein, J. (2012). The history and future of probenecid. *Cardiovascular Toxicology*, 12(1), 1–9. <https://doi.org/10.1007/S12012-011-9145-8>,

52. Ross, J. D. C., Wilson, J., Workowski, K. A., Taylor, S. N., Lewis, D. A., Gatsi, S., Flight, W., Scangarella-Oman, N. E., Jakielaszek, C., Lythgoe, D., Powell, M., Janmohamed, S., Absalon, J., & Perry, C. (2025). Oral Gepotidacin for the treatment of uncomplicated urogenital gonorrhoea (EAGLE-1): a phase 3 randomised, open-label, non-inferiority, multicentre study. *The Lancet*, 405(10489), 1608–1620. [https://doi.org/10.1016/S0140-6736\(25\)00628-2](https://doi.org/10.1016/S0140-6736(25)00628-2)
53. Sabih, A., & Leslie, S. W. (2024). Complicated Urinary Tract Infections. *StatPearls*. <https://www.ncbi.nlm.nih.gov/books/NBK436013/>
54. Salam, M. A., Al-Amin, M. Y., Salam, M. T., Pawar, J. S., Akhter, N., Rabaan, A. A., & Alqumber, M. A. A. (2023). Antimicrobial Resistance: A Growing Serious Threat for Global Public Health. *Healthcare*, 11(13), 1946. <https://doi.org/10.3390/HEALTHCARE11131946>
55. Scarpignato, C., & Hunt, R. H. (2024). Potassium-competitive Acid Blockers: Current Clinical Use and Future Developments. *Current Gastroenterology Reports*, 26(11), 273. <https://doi.org/10.1007/S11894-024-00939-3>
56. Schaefer, K., Matano, L. M., Qiao, Y., Kahne, D., & Walker, S. (2017). In vitro reconstitution demonstrates the cell wall ligase activity of LCP proteins. *Nature Chemical Biology*, 13(4), 396–401. <https://doi.org/10.1038/NCHEM-BIO.2302>
57. Scheeren, T. W. (2015). Ceftobiprole medocaril in the treatment of hospital-acquired pneumonia. *Future Microbiology*, 10(12), 1913–1928. <https://doi.org/10.2217/FMB.15.115>
58. Shapiro, A. B., Moussa, S. H., McLeod, S. M., Durand-Réville, T., & Miller, A. A. (2021). Durlobactam, a New Diazabicyclooctane β -Lactamase Inhibitor for the Treatment of Acinetobacter Infections in Combination With Sulbactam. *Frontiers in Microbiology*, 12. <https://doi.org/10.3389/FMICB.2021.709974>
59. Shi, J., Cheng, J., Liu, S., Zhu, Y., & Zhu, M. (2024). Acinetobacter baumannii: an evolving and cunning opponent. *Frontiers in Microbiology*, 15. <https://doi.org/10.3389/FMICB.2024.1332108>
60. Small World Initiative / Antibiotic Resistance / Crowdsourcing New Antibiotics / Inspiring Science Students. (n.d.). Retrieved April 15, 2025, from <https://www.smallworldinitiative.org/>
61. So, A. D., & Shah, T. A. (2014). New business models for antibiotic innovation. *Upsala Journal of Medical Sciences*, 119(2), 176–180. <https://doi.org/10.3109/03009734.2014.898717>
62. Stokes, J. M., Yang, K., Swanson, K., Jin, W., Cubillos-Ruiz, A., Donghia, N. M., MacNair, C. R., French, S., Carfrae, L. A., Bloom-Ackerman, Z., Tran, V. M., Chiappino-Pepe, A., Badran, A. H., Andrews, I. W., Chory, E. J., Church, G. M., Brown, E. D., Jaakkola, T. S., Barzilay, R., & Collins, J. J. (2020). A deep learning approach to antibiotic discovery. *Cell*, 180(4), 688. <https://doi.org/10.1016/J.CELL.2020.01.021>
63. Suvarna, D. V. (2010). Phase IV of Drug Development. *Perspectives in Clinical Research*, 1(2), 57. <https://doi.org/10.4103/2229-3485.71852>
64. Syed, Y. Y. (2014). Ceftobiprole medocaril: A review of its use in patients with hospital- or community-acquired pneumonia. *Drugs*, 74(13), 1523–1542. <https://doi.org/10.1007/S40265-014-0273-X/METRICS>
65. The Global Antibiotic Research and Development Partnership (GARDP). (n.d.). Retrieved April 15, 2025, from <https://www.who.int/groups/gardp>
66. Van Norman, G. A. (2016). Drugs, Devices, and the FDA: Part 1: An Overview of Approval Processes for Drugs. *JACC: Basic to Translational Science*, 1(3), 170. <https://doi.org/10.1016/J.JACBTS.2016.03.002>
67. Wagenlehner, F., Perry, C. R., Hooton, T. M., Scangarella-Oman, N. E., Millns, H., Janmohamed, S., Kramer, M., Kushner, P., Powell, M., Jarvis, E., Dennison, J., Sheets, A., Butler, D., & Breton, J. (2025). Plain language summary: efficacy and safety of Gepotidacin, a new oral antibiotic, compared with nitrofurantoin, a commonly used oral antibiotic, for treating uncomplicated urinary tract infection. *Future Microbiology*, 20(4), 265. <https://doi.org/10.1080/17460913.2025.2460387>
68. Zhanel, G. G., Pozdirca, M., Golden, A. R., Lawrence, C. K., Zelenitsky, S., Berry, L., Schweizer, F., Bay, D., Adam, H., Zhanel, M. A., Lagacé-Wiens, P., Walkty, A., Irfan, N., Naber, K., Lynch, J. P., & Karlowsky, J. A. (2022). Sulopenem: An Intravenous and Oral Penem for the Treatment of Urinary Tract Infections Due to Multidrug-Resistant Bacteria. *Drugs*, 82(5), 533–557. <https://doi.org/10.1007/S40265-022-01688-1>

69. Zhang, M. ming, Wang, M. ding, Yang, S. yu, Hu, J. qiang, Zhu, B. qiang, Wei, Y. kui, Zhang, C. lan, & Long, E. wu. (2025). The efficacy and safety of vonoprazan-based high-dose dual therapy for eradication of *Helicobacter pylori*: A systematic review and meta-analysis. *Journal of Infection and Public Health*, 18(7). <https://doi.org/10.1016/J.JIPH.2025.102768>,
70. Zimmerman, J., Giuliano, C., & Kale-Pradhan, P. B. (2024). Ceftobiprole Medocaril: A New Fifth-Generation Cephalosporin. *Annals of Pharmacotherapy*. <https://doi.org/10.1177/10600280241293773>
71. Zoffmann, S., Vercruysse, M., Benmansour, F., Maunz, A., Wolf, L., Blum Marti, R., Heckel, T., Ding, H., Truong, H. H., Prummer, M., Schmucki, R., Mason, C. S., Bradley, K., Jacob, A. I., Lerner, C., Araujo del Rosario, A., Burcin, M., Amrein, K. E., & Prunotto, M. (2019). Machine learning-powered antibiotics phenotypic drug discovery. *Scientific Reports*, 9(1), 5013. <https://doi.org/10.1038/S41598-019-39387-9>