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Resistance Pattern of *Acinetobacter baumannii* in Hospitalized Patients

Liqaa Salim Zghair[1], Sabreen G. Ghazal[2], Marwa H. AlMuhammady[3], and Aluaa.A.T[4]

[1,3,4] *Department of Biology, Faculty of Science, University of Kufa, Iraq.*
[2]*Department of Medical Laboratory Techniques, College of Health and Medical Techniques, Al-Furat Al-Awsat Techniques University, Iraq.*
***E-Mail**: liqaas.buhan@uokufa.edu.iq, sabreen.almummar.chm@atu.edu.iq, marwaha.almuhammady@uokufa.edu.iq , aluaa8380@gmail.com

ABSTRACT

One of the most prevalent bacteria in nosocomial infections is Acinetobacter baumannii. Misuse of antibiotics has resulted in an increase in A. baumannii multidrug-resistant (MDR) strain resistance. To assess the resistant gene pattern of MDR A. baumannii, empirical antibiotic therapy is required. In order to do this, the current study used a genotypic diagnostic technique to assess the resistance gene pattern of MDR A. baumannii that was collected from hospitalized patients. A. baumannii has resistance mechanisms against broad-spectrum antibiotics, including β-lactamases, efflux pumps, and aminoglycosides, altering targets, permeability shifts, and enzyme modifications. Efforts have been made to target plant-derived compounds and a combination of antibiotics and phytocompounds to circumvent resistance mechanisms. Many studies have been conducted on plant extract-synthesised nanoparticles. Additionally, we projected contemporary techniques to investigate insights into the mechanisms of action of antibiotics, such as multi-omics analysis. The data implied that A. baumannii putative antibiotic pathways would result in a different approach to treating A. baumannii infections. One of these resilient pathogens is A. baumannii, which is becoming more common in hospitals, resistant to treatment, and linked to higher death rates. Notwithstanding its clinical importance, little is known about this pathogen's behavior outside of hospitals. Additionally, unknown are its virulence factors. Consequently, our goal in this review is to provide light on the most recent findings about the ecological niches, microbiological characteristics, and antibiotic resistance profiles of A. baumannii. According to recent research, this bacterium is found in an increasing number of environmental niches, such as soils, treatment plants, and rivers.

Keywords: Acinetobacter baumannii, Resistance Pattern, Infections.

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INTRODUCTION

According to (Aya A. *et al*., 2021), *Acinetobacter* is a strictly aerobic, Gram-negative, catalase-positive, oxidase-negative, and paired coccobacillus bacterium that moves in twitches. There are more than 50 species of *Acinetobacter*, the great majority of which are not harmful; nonetheless, a small number of these species can lead to opportunistic infections in humans. The two most significant *Acinetobacter* species in terms of medicine are *Acinetobacter calcoaceticus* and *Acinetobacter*

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baumannii. Numerous illnesses, including skin and soft tissue infections, bacteremia, meningitis, pneumonia, and urinary tract infections, are brought on by *Acinetobacter baumannii* in both hospital settings (nosocomial infections) and the general population (Harding *et al*., 2018).

Concern has recently arisen regarding the *Acinetobacter* genus infection, specifically *A. baumannii*. Additionally, *Acinetobacter's* growing resistance to a variety of widely used antibacterial treatments has resulted in ineffective medications and a rise in infection-related mortality (Li *et al.,* 2019). Roughly 80% of recorded Acinetobacter infections are caused by the species *Acinetobacter baumannii*, according to the Centers for Disease Control and Prevention (CDC)(Howard *et al., 2012).* Since the last two decades, *Acinetobacter* has gained recognition as a significant healthcare-associated, opportunistic, multidrug-resistant (MDR) pathogen. The rate of isolation has increased globally, with a high morbidity and mortality rate, particularly in patients with compromised immune systems, ranging from 26.5% to 91. (Howard and others, 2012).

Multidrug-resistant (MDR) pathogens are becoming an increasingly serious concern for infections acquired in hospitals as well as the community. In fact, the World Health Organization (WHO) recently named antimicrobial resistance as one of the three most significant issues affecting human health. The abbreviation "ESKAPE," which stands for *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii*, Pseudomonas aeruginosa, and *Enterobacter spp.,* encompasses the most prevalent and dangerous MDR pathogens (Howard *et al*., 2012). Due to the severely restricted number of available treatments, multidrug resistance (MDR) in Gram-negative bacteria is a global public health concern. These pathogens are very resistant to the various types of antimicrobials that are now on the market (Chukamnerd *et al.,* 2022). Among Gram-negative infections associated to healthcare, *Acinetobacter baumannii* infections have a high average morbidity and mortality rate. They can result in serious infections, septic shock, and even death (Aydın *et al*., 2018). Acinetobacter baumannii infections are highly contagious and difficult to manage in hospitals (Rebmann and Rosenbaum, 2011). Amoxicillin, ampicillin, and first-generation cephalosporins are among the drugs to which A. baumannii is naturally resistant (Fishbain and Peleg, 2010). Over the course of two decades, Acinetobacter spp. developed resistance to numerous antibiotics and demonstrated an exceptional capacity to generate novel resistance mechanisms. These mechanisms ultimately result in pan-drug resistance (PDR) and prolong nosocomial outbreaks. The increased need for broad-spectrum antibiotics like imipenem is a result of Acinetobacter high resistances (Saed *et al*., 2013).

Furthermore, chromosomal efflux system overexpression attracted a lot of interest. On the other hand, overproduction of these systems results in enhanced MDR for antibacterial agents and causes host cell death by targeting of the nucleus and mitochondria. It is believed that OmpA contributes to *A. baumannii* antibacterial resistance during a potential interaction with the efflux pump (Al-Dahmoshi *et al*., 2020). The main mechanisms that are known to give *A. baumannii* resistance to an alternative class of antibiotics are β-lactamases, enzymes that modify aminoglycosides, permeability deficiencies, multidrug efflux pumps, and modification of target sites. The function of bacterial efflux pumps in multidrug resistance has been highlighted among these mechanisms. According to (Lin *et al*., 2017), there are four

different types of efflux pumps: the small multidrug resistance (SMR) family, the multidrug and toxic compound extrusion (MATE) family, the major facilitator superfamily (MFS), and the resistance nodulation division (RND) family. Numerous bacterial taxa have been shown to exhibit efflux-mediated resistance (Coyne *et al*., 2011).

EPIDEMIOLOGY

Throughout the world, *Acinetobacter spp*. are found in a wide range of ecological niches, including those inhabited by humans, animals, and the environment (Doughari *et al* ., 2018). Food can also act as a substantial reservoir for *Acinetobacter spp*., particularly multidrug-resistant (MDR) strains, despite the fact that this field of research has received little attention. These microorganisms have been isolated from a range of dietary items, such as dairy, fish, meat, vegetables, fruit, cheese, and drinking water. Throughout the world, *Acinetobacter sp*. are found in a wide range of ecological niches, including those inhabited by humans, animals, and the environment. (Amorim AM and Nascimento JD, 2017; Carvalheira A *at el*., 2016). In order to prevent *Acinetobacter spp*. from spreading from community to clinical settings, food plays a crucial role as a potential source. The significance of looking into the possible health concerns connected to foodborne pathogens is emphasized by this.(Carvalheira A *at el.*,2021) It is also important to remember that meals provided at healthcare institutions have been known to harbor harmful germs, particularly in susceptible populations, and that outbreaks have occurred there in the past. (Lund BM 2019). At least 25% of healthy people may have *Acinetobacter spp.* in their skin microbiome; prevalence rates among patients and hospital employees are considerably higher. These bacteria have been identified in a variety of human anatomical regions. High rates of *A. calcoaceticus* species colonization in hospitalized patients have been documented, including in the hands of medical personnel. This is especially true during ICU outbreaks linked to mechanical ventilation or other respiratory assistance.

The study of Carvalheira A *et al* ., (2021) conducted in a Chinese university hospital after improved environmental cleaning and hand hygiene led to a reduction in the rate of MDR bacteria colonization in intensive care unit patients. Research conducted in a Chinese university hospital after improved environmental cleaning and hand hygiene led to a reduction in the rate of MDR bacteria colonization in intensive care unit patients. The study of Li Y *et al.* (2021) highlights the difficulties in getting rid of them even with sufficient cleaning methods on sink and floor surfaces in healthcare facilities, A major cause for concern is the ACB complex's resistance to several antibiotics, which is closely linked to high rates of treatment failure and mortality in Brazilian intensive care units as well as around the world. The resistance profile of *Acinetobacter* species has changed recently, with a notable increase in the minimum inhibitory concentration (MIC) to carbapenems, especially imipenem, aminoglycosides, and fluoroquinolones (Kyriakidis *et al*., 2021).

VIRULENCE FACTORS

1. outer membrane proteins (porins)

Are important OMPs that play a key role in regulating *A. baumannii's* cell permeability ((McConnell MJ *et al*., 2013).The regulation of cell permeability in A. baumannii is dependent on OmpA, which was first identified as Omp among these porins . Of these porins, OmpA first recognized as Omp. (Sarshar M *et al.*,2021) is conspicuous for being the most prevalent external porin present in this

bacterium's outer membrane. The virulence factor OmpA in *A. baumannii* is the most widely defined, and it displays a variety of interesting biological features in in vitro model systems (McConnell MJ *et al.*, 2012) . It has the ability to attach itself to host epithelial cells, which releases proapoptotic chemicals like cytochrome c and causes apoptosis..(Lee CR *et al*., 2013).

2. Metal acquisition system

For the purposes of host-pathogen interaction, reproduction, and pathogenesis, *A.baumannii* and other bacterial species must obtain vital micronutrients including iron, zinc, and manganese (Law SKK *et al*., 2022). Although biological systems and the environment are rich in iron, there is still very little availability of physiologically active ferric iron (Fe+3). This restriction stems from its decreased solubility at neutral pH and in aerobic environments, as well as its tendency to be chelated by high-affinity iron-binding molecules like lactoferrin and transferrin (iron-binding proteins) or low molecular weight compounds like heme (AntunesLC *et al*., 2011). The availability of iron in the serum is typically restricted in mammals due to its binding to proteins including ferritin, lactoferrin, and transferrin. All aerobic bacteria, however, produce siderophores high-affinity iron chelating agents to overcome this iron shortage These molecules have a strong affinity and are low in molecular weight (Ferreira D *et al*., 2016).

3. Biofilm/quorum-sensing

The development of biofilms on biotic and abiotic surfaces has emerged as one of the key virulence factors for *A. baumannii*, making the MDR organism difficult to treatment (Russo TA *et al.*, 2016). Biofilms are intricate, three-dimensional structures made of bacteria living in an extracellular matrix consisting of proteins, polysaccharides, cellular debris, and genetic material. Microorganisms produce biofilms to protect themselves from radiation, desiccation, oxidation, and host defense cells (Yang CH *et al.*, 2019).

In biotic conditions, protein-protein interactions form between the bacterial surface and the human cellular matrix, marking a distinct beginning point for biofilm formation compared to abiotic environments. Bacterial contact with a surface in an abiotic environment is dependent on how hydrophobic it is (Flemming HC *at el*., 2023). The same processes take place in both settings: first, the bacteria multiply at the adherent site; then, they are incorporated into the extracellular matrix, where they mature and form biofilms; and last, they disperse. The BfmRS two-component system controls the chaperon/usher pilus system or Csu pili, that is present in 120 *A. baumannii*, In response to environmental stressors and antibiotic exposure, this complex network of molecules is essential in regulating gene expression and facilitating the creation of protective capsule. The synthesis of pili, a crucial step in adhesion and the creation of biofilms for cell attachment is also regulated by this similar mechanism (Greene C *et al.*, 2016).

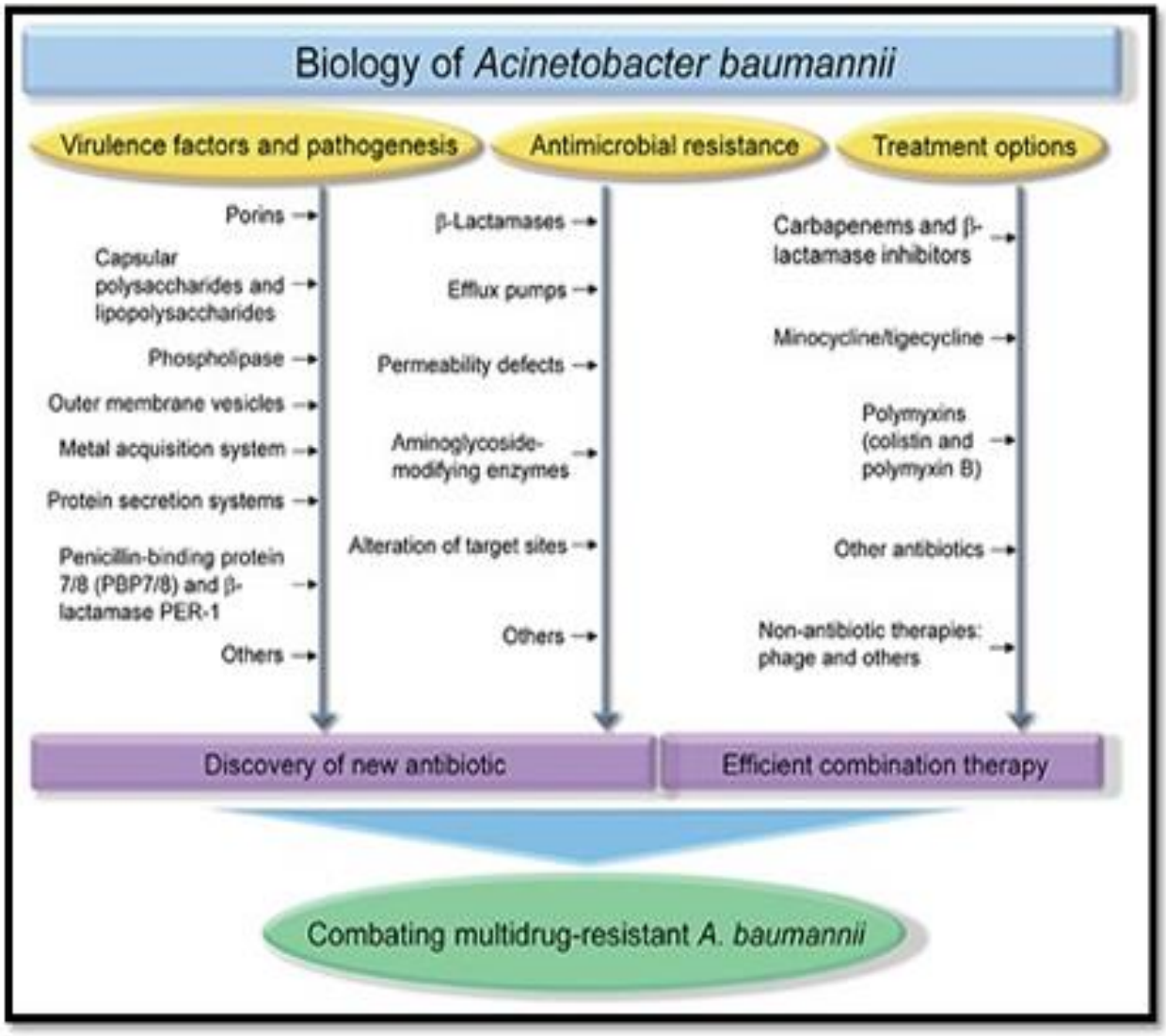

Figure 1: Shows the biofilm formation of *Acinetobacter baumannii* (C. March *et al.*, 2010).

ANTIMICROBIAL RESISTANCE

The mechanism of action of antibiotics is classified as follows: Contributions, 2006; Figure (2) illustrates this division of antibiotics into categories that target the cell wall, protein synthesis inhibitors, DNA replication inhibitors, and folic acid metabolism inhibitors. An antimicrobial agent's ability to cause harm to a bacterium does not always depend on the species or group of bacteria. Within related bacterial taxa, levels of resistance might differ significantly. The three primary ways that *Acinetobacter spp.* cells resist antibiotics are by producing enzymes that hydrolyze antibiotics, blocking the binding of antibiotics to the bacterial cell's target site, and switching target sites or altering cellular functions to evade the activity of antibiotics (Hamzeh *et al.*, 2019). Additionally, the most significant virulence factor exhibited by *Acinetobacter spp*. is the production of biofilms, which are crucial for bacterial survival, infection, and antibiotic resistance (Al-Dulaimi *et al.*, 2021). *A. baumannii* cells readily form biofilm in vitro, and nosocomial strains' capacity to do the same on medical equipment and in host tissues

indicates that the virulence of the bacteria plays a crucial role in this process. The polymeric conglomeration of proteins and polysaccharides includes the cells that produce the biofilms. Antibiotic resistance in these ecosystems can rise up to 1000 times due to the biofilm's resistance to detergents, antibiotics, and the host's immunological responses (Giannouli *et al.*, 2013). The least concentration of a medicine that can stop bacterial growth, known as the minimum inhibitory concentration (MIC), is typically used to test susceptibility and resistance. Indeed, the range of average minimum inhibitory concentrations (MICs) for a particular medicine among the same type of bacteria is the susceptibility. A species is said to have a natural resistance to medicine if its average MIC falls within the resistant portion of the range. Additionally, bacteria may pick up resistance genes from closely related organisms; the degree of resistance varies according on the species and genes taken up (Coculescu, 2009; Martinez, 2014). Based on automated testing for antimicrobial drug susceptibility (Vitek, bioMérieux) or evaluation using the disk diffusion antimicrobial method in compliance with guidelines from the Clinical and Laboratory Standards Institute, the *Acinetobacter* isolate was classified as multidrug-resistant (MDR) if it exhibited resistance to more than three classes of antimicrobial agents (Davis *et al.*, 2005).

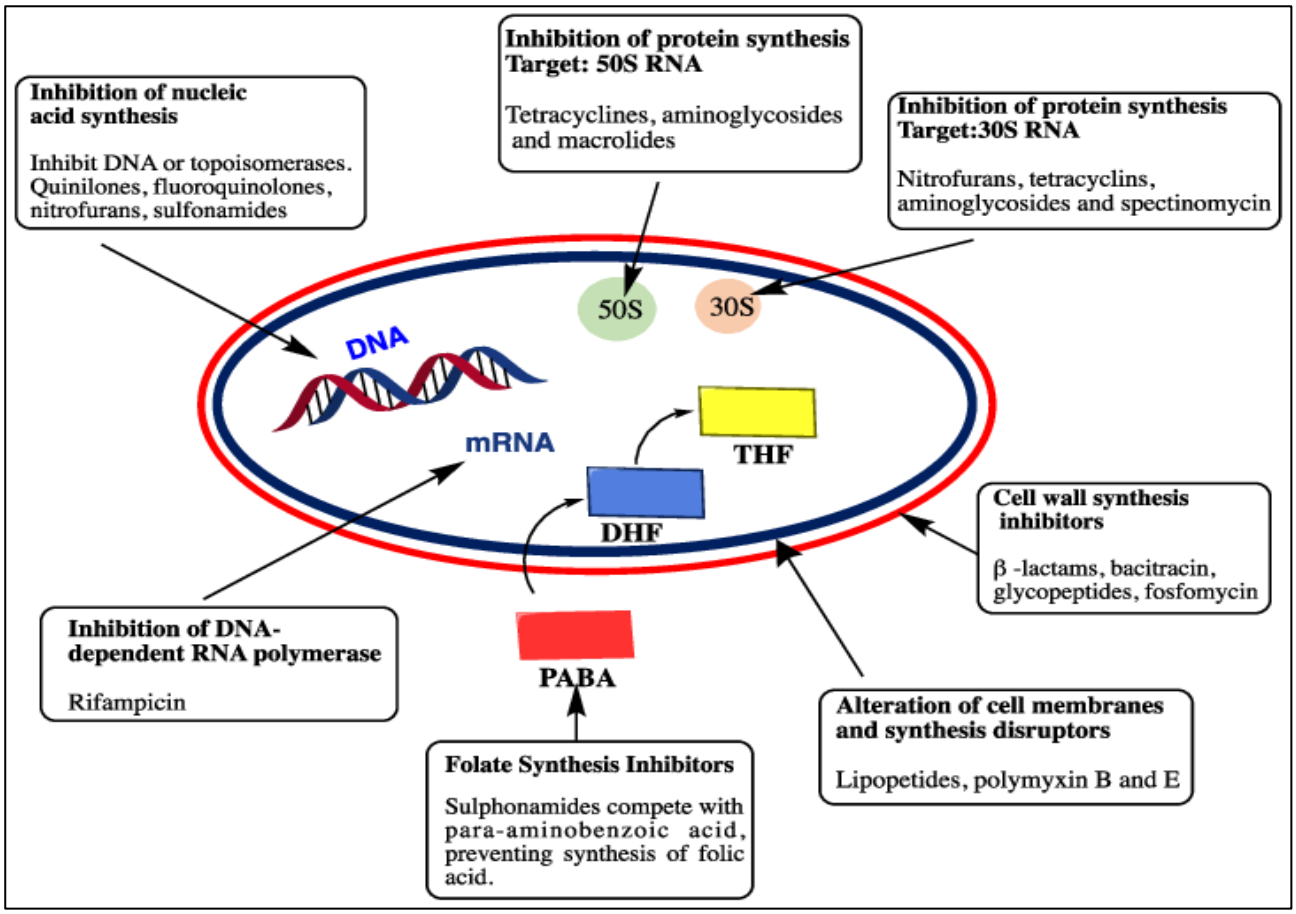

Figure 2: Action and mechanisms of antibiotics.

Antibiotics with a beta-lactam ring in their chemical structure are known as beta lactamases show in Figure (3). This comprises monobactams, carbapenems, carbacephems, cephalosporins, and cephamycins (cephems), which are derivatives of penicillin. The most commonly used class of antibiotics, β-lactams, function by preventing the bacterial organism from synthesizing its cell walls. The extensive utilization of β-lactam antibiotics and β-lactamase inhibitors results in the upregulation of chromosomal-mediated AmpC production and confers resistance to many drugs, including carbapenem and the third generation of cephalosporins (Moehario *et al*., 2019). Beta-lactam resistance is a concerning and expanding problem that poses a threat to public health. Other processes are involved, even though the creation of beta-lactamases is the primary way that bacterial resistance to beta-lactams manifests itself. The resistance mechanisms are listed below (Ibrahim *et al*., 2019). Because they may impart resistance to penicillins, cephalosporins, oxyimino-cephalosporins (such as ceftriaxone, cefotaxime, and ceftazidime), cephamycins (such as cefoxitin and cefotetan), and monobactams, AmpC β -lactamases are clinically relevant. Clavulanic acid, an ESBL inhibitor, has no effect on AmpC b-lactamase activity (Tan *et al*., 2009).

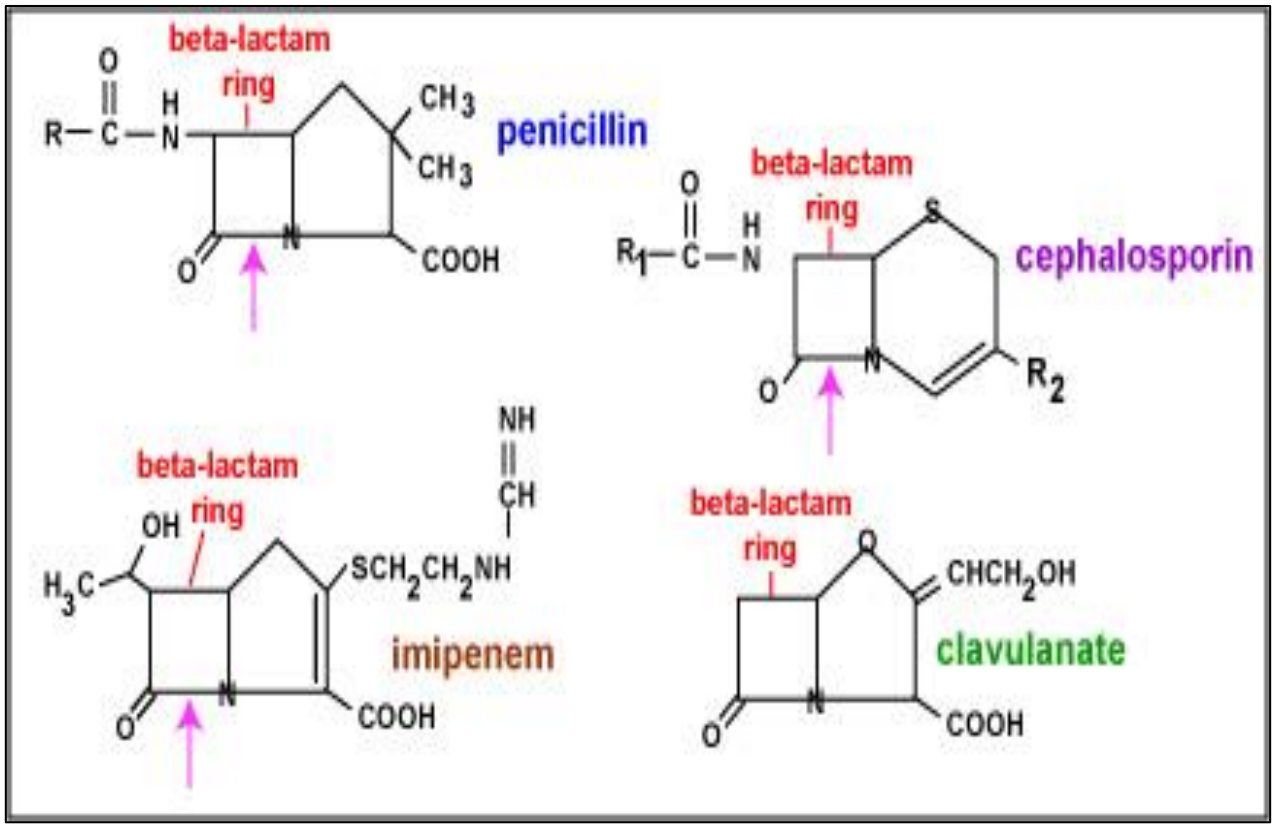

Figure 3: Example structures of several classes of β-lactam antibiotics. The β-lactam ring is highlighted in red.

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