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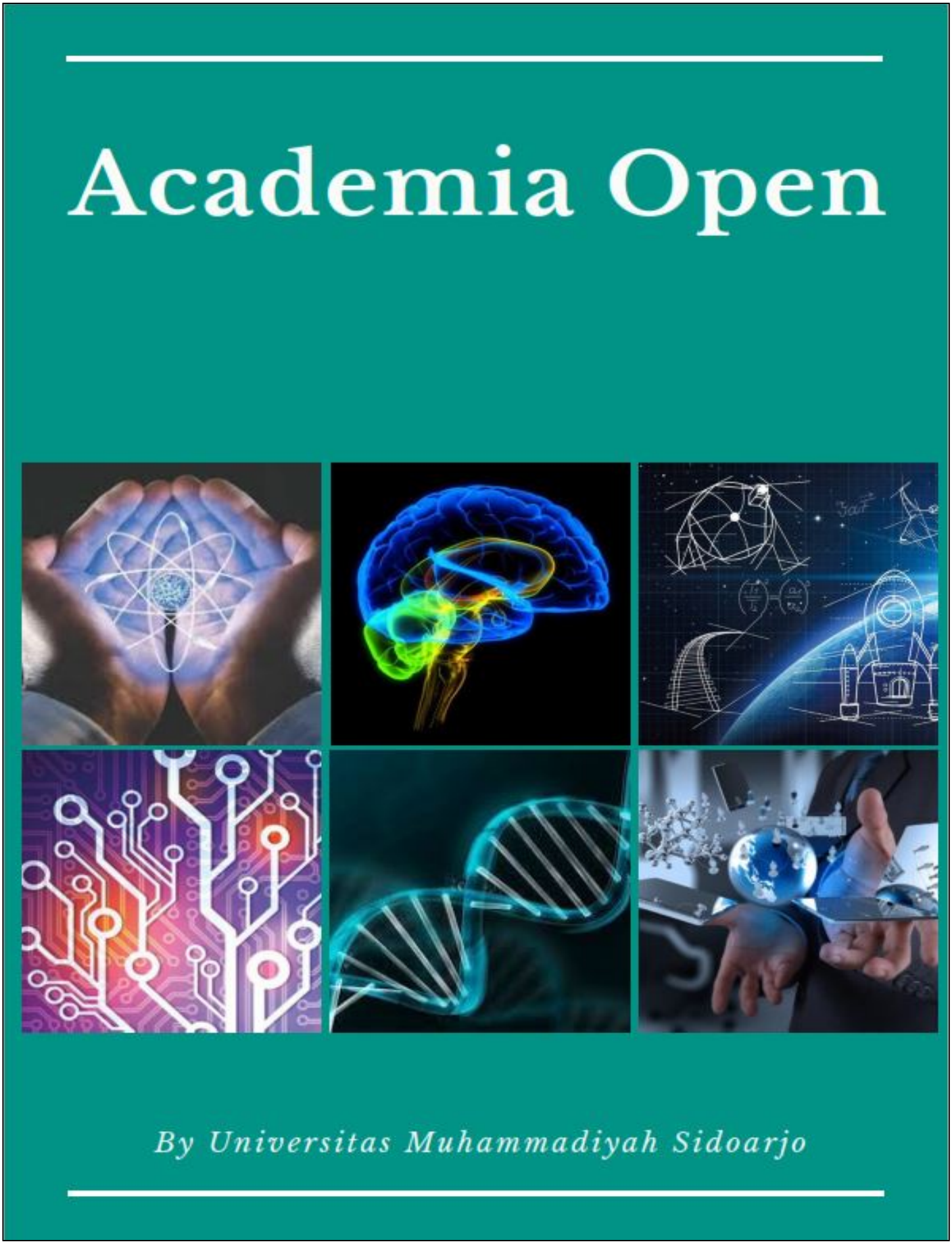

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Unmasking Hidden Threats Global Spread of MBL Resistance Exposed

Membuka Kedok Ancaman Tersembunyi Penyebaran Global Resistensi MBL yang Terekspos

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Abstract

This study aims to establish a routine monitoring system for MBL enzymes to provide timely data to healthcare professionals and policy makers, enabling informed decision making on antibiotic use and resistance management. Using a combination of molecular biology techniques and data analysis, we monitor MBL activity in various institutional settings. The increasing prevalence of multidrug-resistant (MDR) bacteria is a significant threat to public health globally. Metallo-beta-lactamase (MBL), an enzyme that confers resistance to a wide range of beta-lactam antibiotics, is particularly concerning due to its ability to spread rapidly in healthcare and community settings. Despite the importance of this issue, systematic monitoring and understanding of MBL remains inadequate. Our findings reveal a significant, previously unreported presence of MBLs, underscoring the urgent need for targeted antibiotic stewardship programs. The implications of this study emphasize the importance of integrating enzyme monitoring into standard healthcare practices to reduce the spread of MDR bacteria.

Highlights:

- Regular Monitoring: Essential for tracking MBL enzyme prevalence and guiding antibiotic use.
- Advanced Techniques: Molecular biology methods enhance MBL detection and analysis.
- Policy Integration: Crucial for implementing enzyme monitoring in healthcare to combat MDR bacteria spread.

Keywords: MBL Enzymes, Antibiotic Resistance, Healthcare Monitoring, Molecular Biology, Stewardship Programs

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Introduction

Comprehension their method of action requires a comprehension of (Figure 1). Its structure is identical to that of acyl-D-alanyl-D-alanine, the usual substrate required for the production of the linear glycopeptide found in bacterial cell walls. The B-lactam binds to the enzyme, inhibiting transpeptidation and the production of cell walls [1].

Antibiotic ß-lactam structure is shown in Figure (1l). A variety of side chains influence an agent's pharmacological characteristics, degree of activity, spectrum, and resistance to B-lactamases. B. P-lactam rings; C. Thiazolidine rings: C'. Dihydrothiazine rings: D. B-lactamases' sites of action; E. amidase sites of action [2], [3].

Comprehending how they work is contingent upon comprehending what is shown in (Figure 1). The structure of ß-lactam is similar to that of acyl-D-alanyl-D-alanine, which is the normal substrate needed for the production of linear glycopeptide present in bacterial cell walls. B-lactam binds to enzyme thus inhibiting transpeptidation and the production of cell wall— leading to their death [4].

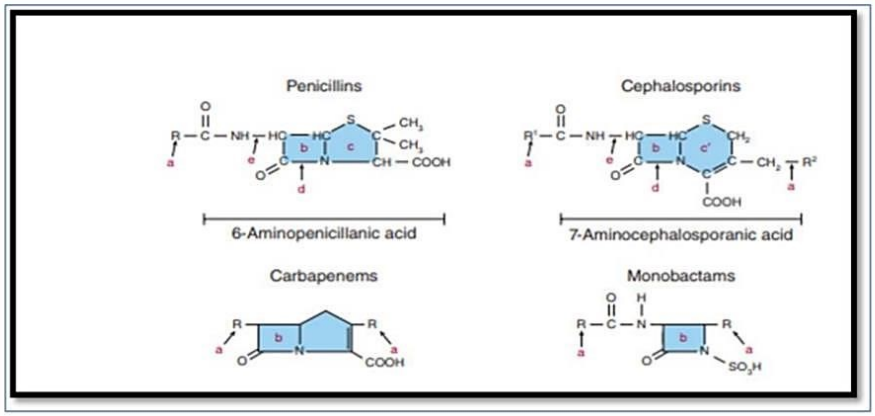

Figure 1. ***Structure of ß-lactam antibiotics***

Antibiotic ß-lactam's structure is represented by Figure (1). An agent's pharmacologic characteristics are affected by a variety of side chains influencing activity, spectrum resistance to B-lactamases because these different sites include P-lactam rings; Thiazolidine rings: Dihydrothiazine rings: B-lactamase action sites amidase action sites [5], [6].

Structure of ß-lactam antibiotics. a. Different side chains determine degree of activity, spectrum, pharmacologic properties, resistance to ß-lactamases; b. ß-lactam ring; c. thiazolidine ring; c'.dihydrothiazine ring; d. site of action of ß-lactamases; e. site of action of amidase [7].

1. Principles of Antibiotic Resistance

Four primary mechanisms induce bacterial drug resistance, as shown in Table (1). (1) Drugs inactivated by enzymes generated by bacteria, such as ß-lactamases, which break the B-lactam ring of cephalosporins and penicillins, rendering them inert [8]. (2) Bacteria create altered targets that are less affected by the drug (for example, a mutated 30S ribosomal subunit protein may lead to streptomycin resistance, and a methylation 23 srRNA can lead to erythromycin resistance) [9]. (3) Drugs are not able to reach an effective intracellular concentration when bacteria lower their permeability (e.g., alterations in porins might diminish the quantity of Penicillin entering the bacterium) [10]. (4) Applying a "eflux" pump, often referred to as a "multidrug-resistance pump". Bacteria actively export therapeutics [11], [12].

2. Lactam Antibiotics Action

Growing bacteria are effectively targeted by all B-lactam drugs due to the specific inhibition of bacterial cell wall formation [13]. While these antibiotics act broadly within the spectrum of their activity, peptidoglycan synthesis suppression is recognized as their major effect because this macromolecule represents an important structural component for most bacteria [14]. Composed of alternating N-acetylglucosamine (NAG) and N-acetylmuramic acid (NAM) molecules, the linear chains are further cross-linked via peptide bridges which result from enzymatic activity during synthesis [15], [16]. When penicillin-based antibiotics interfere with transpeptidases or any other serine protease that constitutes peptidoglycan assembly machinery, there is no room left for doubt about how they do it: in addition to breaking cross-links between peptide stems coming from different chains and hence weakening

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cell walls down to bursting point penicillins bind covalently at active site serines on PBPs which normally participate in cross-linking reactions but cannot continue after such binding takes place [17]. Developing bacteria die as a consequence of compromised integrity [18].

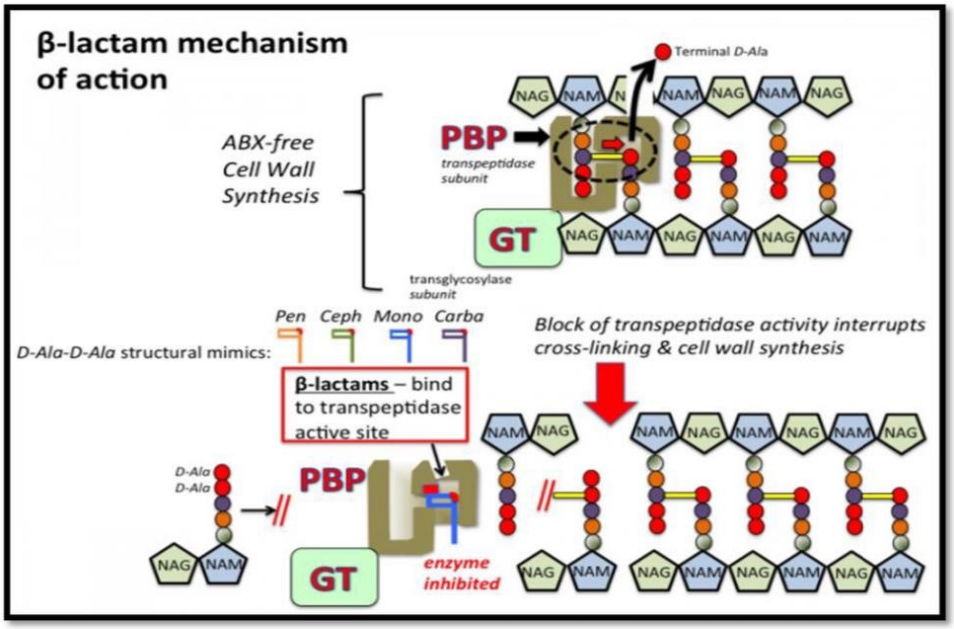

Figure (2): Mechanism of action of β- Lactam Antibiotics .

Figure 2. ***Mechanism of Action of B-Lactam Antibiotics***

Bacterial resistance to B-lactam antibiotics is often caused by the creation of B-lactamases, which bind to and hydrolyze them [19]. These enzymes are intended to preferentially detect and hydrolyze quaternary B-lactam rings, resulting in inactive products that can no longer inhibit transpeptidases or TPs [20].

Escherichia coli was determined to have the original B-lactamase, which hydrolyzed penicillin [21]. Because B-lactamases are extensively dispersed and encoded on mobile genetic components, their proliferation and transmission have increased [22]. As a consequence, it is common to encounter bacteria with up to eight distinct forms of B-lactamases, each of which specifically inhibits a family of antibiotics known as beta-lactamases. With over 4300 distinct kinds of enzymes, it is vital to have a reliable and understandable nomenclature to differentiate between them [23].

3. Bactamases Classification

The Bush-Jacoby classification system and the Ambler classification system (AMB) are the two most often used categorization methods for B-lactamases [24]. Bush-Jacoby-Medeiros divided B-lactamases into three groups and sixteen subgroups according to their hydrolytic and inhibitory characteristics [25]. The newest functional categorization has three categories: Cephalosporinases (category C) comprise group 1.

Describe group 3 (class B) and group 2 (class A and D) metallo-β-lactamases as broad-spectrum serine carbapenemases that are resistant to inhibitors [26].

Ambler used a fundamental amino acid sequence homology classification approach to divide B-lactamases into four groups (A, B, C, and D). The active sites of class B enzymes include zinc residues, while class A, C, and D enzymes have serine residues [27]. Table 2 shows two categorization algorithms [28].

4. Metallo B-lactamase

Sabath and Abraham discovered metallopore lactamases (MBLS) in 1966, which were later identified as class B lactamases in 1980 [29]. Without zinc ions, these enzymes cannot act. Except for monoaminases, almost all metallo-β-lactamases are multiple metalloenzymes capable of hydrolyzing other metallo-β-lactamases. Commercially available metallo-β-lactamase inhibitors including sulbactam, tazobactam, and clavulanic acid do not inhibit them [30]. Furthermore, they are not inhibited by NXL-104 (avibactam sodium hydrate), a class A and C B-lactamase inhibitor [31]. These bacteria are commonly spread by mobile genetic elements such as transposons, plasmids, and

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endoviruses, which may infect and disseminate to a range of bacteria, including Enterobacteriaceae and Acinetobacter spp. [32]. The best-known acquired MBLs are IMP- and VIM-type enzymes, which were identified in the early 1990s. Other forms of acquired MBL enzymes discovered include SPM, GIM, SIM, KHM, NDM, AIM, DIM, SMB, TMB, and FIM [33].

Revealed that the most commonly employed and therapeutically helpful class B enzymes are New Delhi MBL (NDM), iminotropase (IMP), and verona integrin-encoded MBL (VIM) [34].

5. Mechanism of Action of B-lactamase

TEM-1 has been the best researched regarding how β-lactamases hydrolyze β-lactams. TEM-1 β-lactamase hydrolyzes β-lactams by first cleaving their amide bonds in two steps [35].

The positively charged enzyme residue at serine B lactamases then attracts the negatively charged carboxylate group of the B-lactam antibiotic to the active site— where the beta-lactam positions itself correctly and forms significant hydrogen bonds with the enzyme. The residues that make up this interaction in the active site are often referred to as oxyanion pore or electrophilic core. The next step is acylation [36].

Methods

Sample collection and processing: Fifty urine samples from UTI patients were taken between April 1 and May 15, 2023, when the patients were registered at Al-Hussein Hospital in Nasiriyah Province. Ten milliliters of clean-catch midstream urine were transferred into sterile containers first thing in the morning [37]. Each specimen was brought into the lab and left there for an hour; if not, it was refrigerated at 4 °C until processing. A standard urine test was performed on each sample to check for the presence of bacteria, white blood cells, and other impurities. In order to isolate bacteria, urine samples were streaked on agar plates (MacConkey, Blood, and Mannitol Salt). The lab's Vitek equipment was utilized to detect the findings. of the same healthcare institution [38].

1. Analyzing Metallo-Beta-Lactamases (MBLs) Phenotypically

Phenotypic characterization of MBL was done using CDDT. Test isolates were streaked on MH agar and dried for three to five minutes to produce turf cultures with 0.5 McFarland opacity standard. Agar plates had imipenem and imipenem/EDTA combination discs (10/750) overlaid on them (Bioanalysis/Turkey) [39]. The inhibition zones of imipenem and imipenem-EDTA disks were measured after overnight incubation at 37°C — indicating positive MBL based on the paper test results, showing that the inhibitory zone of IMP-EDTA paper increased by approximately 7 mm [40].

Results and Discussion

The distribution of bacterial species was the same across the two patient groups with and without bacteriuria, but no multiple isolates were found [41]. The common pathogenicity of E. coli — in patients with symptomatic urinary tract infection — includes pyelonephritis, cystitis and asymptomatic bacteriuria; risk factors for infection include recent sexual intercourse, diaphragm-spermicide use and a history of recurrent infections [42]. The host immune response plus characteristics of bacteria contribute to determining which patient will develop disease due to uropathogenic E. coli (UPEC)..

Hemolysin is a cytotoxic chemical that helps these organisms invade tissue and is often produced by them. P pili are a specific type of pilus that bind to the P blood group antigen and are produced by strains that cause pyelonephritis and express the K antigen [43]. In terms of MBL results, Pseudomonas aeruginosa was the lowest producer, while Klebsiella pneumoniae and E. coli were the highest producers in the study. 80% of MBLs were generated from a total of 35 isolates. With the recent acquisition of genetic constructs, metallo-B-lactamases have emerged as very potent resistance determinants in drug-resistant Gram-negative bacteria, posing a serious risk to human health [44]. Our results support those of [45], who stated that E. coli produced the most MBL. In contrast, [46] found no MBL-positive E. coli in Zanjan city, Iran.

Conclusion

The awareness of MBL acts as the first indicator that antibiotics must be utilized appropriately to limit the spread of MDR bacterial strains inside these hospitals and communities. A new technique of alerting care providers and policy makers about the nature and development of this sort of resistance is to continually monitor MBL enzymes in these surroundings.

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