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# Toxicity of $\beta$ -Lactam Antibiotics: Pathophysiology, Molecular Biology and Possible Recovery Strategies

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## Abstract

Beta ( $\beta$ )-lactam antibiotics are wide-spectrum antibiotics used for various bacterial infections. The aim of this chapter is to summarize the knowledge about the toxicity of  $\beta$ -lactam antibiotics and issues associated to their inappropriate use. This review has highlighted that  $\beta$ -lactam antibiotics are a group of products that have a chemical structure characterized by a  $\beta$ -lactam ring and are one of the most common antibacterial agents. However, due to the inappropriate use including abuse and misuse, resistance to the  $\beta$ -lactam antibiotics is currently a global crisis. Moreover, even when used appropriately, they have been linked to triggering allergic reactions like urticaria, bronchoconstriction, also severe conditions like immune-mediated haemolytic anaemia and intravascular haemolysis. It is known that some  $\beta$ -lactam antibiotics are neurotoxic, some are nephrotoxic, some are genotoxic and some are toxic to urogenital system. Several factors are involved in the occurrence of toxic effects including the dosage and renal status. Several strategies are possible to overcome  $\beta$ -lactam antibiotics-triggered toxicity, including rational prescribing, substitution combination and phage therapy which seems promising. Public health education for clinical teams and patients is essential in ensuring that this group of antibiotics are retained in therapeutics.

**Keywords:**  $\beta$ -lactam antibiotics,  $\beta$ -lactamase, toxicity, side effects, treatment strategies

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## 1. Introduction

Beta ( $\beta$ )-lactam antibiotics are one of most commonly used class of antimicrobial agents around the world.  $\beta$ -lactam or  $\beta$ -lactamase inhibitor antibiotics are substances that disrupt bacterial cell-wall formation via penicillin-binding proteins (PBPs) where they bind covalently at the terminal step of peptidoglycan cross-linking in bacteria [1]. The first generation

of  $\beta$ -lactam antibiotics were penicillins, followed by cephalosporins; later carbapenems and monocyclic  $\beta$ -lactams that have been recently introduced and are currently in service for the treatment of infectious disease caused by pathogenic bacteria [2]. However, following the occurrence of resistance to the penicillin, new  $\beta$ -lactam antibiotics are being researched for enhancing the spectrum efficiency against the  $\beta$ -lactam-resistant bacteria [3]. In terms of life-threatening infections,  $\beta$ -lactam antibiotics are almost indispensable for therapies in intensive care units (ICUs). However, the therapy with  $\beta$ -lactam antibiotics remains unresolved since  $\beta$ -lactamase resistance is disseminating rapidly among pathogenic bacteria. The most serious types of  $\beta$ -lactamase resistance today are extended-spectrum  $\beta$ -lactamases (ESBLs), carbapenemases and metallo- $\beta$ -lactamases (MBLs) [1, 4, 5].

The large amount of use and misuse of  $\beta$ -lactam antibiotics has been inducing the  $\beta$ -lactam resistance for decades; besides  $\beta$ -lactam antibiotics have many side or adverse effects including allergy and toxicity [6, 7]. Since beta-lactam rings are different in their structure, they can be recognized by the immune system and this leads to hypersensitivity in some patients [8]. For example, cephalosporin can induce a range of hypersensitivity reaction and anaphylaxis in patients with IgE-mediated allergy [9]. Also,  $\beta$ -lactams are the most known causes of drug-induced fevers [10].  $\beta$ -lactam antibiotics are neurotoxic, nephrotoxic, genotoxic and some are reproductive toxic. The nephrotoxic effects of  $\beta$ -lactams lead to proximal tubular necrosis [11]. Some are toxic to reproductive system; tazobactam/piperacillin has a toxic effect on reproductive systems and also developmental toxicity reported that tazobactam has an influence on maternal toxicity [12]. Another significant point for the side effects of  $\beta$ -lactams is the toxicity on central nervous system. It can be observed after the administration of  $\beta$ -lactam antibiotics such as penicillin; hence, clinical data have reported disorientation, twitching, somnolence and myoclonus [7].  $\beta$ -lactam antibiotics such as imipenem and cephaloridine have been reported to cause an irreversible injury to the renal anionic substrate uptake and respiration [13]. Since this effect is dose-dependent, it can be resolved through dosing reduction based on renal function test results [6].

To overcome the resistance and toxicity of  $\beta$ -lactam antibiotics, many attempts have been reported. Developing more stable and more effective strategies is the key factor. For instance, ampicillin/sulbactam, amoxicillin/clavulanate, ticarcillin/clavulanate and piperacillin/tazobactam are the most used  $\beta$ -lactamase inhibitor combinations for clinicians [2]. Moreover, the selection of right  $\beta$ -lactam antibiotics for patients who have an antibiotic allergy is important. To overcome this issue, some of allergy tests are available, for example, penicillin skin testing [14]. Fighting with bacteria via the phage therapy is another option to overcome toxicity/allergy of  $\beta$ -lactams and it reduces the resistance risk of  $\beta$ -lactams. A unique and effective phage against metallo- $\beta$ -lactamase producing *Pseudomonas aeruginosa* (*P. aeruginosa*) has been used to treat a catfish infection. However, this phage is not useful for the treatment of infections in human [15]. By the way, combination of phages and antibiotics is possible; it is called phage-antibiotic synergy (PAS) and has been proven successful in some bacteria normally resistant to  $\beta$ -lactam antibiotics such as cefotaxime [16]. Interestingly, some studies have reported that phages were not toxic on mammalian cells [17, 18]. Thus, the aim of this chapter is to summarize the knowledge about the toxicity

of  $\beta$ -lactam antibiotics and issues associated to their inappropriate use. It is hoped that a good understanding of the structures, mechanisms of action and risk factors leading to resistance to  $\beta$ -lactam antibiotics will assist both clinicians and researchers in the design of anti-resistance interventions.

## 2. Classes of beta ( $\beta$ )-lactam antibiotics

Beta ( $\beta$ )-lactam antibiotics are a class of antibiotics that contain a  $\beta$ -lactam ring in their molecular structures. Generally,  $\beta$ -lactam antibiotics have a common function: inhibition on cell-wall biosynthesis of the peptidoglycan layer in the bacteria. And this makes  $\beta$ -lactams the most extensively used antibiotics [19]. For over 70 years, penicillin and related antibiotics have been used extensively for the control and treatment of bacterial infections. Improving the efficiency of these antibiotics is still important, and it captivates increasing attention of researchers to overcome the infections depending on highly resistant bacteria. Development of new  $\beta$ -lactam group of antibiotics generally depends on enhancing the spectrum efficiency against the pathogenic bacteria. Besides, resistance mechanisms with special features may be targeted [1].

Over the years, countless penicillin derivatives have been produced including penicillins, cephalosporins, carbapenems, oxapenems, oxacephams as well as monocyclic, spirocyclic and multicyclic ring systems [2]. The first  $\beta$ -lactam antibiotic was 'penicillin G' in the beginning of 1940s [1]. Afterwards, naturally occurring penicillin was 'penicillin V' which was an oral formulation, still in use for the therapeutic purposes. Followed by the occurring resistance to the penicillin, semi-synthetic penicillins were developed such as methicillin [20]. Moreover, some of the significant penicillins from the beginning up to date are the following: oxacillin, cloxacillin, ampicillin, nafcillin, amoxicillin, carbenicillin, ticarcillin, piperacillin, termocillin and mecillinam [20].

Cephalosporins are another subgroup of  $\beta$ -lactam antibiotics, and the first penicillinase-stable cephalosporin was discovered during 1950s [21]. It was efficient for the treatment of infectious diseases mainly caused by penicillinase-producing pathogenic bacteria [22]. Numerous cephalosporins are in use nowadays including cefotaxime, ceftriaxone, cefepime, ceftazidime and cefuroxime [23]. A new addition has been made to the cephalosporin family with a siderophore-substituted cephalosporin (S-649266) that contains a catechol segment which facilitates entry into bacterial cells through iron transportation system. Moreover, this cephalosporin is stable against several carbapenemases [24].

Furthermore, carbapenems are also members of the  $\beta$ -lactam antibiotics which act by binding to penicillin-binding proteins and lead to the inhibition of bacterial cell-wall synthesis. However, they have broader spectrum than other cephalosporins and have been proven successful against *Enterobacteriaceae* including ESBLs [25]. Carbapenem-related agents and other carbapenems that have extended-spectrum activity include meropenem, imipenem, ertapenem and doripenem which have been used widely [1].

Finally, at molecular level, it is worth noting that there is a peptidoglycan layer which is critical for bacterial cell-wall structural wholeness and stability, particularly in Gram-positive organisms, being the outermost and primary component of the wall [26]. During the final stage formation of the peptidoglycan, there is a transpeptidation step catalysed by DD-transpeptidases which are PBPs.  $\beta$ -lactam antibiotics inhibit these PBPs and ultimately lead to cell lysis [27]. It should be noted that PBPs are classified according to their molecular mass: the first category is low-molecular-mass PBPs that are monofunctional, for example, D-Ala-D-Ala carboxypeptidases; the second category is high-molecular-mass PBPs that are bifunctional enzymes containing a transpeptidase (D-Ala-D-Ala-dependent) and a transglycosylase [1, 28, 29].

### 3. Specific cases of resistance to $\beta$ -lactam antibiotics

In most instances, particularly in case of life-threatening bacterial infections, antibiotics are the core of treatment [19]. Two of the main goals of  $\beta$ -lactam antibiotics are prevention and treatment of bacterial infections occasioned by susceptible bacteria [1]. Antimicrobial resistance has a greater risk for critically ill patients. For example, it is well known that ICUs are facing a major problem with  $\beta$ -lactam antibiotics [30]. Moreover, many case studies have been reported issues intensively with regard to resistance to the  $\beta$ -lactam antibiotics. A recent case was reported about extensively drug-resistant (particularly  $\beta$ -lactams) *Escherichia coli* (*E. coli*), which was isolated from the urine of a 63-year-old man from Phetchabun, Thailand. A craniotomy resulted that it is also difficult to treat infections like this via  $\beta$ -lactam antibiotics [31]. Another case was reported from an 87-year-old woman, who had clinical signs, for example, fever, dysuria and suprapubic pain. Urine culture produces a positive result for *Klebsiella pneumoniae* and *E. coli*, both resistant to multiple antibiotics including  $\beta$ -lactams [32].  $\beta$ -lactam resistance can be seen in serious infections such as cystic fibrosis. Pollini and coworkers reported that a metallo- $\beta$ -lactamase-producing *P. aeruginosa* identified in a cystic fibrosis patient was resistant to carbapenems [33]. Furthermore, New Delhi  $\beta$ -lactamase-1 (NDM-1) producing *Enterobacteriaceae* infections have been found in patients suffering from type 2 diabetes mellitus infections [34]. Bacteria that produce NDM-1 have been dealt with resistance also in other classes of antimicrobials and virulently restrict treatment options [34].

It is important to note that the clinical outcomes in patients with *P. aeruginosa* infection are poor, with a case fatality rate being higher in patients with MBL-producing *P. aeruginosa* [35]. A recently approved antibiotic is ceftolozane (cephalosporin), which is a combination with tazobactam, has shown a potent activity and has been used successfully for treatment of the urinary tract and intra-abdominal infections [36]. Furthermore, there was a report from an organ transplant unit where a 61-year-old lung transplant patient in Chicago had *Serratia marcescens* (*S. marcescens*) infection with imipenem resistance. Since beta-lactam antibiotics could not be used, several antibiotics were prescribed instead such as trimethoprim-sulfamethoxazole, itraconazole, ceftriaxone, cefepime and levofloxacin; this is clearly a costly exercise [37].

There is an observation that patients at a high risk for developing colonization with  $\beta$ -lactam resistance include both the severely ill and well-on patients. Likewise, patients with medical



devices like urinary catheters are also prone to antibiotic-resistant bacteria [38]. Moreover, the length of hospital stay is another risk factor; patients who have stayed more than 3 days in hospitals and who have been previously treated with  $\beta$ -lactam antibiotics might be considered as a risk factor for the acquisition of  $\beta$ -lactamase resistance [39]. Furthermore, it has been reported in Italy that the risk factors for ESBL-producing *S. marcescens* and *K. pneumoniae* acquisition in neonatal ICU include low birthweight, gestational period and the use of invasive devices [40].

Further observations have noted that clinical isolates that have ESBL-produced *E. coli* strains occur generally in hospitalized patients exposed to invasive procedures [41]. It is also noted that when antibiotics are cheap and accessible, this encourages their overuse and subsequent resistance [42]. It has been reported that there is a positive relationship between antibiotic consumption and the emergence and spreading of resistant bacterial strains. One of the most significant reasons of this is the lack of enforcement of legislation which result in the sale of antibiotics without a prescription in many countries [43].

#### 4. Factors and mechanisms involved in resistance to $\beta$ -lactam antibiotics

Clinicians can prescribe beta-lactams without a real need; yet the health condition could have been treated by diet or rest. Sometimes, the consumers can take drugs without a medical advice or can take more doses than prescribed doses because of mental illnesses like Alzheimer's disease or dementia. Though some people know that antibiotics are used against bacterial infections, few are aware that antibiotics are not useful for viral infections [44]. When antibiotics are used in viral infections, they can trigger bacterial resistance while infections are not cured because of their viral background. Clinicians, surgeons, patients, consumers and caretakers as well require up-to-date information about the appropriate usage of  $\beta$ -lactam antibiotics because their misuse can cause severe conditions including bacterial resistance or allergic/toxic side effects [45].

It should be remembered that resistance to penicillin was noted in early 1940s; this finding has no clinical significance until the 1970s [20]. However,  $\beta$ -lactam resistance became a global crisis nowadays [46]. Resistance to the  $\beta$ -lactams usually occurs by three different mechanisms: decreased access of antimicrobials to the target PBPs (efflux pumps), altered PBPs (affinity of binding decreased) and  $\beta$ -lactamase production [1].

Although efflux pumps are found in almost all bacterial species, the  $\beta$ -lactamase production is the most efficient of the three mechanisms. This resistance mechanism generally depends on plasmids that include various virulence genes consisting of multiple  $\beta$ -lactamases of different classes in this way. This is why  $\beta$ -lactamase resistance can sprawl among various bacterial species. There are two types of  $\beta$ -lactamases: (a) serine- $\beta$ -lactamases and (b) MBLs. Serine- $\beta$ -lactamases comprise ESBLs and carbapenemases that hydrolyse carbapenem antibiotics and cephalosporins [2, 20]. We can suffice to say that the most common mechanism for drug resistance to  $\beta$ -lactam antibiotics is bacterial synthesis of  $\beta$ -lactamases. Many bacteria synthesize beta-lactamases that degrade beta-lactam antibiotics before they reach the cell wall. Gram-positive bacteria that produce beta-lactamase excrete the enzyme into the

extracellular space. Gram-negative bacteria excrete beta-lactamase into the periplasmic space located between the cytoplasmic membrane and the outer membrane, where the cell wall is located; while the genes that encode beta-lactamases can be located on either (a) the bacterial chromosome; (b) plasmids; or (c) transposable elements which enhance the spread of beta-lactamases among different bacterial species [47].

Carbapenemases are distinct among the  $\beta$ -lactamases; they are able to hydrolyse most of the penicillins, cephalosporins and carbapenems. In 1980s and 1990s, carbapenems were considered as the 'last resort antibiotics' which used primarily against ESBL- or AmpC-producing bacteria. Molecular classes of A, B and D  $\beta$ -lactamases are known as carbapenemases. The carbapenemase resistance generally occurs in bacteria involving OprD porin loss, overexpression of efflux systems, overproduction of AmpC-type  $\beta$ -lactamase and acquisition of carbapenemase-encoding genes [46]. A and D enzymes are the group of carbapenemases having serine-based hydrolytic mechanisms; however, the group of B carbapenemases are known as MBLs [48]. Also, MBLs are inhibited by chelate-divalent cations like EDTA. The group A carbapenemases include members of the *S. marcescens* enzyme (SME), imipenem-hydrolysing- $\beta$ -lactamase (IMI), not metallo-enzyme carbapenemase (NMC), Guiana-extended-spectrum (GES) and *K. pneumoniae* carbapenemases (KPC) families and their hydrolytic mechanism requires their active serine site at position 70 [37]. This feature gives them the ability to hydrolyse many  $\beta$ -lactam antibiotics like carbapenems, cephalosporins, penicillins and aztreonam, and all are inhibited by clavulanate and tazobactam [37]. SME-1 was first reported in England from two *S. marcescens* isolates. SME-1 has identical features with SME-2 and SME-3. SME-3  $\beta$ -lactamases differentiate from SME-1 gene by a single amino acid substitution of tyrosine for histidine at position 105 [49], and SME-1 is encoded by chromosome in *bla*<sub>SME-1</sub> gene [37]. Since chromosomally encoded *bla*<sub>SME-1</sub> gene was not detected in any plasmids, mobile genetic elements can be concluded that there is a limitation of SME-1 enzyme distribution [50]. The IMI and NMC-A enzymes have been found in clinical isolates of *Enterobacter cloacae* from the United States, Croatia, Finland and France. Most *bla*<sub>IMI-1</sub> genes are located on chromosome and it is related to *imi-R* gene that limits their dissemination and their expression at a high level [51]. NMC-A and IMI-1 have 97% amino acid similarity and they are similar to the SME-1, with approximately 70% of amino acid identity encoded by bacterial genome B [52]. The GES family enzymes consist of 26 variants of GES. For example, GES-1 was reported from *K. pneumoniae* strain in year 2000. The other GES enzymes are the following: GES-2, GES-4, GES-5, GES-6, GES-11, GES-14 and GES-18 are able to hydrolyse imipenem. Among these enzymes, GES-2 and GES-5 have carbapenemase activity. *K. pneumoniae* carbapenemases are another carbapenemases, identified in *K. pneumoniae*. These enzymes are known as one of the most significant enzymes due to their effectiveness to the carbapenems [53].

OXA-type  $\beta$ -lactamases include Group D carbapenemases and OXA referred to oxacillinases since they hydrolyse isoxazolyl penicillin oxacillin [51]. Nowadays, OXA-type enzymes contain over 400 enzymes. With regard to their amino acid sequences, OXA-type enzymes have 12 subgroups accommodating OXA-23, OXA-24/40, OXA-48, OXA-51, OXA-58, OXA-134a, OXA-143, OXA-211, OXA-213, OXA-214, OXA-229 and OXA-235 [54]. In spite of OXA enzymes that were generally detected in *Acinetobacter* species, these enzymes were started to be reported in other *Enterobacteriaceae* members such as *Salmonella* spp. and *P. aeruginosa*; this showed that OXA-type  $\beta$ -lactamases can spread to the *Enterobacteriaceae* members [54–56].

ESBLs are implicated in serine  $\beta$ -lactamases [48]. ESBLs are able to hydrolyse extended-spectrum cephalosporin; thereof they are active against the  $\beta$ -lactam antibiotics such as ceftazidime, ceftriaxone and oxyimino-monobactams. ESBLs are generally produced by Gram-negative bacteria including *Enterobacteriaceae* such as *E. coli* and *K. pneumoniae* [57]. The types of ESBLs are TEM-  $\beta$ -lactamases, SHV- $\beta$ -lactamases and CTX-M-type  $\beta$ -lactamases. TEM-type ESBLs are originated from TEM-1 and TEM-2; however, the number of TEM-type ESBLs is over 100. The most prevalent TEM-type ESBLs were detected in *E. coli* and *K. pneumoniae* [58]. SHV-type ESBLs are more widespread according to the TEM-type ESBLs and more than 100 SHV-type ESBLs are known around the world mainly reported from *Enterobacteriaceae*, *P. aeruginosa* and *Acinetobacter* spp. CTX-M-type ESBLs have the ability to hydrolyse cefotaxime and cefepime. In contrast to TEM and SHV enzymes, CXT-M-type ESBLs have no point mutations in their structures [58]. Until today, 128 different types of CTX-M were reported such as CTX-M-1, CTX-M-2, CTX-M-8, CTX-M-9 and CTX-M-25. Likewise, the type of CTX-M-15 is the most prevalent in *E. coli* strains [59].

The class B MBLs can be divided into four subclasses according to their structure: (a) B1aVIM, imipenemase (IMP), DIM, SPM; (b) B1b: NDM, (c) B2: cphA, (d) B3: LI and AIM [37, 60]. Moreover, Tripoli metallo- $\beta$ -lactamase (TBM-1) was also included in MBLs [58, 61]. The earlier MBLs were reported in Japan in 1980s called imipenemase in *P. aeruginosa* [62]. After that, several varieties of IMP were reported such as Verona integron-encoded metallo- $\beta$ -lactamase (VIM) and SPM-type enzymes and it was reported that VIM-producing bacteria are distributed intensely [63]. The New Delhi metallo- $\beta$ -lactamase is a globally distributed enzyme discovered of late. NDM was reported for the first time in year 2009 and referred to as NDM-1. NDM-1 can bind and hydrolyse all beta-lactams with the exception of aztreonam. There are 13 different NDMs reported: NDM-1 to 14. The variation of these NDM types results from mutation within the gene encoding the  $\beta$ -lactamase [64]. #NDM-1 has drawn attention since the gene encoding these MBLs is located in a mobile genetic element and the pattern of spread proves to be more complex [65]. NDM can coexist with other antibiotic-resistant genes. Recently, plasmid-mediated NDM was reported in Thailand and coexisted with colistin resistance [31]. Co-carriage of ESBL, AmpC and NDM-1 genes among carbapenem-resistant *Enterobacteriaceae* in India [66] was reported. There are several MBL types reported occasionally. For instance, GIM-1 MBL was reported in a clinical isolate (*P. aeruginosa*) in Germany in year 2002, firstly. In recent years, GIM-1 was started to be reported in other bacterial species such as *S. marcescens*, *E. cloacae* and *Acinetobacter pittii* [60, 67]. Similarly, SIM-1 was obtained uncommonly and an integron-encoded blaSIM-1 was reported from *Acinetobacter baumannii* in Korea firstly [68]. Moreover, TMB-1 was reported in an *Achromobacter xylosoxidans* strain isolated from a hospital environment sample in Tripoli, Libya [69].

## 5. Toxicity of $\beta$ -lactam antibiotics

There are several  $\beta$ -lactam antibiotics, and they have various side effects (**Table 1**). Although it is very hard to gather data on all the adverse effects and present them in this section, a description of toxic side effects known to be associated with the use of this category of antibiotics is subsequently presented.



Antibiotic	Adverse/side effects	Toxicity grade	Populations-circumstances	Type of study	References
Cephaloglycin	Nephrotoxicity	Moderate	Rabbit kidney extracts	Experimental	[13]
Imipenem	Nephrotoxicity	Severe	Rabbit kidney extracts	Experimental	[13]
L-695,256 is a novel 2-fluorenonyl carbapenem	Haemolytic anaemia	Moderate	Rhesus monkeys	Experimental	[70]
L-695,256 is a novel 2-fluorenonyl carbapenem	Regenerative anaemia	Mild	Squirrel monkeys	Experimental	[70]
Penicillin	Epileptic seizures	Moderate	Rats	Experimental	[71]
	Hemorrhagic cystitis	Moderate	Infection patient adult	Case	[88]
Piperacillin	Nephrotoxicity	Moderate	1200 patients	Randomized control trial	[83]
	Convulsion	Mild	Schizophrenic adult, ECT taken	Case	[72]
Cefotiam	Convulsion	Mild	Schizophrenic adult, ECT taken	Case	[72]
Cefuroxime	Retinal toxicity	Mild	Cataract patient adult	Case	[73]
Cefazolin	Nephrotoxicity	Mild	Hospitalized adult infectious patients	Case-control	[81]
Ceftriaxone	Nephrotoxicity	Mild	Hospitalized adult infectious patients	Case-control	[81]
	Genotoxicity	Moderate	Human lymphocytes	Experimental	[85]
Amoxicillin	Genotoxicity	Severe	Human gastric cells	Experimental	[86]
FCE 22891 a penem antibiotic	Urotoxicity	Severe	Rats	Experimental	[87]

**Table 1.** Illustrative adverse effects of  $\beta$ -lactam antibiotics.

The use of  $\beta$ -lactam antibiotics has been linked to triggering allergic reactions like urticaria, bronchoconstriction, also severe conditions like immune-mediated haemolytic anaemia and intravascular haemolysis [70]. It is known that some  $\beta$ -lactam antibiotics are neurotoxic, some are nephrotoxic, some are genotoxic and some are toxic to urogenital system.

Neurotoxic side effects of  $\beta$ -lactam antibiotics are well-known conditions for decades. The administration route and the dose of antibiotic are important factors that determine whether a neurological dysfunction would occur.  $\beta$ -lactam antibiotics can trigger epilepsy or seizures because of their chemical structures of  $\beta$ -lactams that make them capable of binding to the gamma-aminobutyric acid (GABA) receptors in the brain. Some of the  $\beta$ -lactams are GABA receptor antagonists [7]. This is the reason why penicillin injection can be used as an epilepsy model in rats [71]. In a case report, it was proposed that  $\beta$ -lactams triggered a tardive seizure in a patient after an electroconvulsive therapy [72]. It has been noted also that the retina is a target for neurotoxic pathologies. In a case report after the cataract surgery, cefuroxime

was given in normal dosing ranges but it induced a retinal toxicity; fortunately, the resulting visual loss was recovered after a week [73]. Neurotoxicity induced by  $\beta$ -lactams can be a result of renal failure, which increases the amount of the antibiotic in the circulating blood. Hence, even in normal dosing ranges,  $\beta$ -lactam antibiotics pose risks in case of renal failure [74]. The relationship between the nervous system and  $\beta$ -lactams is not just the toxicity, but the molecular interaction may also have positive consequences.  $\beta$ -lactams may have neuroprotective roles in some instances [75]. The molecular glutamate mechanism takes place for that protection [76]. Also,  $\beta$ -lactams can help in treating ischaemic rat brain during the acute phase [77]. The effect of  $\beta$ -lactams on the glutamate receptors affects the lab animals' behaviour. Rats' dependence on alcohol and morphine may be decreased with the  $\beta$ -lactam application [78–80].

Nephrotoxicity is a very serious side effect of antibiotics generally.  $\beta$ -lactam antibiotics are both dangerous as a mono therapy or as a combination therapy agent [81]. These chemicals induce toxicity in kidneys via a couple of molecular mechanisms. Tubular cells are under threat because of the excess active transport from blood to these cells; however, less efflux and accumulation happens. The other mechanism is acylation of target proteins, which cause respiratory arrest by inactivation of mitochondrial anionic substrate carriers in cells. The other nephrotoxic side effects occur via lipid peroxidation of renal cortex [11, 82]. For critically ill patients, it is very dangerous to use antibiotics such as tazobactam with piperacillin because of the toxic effect on renal tubule [83].

Genotoxic effects of some  $\beta$ -lactams have been shown in some studies done in vitro. Ceftazidime is toxic to bone marrow stromal cells via DNA polymerase inhibition [84]. Ceftriaxone genotoxicity was shown in human peripheral blood lymphocytes, while amoxicillin genotoxicity was studied with both human lymphocytes and gastric mucosa cells resulting in  $\beta$ -lactams having genotoxicity risk [85, 86].

Also,  $\beta$ -lactam antibiotics have toxic effects on the urogenital system. A synthetic  $\beta$ -lactam caused urothelial hyperplasia in rats but scientist suggested that chemical is not toxic to human [87]. In a case study, it has been reported that penicillin-G induced haemorrhagic cystitis, but the patient recovered in 8 days [88]. Some of the  $\beta$ -lactams toxicity grades and possible adverse effects were shown in **Table 1**.

## 6. Strategies to overcome $\beta$ -lactam antibiotic-triggered toxicity

After any toxic reaction in an organism, the resulting defects could be very severe and cannot be reversed; hence, there is a need for special care for recovery. When it is established that there is no recovery, substituting the toxic chemical or product can help reduce the risk of side effects.

The potential strategies to overcome  $\beta$ -lactam antibiotic-triggered toxicity are as follows:

1. Replacing the toxic  $\beta$ -lactam with a non-allergic/toxic one,
2. Using phage therapy instead of chemicals,

3. Using  $\beta$ -lactamase inhibitors,
4. Using other chemicals in combination with  $\beta$ -lactams,
5. Performing a dialysis (for very severe cases),
6. Rational drug prescribing and treatment monitoring.

In implementing the substitution strategy, one way is to use other available  $\beta$ -lactam antibiotics for clinical use called ESBLs such as cephalosporins, carbapenem, imipenem, monobactam and aztreonam [2]. Another strategy is designing/choosing a  $\beta$ -lactamase inhibitor which makes it possible to use a smaller dose of or a mild  $\beta$ -lactam. Clavulanic acid, tazobactam and sulbactam are known inhibitors that are used for this purpose [2, 89].

With regard to phage therapy, it has always been an alternative to the antibiotics; however, the concerns about the production cost have made it difficult. The phage therapy has been kept on the shelves for decades: a less toxic option which was as effective as antibiotics [90]. But it is nowadays on the table as a potential replacement for  $\beta$ -lactam antibiotics in the near future. It has been successfully applied to cultured African catfish, which were infected by *P. aeruginosa* and positive results have evaluated, while there was a resistance for  $\beta$ -lactam antibiotics [15], and phage therapy may be a logical substitute for  $\beta$ -lactam antibiotics in the near future.

With regard to combination strategy,  $\beta$ -lactam antibiotics have been used with aminoglycosides and they created a synergistic effect, which helped to reduce the doses required for both groups. This strategy has been able to increase the efficiency of the  $\beta$ -lactam antibiotics [91–94]. But clinicians should be aware that, because of a possibility of unexpected adverse effects, dialysis facilities should be available [95].

With regard to rational prescribing, clinical teams including doctors, nurses and pharmacists need to work hand in hand in order to select, purchase, control, restrict and ensure that patients are prescribed  $\beta$ -lactam antibiotics only when needed and that the patients must be counselled on the appropriate use thereof. Considering preventive medicine perspective, it is cheaper trying to limit the misuse/abuse of  $\beta$ -lactam antibiotics.

## 7. Concluding remarks

The above review has highlighted that  $\beta$ -lactam antibiotics are a group of products that have a chemical structure characterized by a  $\beta$ -lactam ring and are one of the most common antibacterial agents. However, due to inappropriate use including abuse and misuse, resistance to the  $\beta$ -lactam antibiotics is currently a global crisis. It usually occurs by three different mechanisms: decreased access of antimicrobials to the target PBPs (efflux pumps), altered PBPs (affinity of binding decreased) and  $\beta$ -lactamase production.

Moreover, even when used appropriately, they have been linked to triggering allergic reactions like urticaria, bronchoconstriction, also severe conditions like immune-mediated haemolytic anaemia and intravascular haemolysis [70]. It is known that some  $\beta$ -lactam antibiotics

are neurotoxic, some are nephrotoxic, some are genotoxic and some are toxic to urogenital system. Several factors are involved in the occurrence of toxic effects including the dosage and the renal status. Several strategies to overcome  $\beta$ -lactam antibiotics triggered toxicity include rational prescribing, substitution combination and phage therapy which seems promising. Public health education for clinical teams and patients is essential in ensuring that this group of antibiotics are retained in therapeutics.

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