

Beta-lactamases and their Global Health Implications-Two: Resistance Profile and Global Health Risk

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Abstract

Beta-lactamases are enzymes produced by some bacteria, which makes them resistant to β -lactam antibiotics such as penicillins, cephalosporins, cephamycins and carbapenems. In this article, global health implications, resistance profile and treatment options were reviewed. Extended-spectrum β -lactamases produced by enterobacteria and methicillinases produced by Staphylococci have been shown to constitute the growing strains of bacteria that confer resistances to all β -lactam agents to many non- β -lactam antimicrobials, including fluoroquinolones. Their continued detection in animal species and food products poses a great challenge to diagnosis and treatment of resulting infections, thus, emanating to serious global health implications. Although much works on β -lactamases have been directed towards the search for molecules which can inhibit these enzymes, the beta-lactamase producing bacteria are not leaving any stone to chance. Investigations targeted at identifying the carriers of these enzymes and intercepting their transmission will help curb the emergence and spread of the β -lactamases and their menace to public health.

Keywords: Beta-lactamase; *Escherichia coli*; *Staphylococcus aureus*; Epidemiology; Resistance; Health implications.

Introduction

One of the most important mechanisms of resistance in bacteria is the production of β -lactamases, which inhibit protein transpeptidases and carboxypeptidases participating in bacterial cell wall synthesis, thereby disrupting cell wall formation of the pathogen [1 - 3].

Much of work on β -lactamases over the past decades has been directed to the search for molecules that can resist β -lactamase-producing organisms, or which can inhibit these enzymes [4]. β -lactam antibiotics have recently been on the list of the most frequently prescribed drugs used worldwide in the control of *S. aureus* and *E. coli* infections, but the efficacy of these antimicrobials have suffered setback by the growing trend of multidrug resistant (MDR) strains of these β -lactamase-producing bacteria [5].

The present paper focused on resistance profiles and global health implications of β -lactamases, with overview of the control options. There was a renaissance in the therapy of bacterial infections in the late 19th century when the third-generation cephalosporins were first introduced into clinical practice in both human and veterinary medicine. But sooner than realised, after the development and widespread use of these oxymino-cephalosporins there was an emergence of extended-spectrum beta-lactamases in bacteria that hydrolyze both penicillins and the extended-spectrum cephalosporins and aztreonam [2, 4, 6]. These emergent resistant ESBLs in various bacterial organisms creating a huge public health concern worldwide. Resistance by β -lactamase-producing strains of Enterobacteriaceae against the extended-spectrum cephalosporins have widely been studied and documented in human isolates, and increasing reports in isolates from food-producing animals [7, 8], companion animals [9] and wildlife [10 - 12]. Resistance to β -lactam antibiotics by *E. coli* is by the production of extended-spectrum β -lactamases and AmpC type β -lactamases that confer resistance to the penicillins, cephalosporins and aztreonam, and cephamycins [2, 7]. The extended-spectrum cephalosporins-resistant strains of *E. coli* often carry integrons that encode resistance to fluoroquinolones and many newer antibiotics [13] which further sabotages therapeutic options.

S. aureus exhibit resistance to β -lactam antibiotics by the expression of a low-affinity penicillin binding protein (PBP2a) encoding the resistance gene, *mecA*, or by the production of the chromosomally-mediated β -lactamases [2, 3, 14]. The ability of β -lactamase-producing strains of *S. aureus* to exhibit multiresistance to antibiotics is largely determined by the location, kinetics, quantity Physiochemical conditions and interplay of the produced enzyme or expressed PBP2a [15, 16], and the capacity of the enzyme to hydrolyze the β -lactam ring of β -lactam antibiotics and inactivates them, thereby rendering the cells resistant to β -lactam antibiotics [17, 18].

Health Implications

The production of β -lactamase enzymes has been reported to be the most common cause of bacterial resistance to β -lactam antibiotics in both humans and animals. β -lactam antibiotics are widely used in humans and veterinary medicine to treat human and animal infections [19]. This wide spread use of these antibiotics could be associated with the selection of antibiotic resistance mechanisms in both pathogenic and nonpathogenic bacteria, as well as, the production of β -lactamases.

There are now well over 200 recognized ESBLs in a variety of Gram-negative bacteria, conferring resistance to penicillins, cephalosporins, monobactams and even carbapenems [4]. Extended-spectrum β -lactamases represent an impressive example of the ability of Gram-negative bacteria to develop new antibiotic resistance mechanisms in the face of introduction of new ones [8]. Plasmids responsible for ESBLs production frequently carry genes encoding resistance to other drug classes such as aminoglycosides, sulfanamides, chloramphenicol, rifampin, aminoquinolones or quinolones [8, 20]. The resistance plasmids can also be transferred to other bacteria, not necessarily of the same species, conferring resistance to them. Resistance plasmids or transposons have been reported to transmit multiple resistance traits among Enterobacteriaceae [21]. This implies that therapeutic options in the treatment of ESBLs-producing organisms are extremely limited [22 - 24, 8]. The use of extended-spectrum antibiotics have been said to exert a selective pressure for the emergence of ESBLs-producing bacteria. Involvement of many bacteria organisms producing ESBLs and the emergence of multiple β -lactamases-producing strains of some bacteria are of grave global health implication [25 - 27]. Organisms resistant to multiple antibiotics pose a special threat particularly among transplant patients [28]. The intestine of healthy animals is a reservoir for bacteria carrying CTX-M, mainly *E. coli*, and transmission to humans through the food chain have been emphasized [10]. The enzymes of CTX-M and SHV-12 family are implicated mainly in urinary tract infections [13]. Epidemic clones of these enzymes and their dissemination from a specific group of enzymes have been described to be through the mobile elements called integrons [13]. This implies possible dissemination of these β -lactamases from food animals to humans can occur, since both enzymes have been reported in healthy animals destined for human consumption including chickens [10]. Integrons are important, both in terms of the mechanisms of resistance and the dissemination of resistance genes with or outside the health care setting [29]. Integrons are also known to be associated with multiple-drug resistance in enteric organisms [30] and have been reported to be implicated in the dissemination of ESBLs in gram-negative bacteria [31 - 33].

The transmission of resistance between bacteria harboured within the gut can occur both horizontally through the movement of these mobile genetic elements (integrons), and vertically through proliferation and subsequent dissemination of resistant bacterial strains [34]. These mobile elements can thus diffuse resistance genes to many other antibiotics [20].

Resistance in bacteria isolated from food animals is in itself not a problem, but the possible transfer of resistance elements to zoonotic pathogens within the gut has serious public health implications [34]. The strain of *E. coli* producing CTX-M has been described as the most frequent cause of community-acquired urinary tract infections, and its increase is mostly due to the dissemination of IncK plasmids among *E. coli* isolates [35]. CTX-M β -lactamases, which show a high cefotaxime hydrolytic activity, constitute the most prevalent ESBL type found among clinical isolates of *E. coli* [36], and these enzymes have emerged as the most common type of ESBLs globally [37], and are therefore, of global health implications. TEM-52, SHV-2 and CTX-M-1 isolated from chickens and SHV-12 isolated from swine were observed to exhibit high clonal diversity, and contain transferable bla ESBL genes which might be acquired by humans via the food chain [38]. Infections caused by ESBL-producing strains of gram-negative bacteria have been on the increase, and were associated with higher morbidity and mortality in humans [13, 24, 39], particularly the worldwide growing carbapenemase-producing organisms [40, 41]. Treatments of such infections have been reported to be associated with high failure rates [8]. The possession of additional fluoroquinolones resistance by some ESBL-producing bacteria has further undermined therapeutic options.

Clonal outbreaks of CTX-M-15-producing Enterobacteriaceae, most frequently involving *E. coli* have been reported in France, Italy, Spain, Portugal, Austria, Norway, the UK, Tunisia, South Korea and Canada [42]. Plasmids encoding [bla.Sub CTX-M-15] have been reported from clinical isolates of *E. coli* in France, Spain, Portugal, UK, Canada, India, Pakistan, South Korea, Taiwan, The United Arab emirates and Honduras [43 - 45].

Infection caused by plasmid AmpC-producing isolates was said to significantly increase treatment failure at 72 hrs and that prior use of an oxyimino-cephalosporins is said to be a risk factor for infections caused by plasmid AmpC-producing Enterobacteriaceae [46]. AmpC β -lactamases are typically associated with broad-spectrum multi-drug resistance, which usually is a consequence of genes for other antibiotics resistance mechanisms residing on the same plasmids as the ESBL and AmpC genes [25].

Methicillinase-producing *S. aureus* strains have gradually become resistant to almost all hospital disinfectants, and bacteria which survive attacks by biocides

are becoming ultra-resistant super bugs [47]. Molecular studies of animal isolates of β -lactamase-producing *S. aureus* has demonstrated that MRSA producing the *MecA* gene had similar nucleotide substitutions at same positions in their *MecI* genes as those described previously in humans [48]. These alterations within the *Mec* genes of animal MRSA strains which are homologous to that occurring in human MRSA strains, signals a transfer of such genes between humans and animals, possibly through the food chain. The risk of transfer of MRSA from animals and animal products has been described [49], and the transfer of both resistance and genetic markers from poultry to humans has been reported [50], as well as, the transmission of MRSA between dogs and humans [51] and between humans and horses [52]. MRSA infections thus have zoonotic potential to portend serious human health dangers. Although Staphylococci isolated from animals are generally thought to be host-adapted, the MRSA similar to human epidemic cluster 257 was isolated from fistula of a dog in The Netherlands [53]. The MRSA transmitted to the community by foodstuffs such as chicken meat and cow milk, still has the potential of causing human infections [49].

A serious challenge facing clinical laboratories is that clinically relevant ESBLs-mediated resistance is not always detectable in routine susceptibility tests [25]; and most hospitals in rural settlements do not even use routine diagnostic tests for detecting resistant organisms, especially β -lactamase-producers [54]. Such laboratories may also lack the resources to prevent the spread of these resistance mechanisms. This lack of resources according to Thomson [25] is particularly responsible for a continuous failure to address the rapid global spread or dissemination of pathogens producing these enzymes.

Treatment and Control

ESBL-producing bacteria have shown some susceptibility level to cephamycins and carbapenems *in vitro* [55]. Some TEM and SHV type ESBL-organisms have *in vitro* susceptibility to cefepime and piperacillin/tazobactam, but both drugs have exhibited diminished susceptibility alongside inoculum effect [56]. Bacterial strains possessing some CTX-M-type and OXA-type ESBLs were resistant to cefepime on testing, despite the use of a standard inoculum [2, 4, 6]. AmpC-producing strains typically shown to resist oxyimino-cephalosporins and cephamycins were initially susceptible to carbapenems, but were however, shown resistant to the carbapenems due to loss of membrane porins [19]. Strains possessing IMP-, VIM- and OXA- type carbapenemases are said to be susceptible to aztreonam whilst resistance to non- β -lactam antibiotics is said to be common in strains making any of these enzymes, such that alternative options for non- β -lactam therapy needed to be determined by direct susceptibility testing [57].

ESBLs have been shown to exhibit *in vitro* resistance to cefotaxime, ceftazidime and aztreonam [1]. However, Infections caused by ESBL-producing *E. coli* and *K. pneumoniae* have been treated with the best outcomes in terms of survival and bacteriologic clearance using imipenem or meropenem[58]. But KPC-producing bacteria have been shown to inactivate carbapenems and other β -lactam antibiotics, and have also demonstrated typical resistance to trimethoprim-sulfamethoxazole, quinolones, and aminoglycosides, thereby making these pathogens truly multi-drug resistant [58]. Some resistance profiles are shown in table 1 below.

Similarly, the β -lactamases produced by *S. aureus* have shown resistance to a wide variety of β -lactam antibiotics and many non- β -lactam antibiotics as well [49,

59, 60]. However, some strains have shown *in vitro* sensitivity to vancomycin and teicoplanin[48, 53], But surprisingly, however, several newly discovered strains of methicillinase-producing *S. aureus* have been reported to resist vancomycin and teicoplanin[61]. This new evolution of β -lactamase *S. aureus* have been dubbed vancomycin-intermediate resistant *Staphylococcus aureus* or VISA [61]. Monitoring and control of extended-spectrum cephalosporins usage, and regular surveillance of antibiotics resistance patterns, as well as efforts to decrease the use of empirical therapy have been recommended to help control the spread of β -lactamase-producing organisms. The need for extensive research into plant materials that could elicit permanent activity against these growing β -lactamase-producing strains of bacteria is also a prerequisite.

Table 1: Antibiotics resistance profiles of some beta-lactamases previously reported

Bacterial species	Beta-lactamases	Resistance profile (*)	Reference
<i>E. coli</i>	CTX-M-1, CTX-M-2, CTX-M-14, CTX-M-15	A, Ac, Ce, Cx, No, Fx, St, K, T, C, G, At, Ct, Cp, Cz, CT, An	Vo et al., [62]
<i>K. Pneumoniae</i>	CTX-M-9-like	A, Ac, Cx, Cz, Ce, Pi, Tz, I, M	Woodford et al., [63]
	TEM-1, TEM-2	I, M, ce, Cz, Cx, Ct, At, Tz, G, A, Cp, Tg, Fx, Ax, Ti, Pi	Park et al., [46]
	OXA-1 to OXA-10	Fx, Cx, Cz, At, C, G, S, T, St, CT, cp, A, Ti, Pi, I, M, Ce, CtTz, Fx, CT, Cx, Cz, Ce, An, G, Cp	Monteiro et al., [64]
	SHV-1, SHV-11, SHV-12	I, M, Ct, At, Tz, G, Cp, Tg, Fx, A, Ti, Pi, A, CT, Cx, Ce	Mirzae et al., [6]
<i>Salmonella spp</i>	KPC-2, KPC-3	Cz, At, I	Jacoby and Sutton, [65]
	DHA-1,	Fx, CT, Cx, Cz, G, Cp, A, Ce, No,	Moland et al., [66]
	CMY-1, CMY-2, CMY-16	Pi, Tz, St, G, K, T, Ac, At, I	Briñas et al., [19]
	ESBL- <i>K. pneumoniae</i>	P, A, Co, Ct, Ce, G, T, C, O,	Luzzaro et al., [67]
<i>S. aureus</i>	AmpC- <i>E. coli</i>	Cd, A, Fx, Ct, Cz, At, Ce, Tz,	Song et al., [68]
	β -lactamase- <i>S. aureus</i> (not characterized)	A, Ti, Ac, Cf, Fx, Cz, P, A, Co, Ct, G, Ce, T, C, Ox, Ax, Cn, Cm, Cp	Akindele et al., [69]
			Yu et al., [70]
			Mamza et al., [60]

(*) A:ampicillin, Ac:amoxiclav, Ce:cefepime, Cx:cefotaxime, Fx:cefoxitin, No:Norfloxacin, St:Sulfamethoxazole-trimethoprim, K: Kanamycin, T: Tetracycline, C: Chloramphenicol, G: Gentamicin, Cz:Ceftazidime, Ct:Ceftriazone, CT:Cefotatan, At: Aztreonam, P: Penicillin, pi:piperacillin, Tz:Piperacillin/tazobactam, I:Imipenem, M:Meropenem, Cp: Ciprofloxacin, Ax: Amoxicillin, S: Streptomycin, An:Andriamycin, Ox:Oxacillin, Co:Cloxacillin, Cd:Cefamandole, Cf:Cefazoline, Cn: Cephalixin, Cm: Cefuroxime

Conclusion

Bacterial organisms have adapted to both broad-spectrum and β -lactam antibiotics by modifying substrate spectrum of common plasmid-mediated β -lactamases, and by mobilizing resistance-promoting chromosomal β -lactamase genes into plasmids, thereby enhancing their spread to new hosts. The persistence of β -lactamase-

producing bacteria in our healthcare centers and the emergence of same in the Veterinary field is a threat to both therapeutic and healthcare services. Although the precise cause and route of β -lactamase-producing strains into the Veterinary field could not be determined, it is clear that β -lactamases-producing bacterial strains do exist, and are being transmitted regardless of the use of β -lactam antibiotics in this field.

Also, the relative ease with which these bacteria organisms become resistant to newly developed antibiotics and the alarming global dissemination of β -lactamases highlights the need for continued epidemiological monitoring of these enzymes and prudent use of antibiotics. Investigations aimed

at identifying the carriers of β -lactamases and intercepting their transmission will play a vital role in curbing the emergence and spread of these β -lactamases and further enzymes and their menace to global health.

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