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A Review of Extended Spectrum β-Lactamase (ESBL) Producing *Klebsiella pneumoniae* and Multidrug Resistant (MDR) on Companion Animals

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ABSTRACT

Klebsiella pneumonia has become most successful and modern pathogen by producing Extended Spectrum β-Lactamase (ESBL). This pathogen can survive as a commensal and can be transferred to humans and animal. This gram-negative bacterium is major source of pneumonia and hospital-based infections. Epidemiological investigation of ESBL produced by Klebsiella pneumonia is main source of epidemic strains. This ESBL producing pathogen is a major clinical threat, involve high rate of morbidity and mortality. Development of novel antimicrobials are required for successful treatment along with infectious disease control. This mini review provides general overview about recent research carried out related to ESBL producing Klebsiella pneumonia. It also briefly shed a light on epidemiological investigation, transmission and possible treatment along with multidrug resistance.

Keywords: ESBL, *Klebsiella pneumoniae*, MDR, Companion Animals

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INTRODUCTION

In the last decade, worldwide prevalence of antibiotic-resistant β-lactam bacteria, such as cephalosporin-resistant Enterobacteriaceae, has increased rapidly in humans, various animal species and the environment [1]. The main causes of cephalosporin resistance are the production of extended spectrum β-lactamase (ESBL) and AmpC β-lactamase [2,3]. Drug-resistant microorganisms that are a problem that develop globally [4] Enterobacteriaceae that produce Extended spectrum β-lactamase (ESBL) have been reported worldwide since the early 1980s. The emergence of bacterial resistance is not only due to the evolution of microorganisms, but also because of excessive misuse of antimicrobial agents, which have speed up this process [5]. Antibiotic resistance genes appeared to originate from environmental bacteria, which effect microbiota in the environment. Excessive use of antibiotics for prophylaxis and curative treatment and release of human and animal microbiota containing resistance genes aggravate this situation [6].

ESBLs catalyze the hydrolysis of penicillins and cephalosporins. Gram-negative enteric bacteria that belong to the family Enterobacteriaceae have become resistant to this class of β-lactam agents by acquiring the ESBL gene and produce related enzymes. ESBL is widespread throughout the world, with more than 1.5 billion people colonized with ESBL-producing Enterobacteriaceae [7]. K. pneumonia shows high resistance to a broad spectrum of antibiotics including β-lactam antibiotics, fluoroquinolones, and aminoglycosides [8,9]. Transmission can involve transfer between bacteria from one host to another, by transfer of clones, or transfer of resistance genes, which are located in a mobile genetic material, between bacterial species that involve horizontal gene transfer, including pathogenic and non-pathogenic strains. These processes are influenced by the use of antibiotics in human medicine and veterinary medicine [10].

Right now, infections caused by Multidrug-resistant (MDR) K. pneumoniae have also become a major issue, because of higher morbidity, longer hospitalizations, increased mortality, and excessive health care costs compared with infections related to antibiotics, because of susceptible microorganisms [11,12]. Pet contact is related to ESBL-E transmission has been mentioned in previous studies [13], but little is known about mode of transmission. In this study we aimed to identify the ESBL-producing Klebsiella pneumonia and MDR in companion animals.

Microbiology Characterstics of *Klebsiella pneumonia*

Klebsiella pneumonia being a pathogen cause animal and human infections throughout the world, and these infections are linked with resistance to very important antimicrobial agents [14,15]. Recently, the World Health Organization (WHO) categorized the ESBL produced by K. pneumonia as a top priority pathogen. The genus Klebsiella belongs to the family Enterobacteriaceae and consists of Gram-negative pathogens with mucoidal aspects. The digestive tract of hosts from both animals and humans work as a reservoir and is often function as a source of infection [16]. The genus Klebsiella is categorized into four species: Klebsiella pneumoniae, Klebsiella oxytoca, Klebsiella terrigena, and Klebsiella planticola, with Klebsiella pneumoniae further consists of three subspecies, Klebsiella pneumoniae subsp. pneumoniae, Klebsiella pneumoniae subsp. ozaenae, and Klebsiella pneumoniae subsp. rhinoscleromatis [17].

Domestic animals infected by K. pneumoniae pose a threat to not only livestock productivity but can also cause danger to public health, because these animals provide reservoir for various K. pneumoniae strains, which have become resistant to drugs. Antibiotics can be used to treat the infections caused by K. pneumoniae, but these pathogenic bacteria can become resistant to these antibiotics. Food producing animals and environment are

important source of these resistant bacteria and has been considered as global health problem [18]. Surface water, wastewater, plants, soil and mucosal surfaces of mammals are important source of K. pneumoniae [19]. These virulence factors facilitate the occurrence of pneumonia, blood flow infections and pyogenic liver abscesses in mammals [19,20]. K. pneumoniae are gram negative pathogenic bacteria and cause diseases including pneumonia, urinary tract infections, bacteremia, burn and wound infection and pyogenic liver abscesses [21].

The pathogenic character of K. pneumoniae is due to the presence of various virulence genes which encode virulence factors and make it able to invade the immune system of mammals and produce different types of diseases. Most important virulence factors are formation of biofilm, hypermucoviscosity, synthesis of capsule, adhesion, absorption of iron and formation of lipopolysaccharides [22,23]. The pathogens belong to klebsiella species can make colonies on mucosal surface without exhibiting pathology. From mucosal surface, klebsiella can penetrate to surrounding tissues and produce lethal infections including pneumonia, UTI, blood flow infections and sepsis [24]. Neonates, elderly individuals, who have immune disorder are particular target of K. pneumoniae infection [25]. This strain of Klebsiella is highly virulent and has specific genetic characteristics [26].

Extended Spectrum β-Lactamase (ESBL), Multidrug-resistant (MDR), Epidemiology and Impact

Extended Spectrum β-Lactamase (ESBL

Gram-negative Enterobacteriaceae has become resistant to β-lactam antibiotics by producing β-lactamase specially ESBL and AmpC β-lactamase [27]. Being Gram-negative bacilli, Klebsiella pneumonia is cause of several clinical infections in humans [28] and rapid increase has observed since last decade because of excessive use of antibiotics and this resistant strain is cause of public health problem. Limited treatment options and high morbidity and mortality aggravate this problem [29]. Certain ecological aspects like soil, wastewater, animals and food products are also influenced by Klebsiella pneumonia. Source of infection in human is due to close contact with blood, saliva, feces and urine of

ESBL-carrying animals or consumption of contaminated water or food products [30].

Patients [31,32], healthy individuals from the community [33,34], meat [32,35], livestock [36,37], and companion animals [36] have been found to be infected with ESBL-producing enterobacteriaceae.

Transmission between humans and animals [10,38] can occur through the food chain [31,32], contact with livestock [39], or the environment [36].

Resistance developed against broad spectrum cephalosporins is due to common lactamases, most important among them are ESBLs and AmpC-type β-lactamases (AmpC).

Excessive clinical use of cephalosporins, carbapenems, and monobactams [40], which are new generation drugs has caused diversification among β-lactamases. Right now, β-lactamases has been classified into two categories. First class of β-lactamases based on the sequence of amino acids [41,42], whereas second class based on the activity. This class further divided into three groups:

Group 1: Cephalosporinases are encoded in genetic material of enterobacterales, that include AmpC, CMY, ACT, FOX and MIR. Many variants of this enzymes are present plasmids.

Group 2: This group includes serine bases β-lactamase and it represents largest group with broad spectrum of penicillins, cephalosporins, and carbapenems. Enzymes included in this group are TEM, SHV, CTX, OXA and KPC. Genes of these enzymes are situated in plasmids, which can be transmitted horizontally to other bacterial genera [43].

Group 3: This group includes metal based β-lactamases (MBLs) and depend on zinc. Examples are NDM, IMP, VIM and SPM enzymes [44].

ESBL genes belong to the CTX-M, TEM, and SHV families are most frequent and clinically relevant, whereas most dominant type of enzyme is CTX-M. On the basis of amino acids, CTX-M enzyme is divided into five groups: CTX-M-1, CTX-M-2, CTX-M-8, CTX-M-9, and CTX-M-25 [28]. Although K. pneumonia can produce all group of enzymes but emergence of carbapenemase, which is resistant to colistin [45,28] is cause of concern as far as public health issue is concern. Mobile genetic elements (MGEs) carry resistant genes and facilitate their transmission among bacterial species [30] and their presence increases the chances of K. pneumoniae based infections, which are quite difficult to treat clinically. ESBLs enzymes can hydrolyze encoded by various genes group can hydrolyze most of penicillins and cephalosporins. CTX-M is most important enzyme belong to this class. ESBLs and ESVs are most prevalent groups during recent times [46].

During past decade, throughout the world, presence of ESBL in several ecological niches, like contaminants in environment, commensal in humans and animals has been documented. These ecological niche work as reservoir and mode of transmission. Most common source of spread of ESBL is production animals, because they have direct link with food chain [47]. Acquisition of antibiotic resistant bacteria by host is source of infection, whereas in disease host-microbial interaction cause damage to host and disrupt homeostasis of host [48].

β-lactamase produced by enterobacteriaceae are commonly spread among animal and human populations. Number of risk factors are associated with the transmission of infection. To get knowledge about this transmission within and between animal and human can be an important point for intervention.

Transmission can be confirmed, if spatially related isolates from two individuals are identical with respect to bacterial species, plasmid types and ESBL genes. This is indication of hospital and household transmission of Enterobacteriaceae between humans [49-52].

Multidrug-Resistant (MDR)

Immediate attention is required to deal with the emergence of antibiotic resistant bacteria. Antibiotic resistance in animals is of great concern as far as public health is concern as these resistant strains or their resistant genes can transmit from animals to humans. It is difficult to treat the infections caused by antibiotic resistant bacteria and cause increase in mortality, prolonged hospitalization, which is associated with financial burden on society [53]. Because of continuous waste of antibiotic residues in environment, making it reservoir for bacteria, which are carrying resistant genes [54,55].

WHO recently acknowledged that emergence of antibiotics is a global issue of great concern for human, animals and environment [56]? In environment, some bacteria can

spread among various ecosystems. At the same time, there is an opportunity of exchange of resistant genes among various bacterial strains, thus result in the rise of resistance [57]. Number of studies have indicated that antibiotic/antimicrobial strains are present in different ecological niches [58,59].

Antimicrobial resistance (AMR) is because of excessive and misuse of antibiotics in the treatment of humans and animals and now it has emerged as a global health issue [43]. There is huge spread of bacterial infections, which are resistant to several drugs because of metallo-lactamase, carbapenemase, AmpC β-lactamase and ESBLs [60]. Resistance of microorganisms to antimicrobial drugs, which were initially sensitive called antimicrobial resistance (AMR). It is natural process and facilitated by excessive misuse of antimicrobials [5]. Gram negative pathogens have developed this resistance by developing enzymes which can destroy antibiotics, by having resistant metabolic pathways and by altering receptors for antimicrobial agents [61]. K. pneumoniae has developed two types of antibiotic resistance mechanisms. One mechanism involve expression of ESBLs, which develop resistance in bacteria to cephalosporins and monobactams. Second mechanism involve expression of carbapenemase, which help to develop resistance to all available β-lactams [62].

Because of the presence of ESBLs (SHV, TEM and C-TXM) genes encoded by plasmids in K. pneumoniae, resistance to different antibiotics has been developed [63]. Similarly, Klebsiella spp has also developed antimicrobial resistance, which is alarming situation in the area of human medicine [64]. This failure of antimicrobial treatment is safe for humans and animals [65,66].

In agriculture sector, use of antimicrobials are well known catalyst for developing resistance in bacteria [67], but unfortunately there is no reliable data and information available regarding the use of antimicrobials in animals [68]. It can be assumed that there is excessive use of antimicrobials in livestock sector as compared to pet animals. AMA most often in use in human medicine and there is risk of AMR because of close association between pets and humans and this association provide chances for two ways transfer of commensal and pathogen [68,69].

ESBL is β-lactamase which can hydrolyze oxyimino based β-lactams, like cefotaxime, ceftazidime and aztreonam [44]. It is well documents over the years that most of Klebsiella pneumoniae produce SH-based non-ESBL β-lactamase such as SHV, and some Escherichia coli produce TEM, which is also non-ESBL β-lactamase. Such enzymes like SHV-1 and TEM-1 can hydrolyze ampicillin, but oxyiminocephalosporins including ceftriaxone, cefotaxime and ceftazidime cannot be hydrolyzed. These antibiotics are well designed to resist hydrolysis by these bacterial enzymes [70].

Epidemiology and Impact

Because of physical proximity and close contact with their owners, pet animals have increasing become potential source for the spread of enterobaceriaceae. During current survey of infected dogs and cats in Europe, it has been observed that 1.6% are carrier of ESBL producing enterobacteriaceae in their feces. Although most of these infected dogs and cats carried blaCTX-M, but it is confirmed that these pets might be source of ESBL but may not mainly source of epidemic [71]. This data that can highlight risk associated with public health because microbiomas in intestine of these animals can act as a reservoir for the ESBL & AmpC, resistant genes, which have ability to get to humans [10,38, 72].

Transmission can take place not only through food chain [32,73, 74], but also can result from close contact between humans and animals [39, 75, 76]. Living and working on a farm, working in a slaughterhouse or working as a veterinarian can cause occupational exposure between humans and animals. In such situation's humans can come into contact with domestic animals at open house farming, zoos, or being an owner of these pet animal.

Human to human contacts, especially in the living areas, has also been suggested as a potential source of transmission of ESBL-producing Enterobacteriaceae. Acquiring infection from community in residential areas is very common in these situations [51]. This person to person transmission has also become point of discussion when medical personnel come in close contact with any infected person, but we are not going to this aspect in detail during this study. Most of studies so far address transmission of ESBL producing enterobacteriaceae in general population through person to person contacts

This suggests that patients who recover and discharge from any medical facility and unite with his family members may be an important source of transmission of ESBL-producing Enterobacteriaceae for his family members and even pets. It is speculated that patients and individuals who live or work in agriculture form can be an important source of transmission of ESBL-producing Enterobacteriaceae for other individuals [77].

Human and animal feces are main source of ESBL producing bacteria, through which these bacterial get introduced into the environment. People can get exposed to these infection producing bacteria because of recreation in contaminated surface fresh water, use of contaminated water for drinking purposes, aquatic and marine life and inhalation of bioaerosol. It has been studies in past that chances of contacting Salmonella spp or Campylobacter spp in recreational waters is almost same as to the risk of contracting an organism through chicken consumption [78,79,80].

There are increasing reports regarding the contamination of environment with ESBL-producing Enterobacteriaceae in both developing and advanced countries. In France, through longitudinal survey of various wastewater sources has indicated that ESBL-producing E. coli can be detected in most of samples, containing blaCTX-M, at a significantly higher amount in hospital wastewater than community wastewater [81, 82].

Treatment and Control Strategies

It is pivotal for future research to focus on sources and pathways which are involve in transmission in human, livestock and pet animals and their further elaboration is required.

There are increasing evidences of threats to human health posed by MDR bacteria from companion animals, and at the same time, we must assume responsibility regarding the efficient and effective use of antimicrobials. Current practices of antimicrobial use must be reviewed and analyzed and there must be a process of continuous improvement, which should be institutionalized in order to reduce, improve and replace antimicrobial use wherever it is necessary. Good practices may involve prevention of infection and implements ways to reduce the chances of infection. At the same time, there must be wise use of vaccines, improved ways of animal

management, detection and diagnosis of infectious diseases at their early stage.

Enterobacteriaceae colonizes in digestive tract and there is increase in antimicrobial resistance, which is of great concern in human medical science. Enterobacteriaceae was identified as cause of disease in pet animals in 1998 [83]. There have been many studies regarding the occurance of ESBL in companion animals [68] and the production of β-lactamases by species of commensal and pathogenic Enterobacteriaceae is quite common. [71].

Isolates found in both animals and humans are identical, which provides evidence that transmission between these two subjects is possible [84,71]. Transfer of resistant pathogens between human and animals highlights antimicrobial stewardship, and symbolically show the concept of "One Health". Transfer of isolates and secondary amplification in hospitals and community can cause outbreak of disease [85]. Human, animal and environmental are interlinked with each other, so issue of resistance of AMR among them should be focused equally [86]. Health care providers of human and animals are possible source of antimicrobial resistance and this issue of resistance must be addressed by combined efforts of these health care workers [85]. Mindful applications of antimicrobials included their limited use should be a permanent strategy. This tool would affect resistance, but it would not be completely eliminated.

Bacterial fitness is linked with resistance and it has been investigated that decrease in antibiotic use benefit to those bacteria that are fit, and this fitness help them to outperform resistant strains with the passage of time. Evolutionary compensation and co-selection of resistance to number of antibiotics cause limitation in the reversibility of resistance [87].

A source attribution model, which based on microbial subtyping data can be helpful to understand the determinants of resistance in humans. The rule behind this methodology is to draw comparison between genetic profile of bacteria present in various sources with those found in humans [88]. It has been noticed that similarity index among various isolates cannot be on the basis of sequence type, plasmid family and ESBL-gene alone, especially when isolates are not spatially related [89].

Although sequencing the entire genome can help to provide an excellent alternative, but

Question still exists, if it is more precise to find virulence and content of resistant genes, which is no doubt provide genetic backbone. These informations can help to trace sources of human infection based on subtypes of bacteria, distributed in various sources [88, 90].

Sources and pathways that are involve in the transmission of enterobacteriaceae among humans, between animals and humans has been explained in detail, but still further detail is required. Moreover, further details are required for determining number of infections caused by any specific pathway and source [91, 92, 93].

Conclusion

Human, animal and environment are interlinked with each other. Resistant bacteria develop and eventually spread. This can happen to both humans and animals. These bacteria transmit from person to person and animal to animal, person to animal and animal to person. These modes of transmission can pollute the water sources when human and animal excretions or waste enter these water bodies. Human and their companion animals can come into contact with each other or can ingest resistant bacteria. The resistant bacteria are often transmitted by humans and animals. These bacteria are then often exposed back to more antibiotics. Positive and very dangerous feedback then produces which leads to the very high levels of resistant bacteria found in many people and animals. Excessive use of antibiotics would result in increase of resistance. It is better to focus on human and animal health through better hygiene practices and infection control, so that they should have less chances of getting any infection and there would be minimum utilization of antibiotics and that can result in less chances of transmission of resistant bacteria.

Recent investigations about environmental pollution confirm that MDR has same source of transmission to human and companion animals by using various distribution routes. MDR involvement in Enterobacteriaceae is well established as an important part of world public health policy. This idea that animals are a good sentinel from MDR environmental pollution and argues the importance of the One Health Approach because these companion animals can significantly contribute indirectly to the transmission of resistant genes to other segment of environments.

Immediate efforts are required to deal with the emergence of antibiotic resistance in humans and companion animals. Antibiotic resistance in animals has becomes a public health issue, as there is transmission of antibiotic resistant bacteria, or their resistance genes, between animals and humans. β-lactam based antibiotics are important for the treatment of bacterial infections in human, and resistance to this type of antibiotics mediated by ESBL and AmpC β-lactamases has emerged in Gram-negative bacteria. Companion animals can play a role in the transmission of resistance genes to humans due to the high ESBL / AmpC-producing Enterobacteriaceae among their intestines.

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