A Retrospective Study on Extended Spectrum Beta-Lactamase Bacteria in the Philippines from 1999 – 2013

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ABSTRACT

The introduction of antibiotics has revolutionized the control of infections that remarkably reduced morbidity and mortality worldwide. Antibiotics have been the mainstay of treatment for many bacterial infections since their introduction in the 1940s. Through the years, the number and variety of antibiotics have increased due to the emergence of different bacterial infections. The challenge of antibiotic resistance is global. Many studies have been published showing the gravity of this problem both in the hospital and community setting. An important aspect of antimicrobial resistance (AMR) greatly affecting the medical community are the extended-spectrum beta-lactamase-producing organisms (ESBL).

Objective. The study aims to determine the prevalence, antibiogram, and genotypic characteristics of the different isolates of ESBL in the Philippines.

Methods. Available literature on ESBL in the Philippines from PUBMED and Herdin was collected, and additional microbiological data was gathered from the Philippine General Hospital (PGH). Ten studies and three annual ARSP reports of the 22 sentinel sites were included. The bacterial isolates and sensitivity to extended-spectrum antibiotics were collated and compared with each other.

Results. There is increasing prevalence of ESBL from 1999-2013. The proportion of ESBL *K. pneumoniae* and *E. coli* ranged from 10 – 43.24% and 4 – 20.9%, respectively. There was varying antimicrobial activity against antibiotics. Limited data on the genotypic characteristics of ESBL was reported.

Conclusion. The continued rise in ESBL resistance needs immediate action. Information on ESBLs is limited, particularly in the country. More studies need to be conducted to expand our knowledge of ESBLs.

Key Words: antibiotic, resistance, extended-spectrum, beta-lactamase, antimicrobial resistance, Escherichia coli, Klebsiella pneumonia

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Introduction

Antimicrobial resistance is the result of the natural process of microbial adaptation to the killing effects of various agents. However, the irrational use of antimicrobials speeds up the evolution of resistant microorganisms. Drug-resistant pathogens are commonplace across the world and some acquire resistance to more than one class of antimicrobials. The loss of effective standard treatment against infectious diseases forces the switch to second- or third-line drugs that, besides being more expensive, are associated with adverse reactions. Even if alternative treatment is available, resistant infections have been shown to increase the risk of dying, prolong illness, and increase the cost of healthcare.

In the early 1940s, the introduction of penicillin as an antibiotic cured most infections caused by *Staphylococcus aureus*. Since then, penicillin has been the most widely used treatment for a variety of infections. Resistant organisms emerged 2 years later and by the 1960s, approximately 80% of *S. aureus* isolates were penicillin-resistant.[1] This became an impetus to shift treatment strategies to methicillin. Currently, 90 to 95% of *S. aureus* strains throughout the world are resistant to penicillin.[2] Although still on the rise in Asia and Africa, a downward trend in hospital-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) attributable to improved infection control measures has been observed in the United States and Europe.[3-7] While the occurrence of community-acquired MRSA is increasing in many parts of the world including Africa, Asia, Latin America, and the U.S.

Recent achievements in the control of resistant gram-positive bacteria are in danger of being outweighed by the alarming expression of resistance among gram-negative pathogens.[4] Extended-spectrum beta-lactamase in *Enterobacteriaceae* is increasingly being reported worldwide. It has been shown to spread in both hospitalized and healthy individuals. Meanwhile, the spread of carbapenemase-producing bacteria such as imipinem-hydrolyzing beta-lactamase-1 (IMP-1) *Pseudomonas aeruginosa*, New Delhi metallo-protease-1 (NDM-1) *Enterobacteriaceae*, extensively drug-resistant *Acinetobacter spp.*, *Klebsiella pneumoniae* carbapenemase (KPC), or oxacillinase 48 (OXA-48) is alarming as it leaves the patient with limited to no treatment options. In the United Kingdom, carbapenem resistance in

Acinetobacter baumanii rose from 0% to 55% in a span of 6 years and resulted in higher death rates compared with non-resistant infections.[8]

The vicious cycle of transmission of drug-resistance in humans is compounded by the occurrence of AMR in the environment, particularly in animals and animal food products. Research has documented evidence of transfer of resistant microbes from animals and these microbes' ability to cause illness in humans. Ceftriaxone-resistant *Salmonella spp.* found in a herd of cattle after an outbreak in a family ranch was found to be identical to the strain that infected a 12-year-old child.[9] Conjugative transferability of MRSA from chickens to humans was observed in a poultry farm in the Philippines. The large-scale use of antimicrobials as growth promoters in animals is one major factor that favors the development of AMR.

This serious threat of AMR to human health is recognized worldwide. The World Health Organization declared AMR one of the top three global health issues. Actions geared toward AMR containment such as the banning of antimicrobials in agricultural practice, the improvement of infection prevention and control in the healthcare setting, and AMR surveillance programs were conducted in many parts of the world, especially in the U.S. and Europe. However, there are a dwindling number of antimicrobials in the production pipeline as pharmaceutical companies invest more resources in the development of drugs for non-communicable diseases.[2]

Antimicrobial resistance is also a local public health concern not only in terms of limited treatment options but also because of its economic burden on a developing country like the Philippines. The delay in effective therapy and increased morbidity results in longer hospital stays which, in turn, leads to higher healthcare cost and reduced productivity. Factors such as inadequate access to medicine, non-adherence of health providers to treatment guidelines, self-prescription among patients, and weak implementation of regulations for dispensing of antimicrobials favor the development of resistance.

In response to the danger of AMR, the Antimicrobial Resistance Surveillance Program (ARSP), a nationwide, hospital-based surveillance system, was established in 1988 to regularly monitor resistance of bacteria and provide critical input to the country initiatives against AMR. Susceptibility patterns of common pathogens implicated in diarrheal diseases, urinary tract and bloodstream infections, sexually-transmitted and hospital-acquired diseases from major hospitals are monitored annually.[10] At present, there are 22 sentinel sites participating in ARSP.

Major changes in the resistance patterns of bacteria are observed based on ARSP. Based on recent findings, the antimicrobial susceptibility pattern of *Neisseria gonorrhea* is consistent with the observation elsewhere in the world. Penicillin, tetracycline, and ciprofloxacin have lost effectiveness and only ceftriaxone and cefixime remain active against *N. gonorrhea*.[11] Methicillin resistance among *Staphylococcus aureus* continues to rise. Methicillin resistance was identified in 54.9% of *S. aureus* tested in 2012.[11] The resistance increased to more than twice the prevalence observed in 2004. In addition, the proportion of MRSA isolated from outpatient departments rose to 58.5% and may indicate crossing over of this nosocomial pathogen to the community as observed in other parts of the world particularly in the U.S. and Europe.[11]

For many years, gram-negative bacteria has become a notorious cause of severe infections in man, including sepsis, pneumonia, urinary tract infection, postsurgical infections in acute care hospitals, and intra-abdominal infections.[10] A recent increase in drug resistance among these organisms signaled the shift in the burden of antimicrobial resistance from gram-positive to gram-negative bacteria. Organisms producing extended-spectrum beta-lactamase (ESBL) pose a major therapeutic challenge since they are capable of hydrolyzing penicillins, broad-spectrum cephalosporins, and monobactams.[12]

Although the world prevalence of ESBL is not known, surveillance shows that it is present in almost every country in the world with varying frequency. Sixteen countries in a recent survey conducted in Europe reported a prevalence ranging from 85% to 100% of ESBL *E. coli* and *K. pneumoniae*.[12] In the U.S., 26,000 (19%) healthcare-associated *Enterobacteriaceae* infections are caused by ESBL-producing *Enterobacteriaceae*.[3] In the Asia-Pacific region, 42.2% and 35.8% of *Escherichia coli* and *Klebsiella spp.*, respectively, were extended-spectrum β-lactamase (ESBL) positive.[13] A multi-continental survey revealed that prevalence in Latin America is 45.4% to 51.9% among *K. pneumoniae* and 8.5% to 18.1% in *E. coli*.[14]

ESBL is more commonly found in *E. coli* and *K. pneumonia*.[15-17] However, research has shown that although relatively rare, other gram-negative organisms also exhibit ESBL activity. ESBL-producing *Enterobacter cloacae* was found in 16% of samples and was present in every country in the Asia-Pacific region.[15] ESBL genes were detected in *Enterobacter cloacae*, *Enterobacter aerogenes*, and *Enterobacter gergoviae* isolates from a Spanish hospital.[18] *Citrobacter koseri* and *Citrobacter freundii* harboring ESBL genes were described in India.[19] PER and VEB type ESBL was present in 70% of multi-drug resistant *Acinetobacter baumanii* in Iran.[20] *Proteus mirabilis* with ESBL has also been described in Croatia.[21] *Pseudomonas aeruginosa*,[22-24] *Salmonella spp.*,[25-26] *Shigella sonnei*[27], and *Vibrio cholera*[28] were likewise found to carry ESBL genes.

Most infections caused by ESBL microbes occur in hospitals, but research has shown that it is no longer confined to the healthcare setting. Outbreaks in nursing homes, geriatric centers, and rehabilitation units have also been reported.[29-31] Asymptomatic carriers have also been

found in the community. In the Netherlands, a country believed to have little AMR, ESBL was found in 8% of fecal samples of seemingly healthy urban-dwellers.[31]

The first plasmid-mediated beta-lactamase gene isolated in gram-negative bacteria is TEM and later SHV became apparent. A shift in the genotypic makeup of ESBL became evident at the start of the 21st century.[32] CTX-M enzymes replaced TEM and SHV mutants as the predominant ESBLs in many European countries.[33] The same trend is observed in South America and Asia.[14,34] It is only in North America where TEM and SHV variants remain the major ESBL type.[14,32]

Animals have also been implicated as playing a role in the transmission of ESBL.[35] In the Netherlands, 94% of retail meat samples contained ESBL *E. coli*, 39% of which was similar to isolates in humans.[36] The association of ESBL-positive *E. coli* with clinical disease was described in dogs with bacterial cholangiohepatitis in the United Kingdom.[37] However, the mechanism of ESBL transfer from animals to humans is not well explored in most research.

With the increasing problem of antibiotic resistance, particularly the emergence of ESBL-producing organisms, the study was conducted to determine the prevalence of ESBL in the Philippines. In addition, the antibiogram and genotypic characteristics of the different isolates were identified.

Methods

This is a retrospective study to determine the prevalence of ESBL in the Philippines from 1999 to 2013. A literature search was performed using PubMed and Herdin Neon databases through to November 2013 to identify local studies on ESBL in humans and animals. The search strategy used the terms "ESBL" or "extended-spectrum beta-lactamase". Studies were considered for inclusion if they reported on the prevalence, antibiogram, and phenotypic or genotypic expression of ESBL among isolates in the Philippines. Ten studies and three annual ARSP results from the 22 sentinel sites were included. Microbiologic data, particularly bacterial isolates and sensitivity to antibiotics, specifically on extended-spectrum antibiotics were gathered and analyzed. Microbiological data on bacterial isolates from a government tertiary hospital, the Philippine General Hospital (PGH), was also reviewed. These data were compared with the prevalence of ESBL in other ARSP sites.

Results

Prevalence of ESBL from ARSP sites (2000-2012)

There were seven local reports included in the study to determine the prevalence of ESBL. The ARSP composed of 22 sentinel sites nationwide reported resistance patterns and antibiograms. The distribution of ESBL resistance among the isolates from 1999 to 2012 were *K. pneumoniae* (53.16%), *E. coli* (29.87%) and *Enterobacter* (15.72%).[10,11,15,16,22,23,34,38-44] (Figure 1) The proportion of ESBL *K. pneumoniae* and *E. coli* ranged from 10 – 43.24% and 4 – 20.9%, respectively.[10,11,15,16,22,23,34,38-44] (Figure 2)

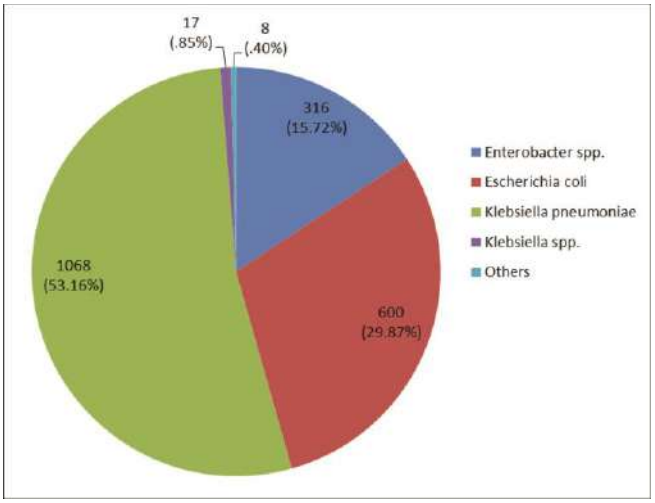
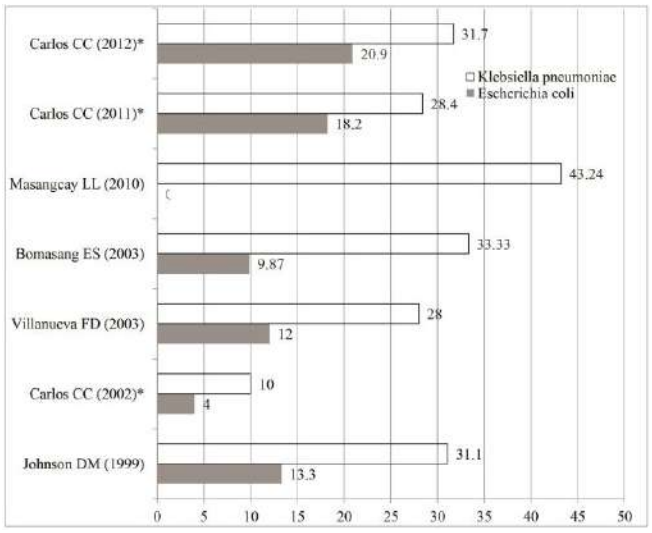


Figure 1. Distribution of ESBL Bacteria in the Philippines (1999-2012)



* using ceftazidime disk diffusion method to screen for ESBL suspects

Figure 2. Prevalence of ESBL *E. coli* and *K. pneumoniae*, Philippines, 1999-2012

ESBL activity was also observed in other bacteria. A study conducted in a tertiary hospital in National Capital Region (NCR) stated the presence of ESBL in 38.5% of *Klebsiella oxytoca*.[38] Antimicrobial susceptibility patterns of *Pseudomonas aeruginosa* strains from burn and intensive care units of a major tertiary hospital revealed ESBL in 5% of organisms tested.[22] *Citrobacter freundii, Proteus mirabilis,* and *Klebsiella ozasaenae* samples from the Philippines were also shown to harbor ESBL genes.[34,42] Further, a case report on

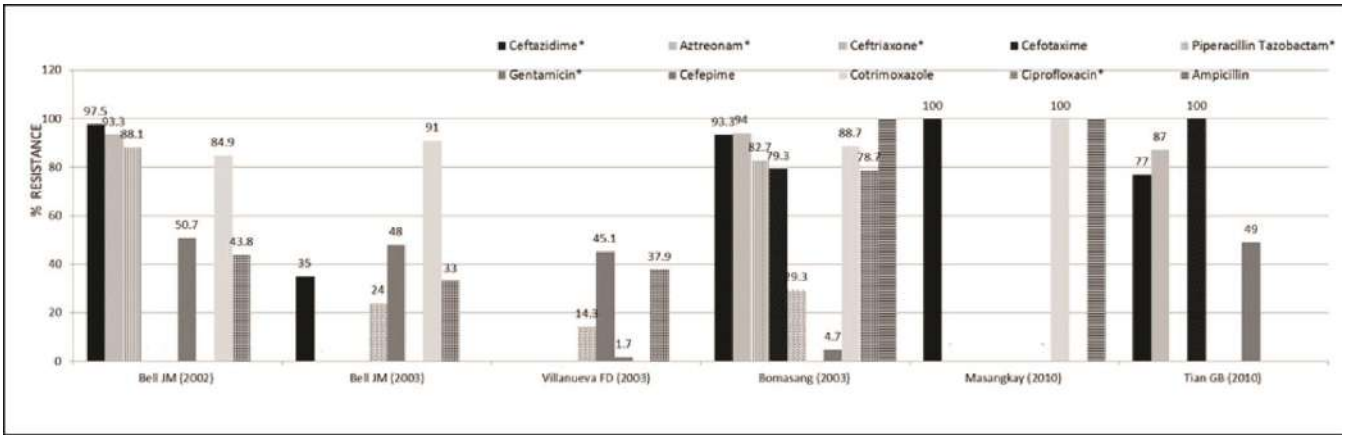


Figure 3. Resistance of ESBL bacteria in the Philippines (2002-2010)

the isolation of *Salmonella enterica* serotype typhi in a 54-year-old male who experienced diarrhea and fever shortly after travelling in the Philippines suggested the occurrence of ESBL-producing *S. enterica* in the country.[25]

ESBL infection was observed mainly in hospitalized individuals, including both adult and pediatric patients in wards, special units, and intensive care units. Urine, blood, and tissues or exudates are specimens in which ESBL-producing organisms have been isolated. There was no data on ESBL carriage among asymptomatic people in the community.

The susceptibility patterns of ESBL-producing organisms showed high resistance to ampicillin (100%), ceftazidime (35–100%), cefotaxime (79.3–100%), astrenonam (87–94%) and ceftriaxone (82.7–88.1%). Resistance was lowest with cefepime (1.7–49%) followed by piperacillin-tazobactam (14.3–29.3%).[15,16,34,38,41,43] (Figure 3)

Prevalence of ESBL in PGH (2013)

The microbiological records of 2,878 bacterial isolates from CSF, blood, urine, exudates, and respiratory samples taken from January to December 2013 in PGH were reviewed. Among *E. coli* and *K. pneumoniae* isolates, 13.2% and 23.3%, respectively, were ESBL positive. ESBL activity was also observed in *K. oxytoca* (13.5%), *P. mirabilis* (7.4%), and *K. ozasaenae*(0.5%) isolates (Figure 4). *E. coli* was most resistant to ceftazidime (86.25%), followed by aztreonam (72.5%), ceftriaxone (73.75%), and cefotaxime (17.5%). On the other hand, relatively low resistance to cefotaxime was observed among confirmed ESBL *E. coli* and *K. pneumonia.* In *K. pneumoniae* isolates, the highest resistance was seen against ceftazidime (91.83%), followed by aztreonam (82.88%), ceftriaxone (74.71%), and cefotaxime (18.29%) (Figure 5).

Other antibiotics were also tested against *E. coli* and *K. pneumoniae*. Gentamycin appears to be the least effective agent against ESBL *E. coli* at 80.9%. High resistance activity against penicillins such as ampicillin (55.9%), ticarcilin-clavulanic acid (47.4%), amoxicillin/clavulanate (40.1%) and cefazolin (23%) was observed. On the other hand, resistance to ampicillin-sulbactam (0.7%) and piperacillin-tazobactam (13.2%), cotrimoxazole (2%), and ciprofloxacin (1.3%) was low.

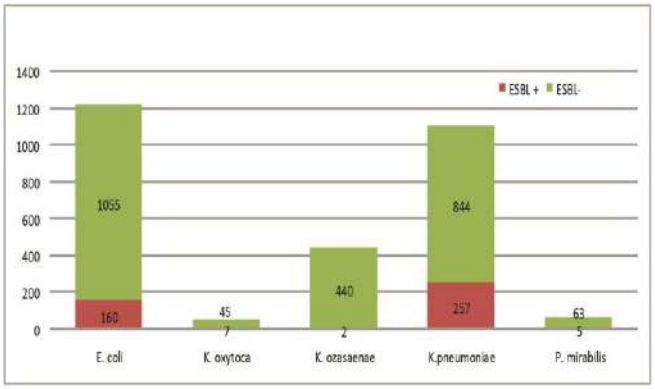
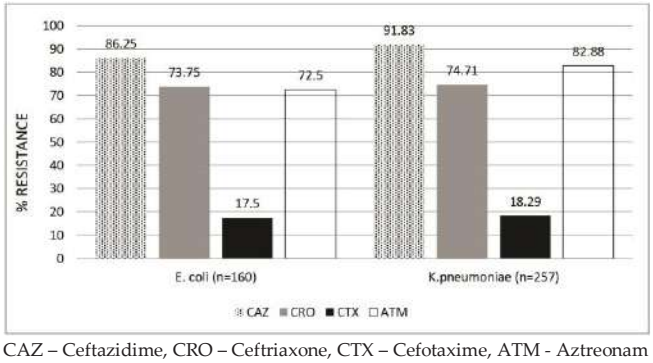


Figure 4. ESBL Isolates from the Philippine General Hospital, 2013



CAZ – Ceftazidime, CRO – Ceftriaxone, CTX – Cefotaxime, ATM - Aztreonam

Figure 5. Susceptibility Pattern of ESBL *E. coli* and *K. pneumoniae* to 3rd Generation Cephalosporin and Aztreonam, Philippine General Hospital, 2013

The resistance rate of ESBL *K. pneumoniae* against gentamicin (78.0%), ampicillin (55.7%), amoxicillin/clavulanate (44.3%), cefazolin (32.9%) and imipenem (25.8%) is high. Low resistance to piperacillin-tazobactam (18.4%), cotrimoxazole (13.3%), moxifloxacin (9.4%), cefoxitin (4.3%), cefepime (3.5%), tetracycline (2.0%), meropenem (1.2%), and cefuroxime (0.8%) was observed. ESBL *K. pneumoniae* showed no resistance to ampicillin-sulbactam and ciprofloxacin.

Genotypic Characterization of ESBL

The first investigation on the genes of microorganisms that were resistant to extended-spectrum cephalosporin discovered *bla*SHV-12 and *bla*TEM-1 carriage among *Enterobacteriaceae* isolated in 2001 from a major tertiary referral hospital.[45] No organisms were found to harbor CTX-M enzyme variants. A similar study on bacterial strains from the same facility in 2007 established the high proportion of *bla*CTX-M with *bla*CTX-M-1 as the most common followed by *bla*CTX-M-9 and *bla*SHV-12 groups.[34]

Currently, the ARSP uses ceftazidime to screen for ESBL production based on the Clinical and Laboratory Standards Institute 2012.[13] The results showed that ESBL-suspects among *E. coli* and *Klebsiella sp*. isolates for 2012 are 20.9% (701/3505) and 31.7% (1224/4010), respectively. These ESBL-suspect isolates were referred to the ARS reference laboratory for further phenotypic confirmation of a subset, revealing 66.8% (135/202) and 70.6% (314/445) for ESBL-producing *E. coli* and *Klebsiella sp*., respectively.

The data gathered from PGH in 2012 showed the presence of ESBL-producing *E. coli* and *K. pneumoniae* at 13.2% and 23.3, respectively. They used the disk diffusion method in screening ESBL and the double-disc synergy test as confirmatory test. These tests remain a reliable method to detect ESBLs in the clinical laboratory but at times can be difficult to read.[9]

Risk Factors for ESBL bacteria

Local data on risk factors associated with infections caused by ESBLs is limited. Among patients in a tertiary care facility, the risk factors included administration of ceftazidime within the past 3 months and additional invasive device present during confinement.[43] The ARSP has not published data on the risk factors for antibiotic resistance. Among patients with complicated urinary tract infection, history of 3rd generation cephalosporin use within the past 3 months, and nosocomial acquisition of UTI were independent risk factors for ESBL development.[44] These conditions were also implicated for diseases caused by ESBL pathogens in other parts of the world. No data regarding risk factors for ESBL carriage among healthy subjects was found.[43,44]

Discussion

The resistance pattern of ESBL in the Philippines is increasing based on local data. This finding was consistent with the global pattern which ranged from 35.8% to 51.9%.[12-14] As reported by Hawser et al., the most commonly isolated ESBL organisms include *K. pneumoniae* and *E. coli* in the Asia-Pacific region, similar to the pattern seen locally. Other ESBL organisms identified locally include *Enterobacter cloacae, Klebsiella oxytoca, Klebsiella ozasanae, Pseudomonas aeruginosa,* and *Salmonella enterica.* Previous studies have also identified these organisms as harboring ESBL genes.[15, 18-26]

The data from the ARSP depicts the trend of ESBL in the country. Their initial report of suspected ESBL *E. coli* of 4% and *K. pneumonia* of 10% increased to 20.9% and 31.7%, respectively, in 2012. However, compared with the other local studies conducted, a wide range of rates was observed. The variability in the results may be due to inadequate reporting and monitoring, especially during the early years. Increased awareness has led to improvements in reporting and monitoring of ESBL.

In general, organisms isolated from various specimens especially urine and stool are caused by *K. pneumoniae* and *E. coli. Enterobacteriaciae* can acquire resistant genes and be passed on to progeny. The presence of plasmids in some of these bacteria allows these organisms to transfer these genes to other members of the species. Furthermore, they acquire the ability to evade the effects of commonly used antibiotics and allow them to become more aggressive, leading to more serious manifestations or even death.

Another possible source of resistance is the use of prophylactic antibiotics among animals. This also contributes to the mutation of bacteria, potentially leading to resistance. The transfer of ESBL bacteria from animals to man may be possible, further complicating the problem. At present, there is no published local data on the occurrence of ESBL in animals.

ESBLs exhibit different levels of activity against various cephalosporins. Resistance patterns differ due to the frequent use of a particular antibiotic in the environment. This can make detection of ESBL more difficult and choosing the appropriate antimicrobial for testing its presence is critical. All microorganisms found to produce ESBL should be considered resistant to all extended-spectrum β-lactams regardless of the results of in-vitro susceptibility tests.[45]

Laboratory detection of ESBL in *E. coli* and *K. pneumoniae* is based on methods recommended by National Committee for Clinical Laboratory Standard (NCCLS). Screening and confirmatory tests for other species belonging to *Enterobacteriaceae* have not been established by NCCLS and methods developed for *E. coli* and *K. pneumoniae* have not been proven to be valid for other ESBL bacteria.[46] Broth microdilution and disk diffusion methods are performed in screening ESBL isolates.

Several studies have documented the failure of methods described by NCCLS to accurately detect ESBL. Polymerase chain reaction, PCR-restriction fragment length polymorphism, and nucleotide sequencing can detect the presence of ESBL genes; however, they are time consuming, expensive, and labor intensive. The need for rapid detection of ESBLs prompted the search for more accurate tests that can easily identify ESBLs in the laboratory.[12]

The detection of ESBL organisms is challenging both in the clinical and laboratory setting. Patients who do not respond to common antibiotic therapy may pose a question of resistance to the clinician. Prior to the final culture results, empiric therapy for possible organisms is the next best option to prevent further deterioration. The microbiology laboratory is crucial in the detection and control of the spread of ESBL. Therefore, it is necessary for laboratory personnel to be well equipped with the knowledge and skill in the detection of these organisms.[19]

There was a paucity of local data on the molecular characteristics of ESBL. Locally, the most common genes produced by ESBL belong to the *bla*$_{CTX-M}$ group. The shift in the genotypic makeup of ESBLs from *bla*$_{SHV}$ and *bla*$_{TEM}$ in less than a decade is consistent with the trend observed in Europe, South America, and North Africa.[42] In 2011, Kanamori et al. reported the predominance of bla$_{CTX-M-15}$ and its significant association with *aac(6')-Ib-cr* conferring quinolone resistance.[42] The association between ESBL production and fluoroquinolone resistance is well documented and may be due in part to the joint transfer of both mechanisms via plasmids.

Most ESBL infections occur in hospital patients, especially those in ICUs. The presence of susceptible individuals and the heavy use of antimicrobials in the healthcare setting create an environment that is conducive to the development of resistant organisms. In recent years, community outbreaks and ESBL carriage in both healthy humans and animals have been described.[12,14] This poses a serious threat to public health and calls for a multidisciplinary approach in infection prevention and control.

Antimicrobial stewardship plays a significant role in controlling ESBL outbreaks. Use of 3rd generation cephalosporins and other antimicrobial agents has been epidemiologically linked to ESBL infection, suggesting the importance of compliance to antibiotic policies or guidelines.[43] Antibiotic cycling and class restriction has been proven to reduce the prevalence of ESBLs in healthcare settings. Switching treatment to piperacillin/tazobactam or imipenem can circumvent the problem of ESBL. However, widespread use of these drugs may result in the emergence of other drug-resistant organisms.

Laboratory surveillance on a continuous basis plays a vital role in identifying patients infected with ESBLs. This will enable healthcare workers to immediately undertake necessary measures. Patient records should be flagged so that contact isolation of known ESBL cases can be considered in case of readmission.[12, 14]

Conclusion

An increase in ESBL production was observed in both *E. coli* and *K. pneumonia* isolates from 1999 to 2012. The reported range of ESBL *K. pneumoniae* and *E. coli* ranged were 10 – 43.24% and 4 – 20.9%, respectively. The continued rise in resistance calls for immediate action as it leaves patients with limited or even no treatment options. However, it is important to note that findings of research done outside the existing ARSP are not incorporated into the local AMR report. In addition, there is no existing laboratory-based surveillance system for animals. Thus, it is possible that data from ARSP is just the tip of the iceberg. The limited data available from hospitals and research centers in the country contributes to the lack of understanding on the current status of ESBL.

The excessive use of antibiotics created a setting for the resistant strains to multiply in the environment. Many types of infection caused by ESBL can only be controlled with newer, broader spectrum antibiotics. Alternative antibiotics are available; however, they may be associated with adverse effects and tend to be more costly. Hospitals should continue to document the occurrence of these organisms to achieve effective control and prevention. It is fast becoming a problem in clinics and its presence in the community is a possible problem. The routine detection of ESBL may compensate for the inadequate data; however, because of the more sophisticated methodology and greater expense associated with the confirmation of ESBL, this is not routinely performed in all cultures.

Data on ESBL carriage in the community is also lacking. Because of the increasing rates of AMR and ESBL, there is a need to closely monitor the occurrence of these organisms in the hospital and community settings.

The strengthening of rational antibiotic use and related policies will control the problem of resistance, especially in hospitals. Meanwhile, collaboration between various institutions and reference laboratories will enable better surveillance of ESBL in the country. Mandatory reporting of ESBL to the sentinel sites or ARSP will also improve surveillance.

Awareness and more laboratory data on ESBL will increase our capacity to understand the behavior of this group of organisms. Controlling resistant strains is vital in the dynamic therapeutic management of infections.

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