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Antimicrobial Resistance in ESKAPE Pathogens and its Effect on Modern Medicine and Treatment

Cameran Runge
University of Nebraska-Lincoln

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By
Cameran Runge, BS
Microbiology
College of Arts and Sciences

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Facility Mentors:
Marissa Stanton, PhD, Microbiology

Abstract

ESKAPE pathogens *(Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter spp.)* are seeing a growing resistance to multiple classes of antibiotics. Misuse and overuse of antibiotics have played directly into the resistance observed, and the problem is growing exponentially. Antibiotic resistance is partially due to several intrinsic factors limiting the drug's uptake. These include efflux pumps, increased biofilm production, and reduced cell wall permeability in the resistant bacteria. ESKAPE pathogens also acquire resistance through horizontal gene transfer and plasmids. As antibiotics have become less effective, the bacteria can continue to thrive, leading to a detrimental outcome of previously treatable infections. Antibiotic resistance has increased the importance of new drug development, greater development of therapies, and improved education surrounding ESKAPE pathogens.

Key Words: ESKAPE pathogens, microbiology, antibiotic resistance

Introduction

Treatment of bacterial infections using antibiotics has continued to increase over the past decades bringing along with it more resistant infections. Bacteria are prokaryotic cells that usually contain cell walls, a cytoplasm, ribosomes, and DNA (Bacteria Characteristics, 2020). Bacteria come in numerous shapes including cocci, bacilli, and spirilla (Bacteria Characteristics, 2020). A further classification of bacteria includes being either gram-positive or gram-negative. If a cell is gram-negative, then the peptidoglycan cell wall is relatively thin, and then that peptidoglycan layer is surrounded by an outer membrane that contains lipopolysaccharide (Silhavy, 2010). Gram-positive do not have this the outer membrane making it generally easier to penetrate (Silhavy, 2010). These structures are essential in understanding how antibiotics can target cells.

Antibiotics target specific disease-causing bacteria; the first one discovered was penicillin by Fleming (Aminov, 2010). There are a variety of classes of antibiotics, including but not limited to penicillin, macrolides, cephalosporins, tetracyclines, beta-lactams, fluoroquinolones, trimethoprim-sulfamethoxazole, and lincosamides (Antibiotic Class Definitions). Each targets a different part of the bacteria to decrease its ability to survive and flourish; specific antibiotics are categorized into classes by their chemical makeup. Penicillin and cephalosporins prevent cell wall formation, whereas macrolides halt the multiplication of the bacteria (Antibiotic Class Definition). The variety of antibiotics and their mechanisms allow them to be used effectively for many infections.

With increased antibiotic use comes resistant strains of the bacteria as they improve their avoidance mechanisms. Which mechanisms have the most significant effects and what all

influences resistance is still being discussed, these mechanisms vary depending on which bacteria is involved. The more technical definition of antibiotic resistance is the ability of a bacterium to grow in an environment with a concentrated enough amount of antibiotic to kill others of its species (Sabtu, 2015). The idea of resistance began with penicillin as there was an increased need for its usage during the World War II and it was given out rapidly (Landecker, 2016). A year later, the first penicillin-resistant bacteria were found. In this case, antibiotic resistance works by the bacteria creating a mutation in its genes that prevents resistance strains from being eliminated, allowing them to continue replicating and flourishing (Uddin, 2021).

Antibiotic Resistance in ESKAPE Pathogens Overview

The term ESKAPE pathogens is an acronym standing for *Enterococcus faecium*, *Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter spp* (Denissen, 2022). These bacteria are a group of pathogens that are of increased concern because of their continued and rapidly rising resistance to many of the main antibiotics (Denissen, 2022). There are a variety of ways that antibiotic resistance is created in these specific pathogens, including biofilm production (Denissen, 2022). A biofilm contains a matrix of repeated monomers of sugar and carbohydrates called exopolysaccharides, which contain clusters of bacteria (Sharma, 2019). A biofilm is effective because it creates an enclosed environment where bacteria can thrive in a group avoiding oxidization, radiation, and other damages antibiotics would generally cause (Kostakioti, 2013).

A second mechanism ESKAPE bacteria use to avoid antibiotic destruction is causing changes to the antibiotic target sites (Denissen, 2022). These site changes occur when there are mutations, often through amino acid substitutions, which then decrease the ability for antibiotics to bind to the bacteria (Spratt, 1994). Penicillin-binding proteins are a specific example of this, which are involved in cell wall creation; they lessen the ability of the antibiotic to destroy bacteria (Indrawattana, 2016). Another way resistance occurs in the ESKAPE pathogens is by reducing antibiotic intake. Porins are channels that different substances can enter, such as antibiotics; the loss of the porin proteins dramatically decreases antibiotics entry, thus their effectivity (Santajit, 2016). Efflux pumps can also decrease the number of antibiotics in the cell's circulation. Efflux pumps work to eject the antibiotic into the external environment leaving an inadequate amount for the acquisition of antimicrobial activity (Santajit, 2016).

An additional theory about an antibiotic resistance mechanism is that transduction occurs; this means that pieces of DNA are moved from a bacteriophage to the bacteria. It then leads to new genetic characteristics which help the bacteria avoid destruction (Landecker, 2016). This idea is supported as people who were not previously exposed to certain antibiotics had a resistance to them (Landecker, 2016). The plasmid and transposon will continue to accumulate different resistant factors leading to a larger future epidemic similar to the dysentery outbreak of 1969. A strain of shigella that was previously thought to be eliminated reemerged after mutating and developing resistance to common treatment. (Landecker, 2016). Reemergence is one primary concern of antibiotic resistance; that previously eradicated diseases may be able to return. The overuse and misuse of antibiotics also contribute to resistance. When antibiotics become more readily available, for example, through telehealth,

the public turns to them as an easy fix since proper labs and tests may be skipped (Kendrick, 2020).

Consequently, it can effectively allow resistant strains to emerge without new treatment methods (Sabtu, 2015). This brings up the debate on what doctors and those in the medical or research field should do to combat the issue. It is, however, essential first to understand what the ESKAPE pathogens are, and which mechanisms of resistance are observed explicitly in each. This allows a complete understanding, leading to many possible solutions with different benefits and drawbacks.

Enterococcus faecium

The first ESKAPE pathogen is *Enterococcus faecium*, a gram-positive bacterium, and coccus, or spherical bacterium. Initially, they were a part of the *Streptococcus* genus; however, the 16S rRNA allowed a better understanding of the difference and, ultimately, the new genus formation (Tyne, 2014). A range of environments, including soil, water sources, human cavities, and food may contain a variety of *Enterococcus* species (Tyne, 2014). Infection from this bacterium type often results in urinary tract infections and endocarditis of various severities, these are frequently acquired from a hospital setting. Often it is seen that catheters are the culprit of these infections but burn, or ulcer infections also can lead to an increased risk (Said, 2022). *Enterococcus* strains reside in small numbers in the gastrointestinal tract. Because it can grow in extreme pH values and a great range of temperatures, this type of bacteria can thrive in the gastrointestinal tract when other bacteria cannot.

Antibiotic resistance has become prevalent in *Enterococcus faecium* increasingly so in recent years. Penicillin, ampicillin, amoxicillin, and cephalosporins are antibiotics with decreased effectiveness due to their resistance in *E. faecium*. These antibiotics, in combination with a beta-lactamase inhibit cell wall formation (Antibiotic Class Definition). There is a Pbp5 enzyme encoded in the operon that shows high amounts of mutation in resistant strains. The mutation in this operon causes beta lactamases to be created which break the beta-lactam ring decreasing the ability of the antibiotic to destroy bacteria (Miller, 2015). L, D-transpeptidase also contributes to ampicillin resistance in Enterococcus faecium by degradation of the cell wall (Miller, 2015).

A second class of antibiotics that Enterococcus faecium show resistance to are cephalosporins which work similarly to penicillin, as they prevent appropriate cell wall formation antibiotic (Antibiotic Class Definitions). Pbp5 is necessary for regular bacterial activity as it works closely with glycosyltransferase, making the peptidoglycan necessary for cell wall stability. So, when a decrease in its ability to bind to antibiotics is seen, and a deletion of an A-class pbp occurs in tandem, resistance to this antibiotic will be present (Munita, 2015). Two-component regulatory systems may also contribute to cephalosporin resistance in *E. faecium*. In this mechanism, CroRS is also essential because CroR allows for the phosphorylation of the regulator protein, CroS, ultimately changing the transcription outcome. IreK and IreP are a second two-component regulatory system seen with cephalosporin resistance in *Enterococcus faecium.* When deletions of these occur, resistance can be seen (Munita, 2015).

A third class of antibiotics, the bacteria *Enterococcus faecium*, shows resistance to are the glycopeptides. These agents also inhibit the formation of the cell wall of bacteria, this time

preventing the cross-linkage of the peptidoglycan cell wall chains. Vancomycin is an antibiotic in this class known to contain clusters of resistant genes, vanA and vanB being two of the most prevalent (Patel, 2000). There is a high level of resistance due to a change in the D-Ala-D-Lac end which results in a deletion of a hydrogen bond, drastically reducing the binding ability of the antibiotic. Low-level resistance occurs with the D-Ala-D-Ser end, which decreases the ability of the antibiotic to bind to the bacteria but at a lower level (Miller, 2015). Resistance to the three types of antibiotics described in this section provides insight into why antibiotic resistance to Enterococcus faecium is a growing healthcare problem.

Staphylococcus aureus

Like *Enterococcus faecium*, *Staphylococcus aureus* is a sphere-shaped gram-positive bacterium. Methicillin-resistant *Staphylococcus aureus* (MRSA) is a strain of *S. aureus* with general resistance to methicillin. *Staphylococcus aureus* arose in the 1880s with an extremely high mortality rate as antibiotics were not developed at this point, and procedures were much less sterile (Deurenberg, 2008). People can be asymptomatic carriers of *S. aureus* (Chambers, 2009). This means it is seen regularly in normal human microbiota, particularly in the nasal passage. If these bacteria enter the bloodstream or soft tissues, it can lead to a dangerous infection. Some illnesses that *Staphylococcus aureus* may cause include toxic shock syndrome, endocarditis, and cellulitis (Taylor, 2022). Infections typically are seen more in health care workers, in those in the military, in children in daycares, and in people who have repeated intravenous needle use (Centers for Disease Control and Prevention, 2019). It is important to note that there are two types of MRSA infections, community-acquired methicillin-resistant

Staphylococcus aureus and hospital-acquired MRSA. One cause of MRSA bacteria resistance is the mecA gene, found on the *Staphylococcal* cassette chromosome, mec (Deurenberg, 2008). Penicillin-binding protein two is encoded by the mecA gene, which is the cause of the resistance observed as it drastically decreases the affinity for the antibiotic.

Staphylococcus aureus has methicillin resistance, but also general resistance to beta-lactam. The resistance to beta-lactams can also be attributed to Pbp2a production, which provides a route to overcome the antibiotic's attempt to destroy the bacteria (Guignard, 2005). A study was conducted, and it found another component of resistance is ClpXP components being inactivated in the community-acquired MRSA (Baek, 2014). ClpXP is a protease that uses adenosine triphosphate and hydrolysis to break down proteins. This differs from the mecA mechanism because the penicillin-binding proteins are unaffected. When bacteria with this type of resistance are observed, thicker cell walls and a greater amount of cross-linking are characteristics are observed, which would be a logical outcome of this type of resistance.

A characteristic of *Staphylococcus aureus* infections that contributes to antibiotic resistance is the production of biofilms, as mentioned with *Enterococcus faecium*. The biofilm produced by *Staphylococcus aureus* has multiple layers surrounded by a glycocalyx coat with extracellular DNA. Ultimately this increases the bacteria's tolerance to antibiotics and the host cell's defenses creating persistent infections (Archer, 2011). Biofilms, the mecA gene, and ClpXP contribute to the increased problematic resistance observed in *Staphylococcus aureus*. These will need to be addressed to combat the diseases that accompany rising resistant strains safely.

Klebsiella pneumoniae

Klebsiella pneumoniae is the third bacterium that makes up the ESKAPE pathogens. Unlike the previous two, this is a gram-negative bacterium that can cause neonatal sepsis, urinary tract infections, and most regularly, pneumonia. It is opportunistic pathogen, targeting infants, the elderly, and those with immune system disorders (Holt, 2015). *K. pneumoniae*, however, it is not limited to human transmission; multiple species of animals and plants are affected by this bacterium (Holt, 2015). In humans, it is frequently acquired nosocomially, as it resides on the hands of hospital staff which is then transferred to the patients. It can also be transmitted through the fecal-oral route outside of a hospital. It should be clear that pneumonia is caused more frequently by other bacteria, not *Klebsiella pneumoniae*, in a community setting (Ashurst, 2022). Alcoholism increases the fatality of illnesses caused by *K. pneumoniae* exponentially because there is an alteration in the microbial intestinal composition (Samuelson, 2017).

Fluoroquinolones are the antibiotics that *Klebsiella pneumoniae* has a growing resistance to. These antibiotics inhibit DNA synthesis and stop bacterial replication (Antibiotic Class Definitions). In resistant strains, the bacteria contain quinolone resistance-determining region mutations. These mutations decrease the affinity of the antibiotics for topoisomerase or DNA gyrase (Minarini, 2012). In susceptible bacteria, fluoroquinolones bind to the gyrase-DNA region, creating a distortion that leaves the bacteria unable to divide. There is also qnr element, a plasmid-mediated horizontal element of resistance, which helps to expand on the reason for such high resistance. Qrn's are repeated peptide proteins that protect the gyrase and topoisomerase enzyme from the detrimental effects of the antibiotic (Jacoby, 2015).

Antibiotic resistance in *Klebsiella pneumoniae* can be partially attributed to an enzyme called Extended Spectrum Beta Lactamase and Carbapenemase (Nirwati, 2019). This enzyme breaks down the beta lactamase antibiotics like penicillin, by reacting it with water producing new fragments. Transfer between bacteria is through the plasmid structure in insertion sequences which alters the amino acid sequences. Examples of the different families of extended-spectrum beta-lactamase, ESBLs, include TEM and SHV, which contain point mutations; however, there are large varieties in the families (Castanheira, 2021). Carbapenemase resistance has also erupted in *Klebsiella pneumoniae*, causing outbreaks of infections with high mortality rates. *Klebsiella pneumoniae* carbapenemases are beta-lactamase enzymes that can be in an intrinsic form and spread on the bacteria themselves or acquired. The acquired form creates resistance when the plasmid genes encode the enzyme and are transferred. The gene blaKPC codes for the KPC enzyme, which is placed on a transposon type Tn3 labeled with the name Tn4401. This is significant because its location is the reason it can be inserted into different plasmids (Arnold, 2011).

A final mechanism for antibiotic resistance in *Klebsiella pneumoniae* is the mgrB regulatory gene. The bacteria containing this mutation present PhoPQ lipid A remodeling, creating more resistant strains that show polymyxin resistance (Kidd, 2017). Polymyxins work by attaching to lipopolysaccharides and interrupting the phospholipid interactions, breaking down the cell membrane (David, 2015). Another way of LPS change would be when PmrB activates PmrA using phosphorylation, then regulating different operons and pmrE occurs (Aghapour, 2019). The increased virulence of *Klebsiella pneumoniae* can be attributed to a combination of all the mechanisms listed above. Over time more properties that create

resistance to antibiotics for this bacterium are being discovered, leading to rising concern over this ESKAPE pathogen.

Acinetobacter Baumannii

Acinetobacter baumannii is a nonmotile, gram-negative bacterium that uses oxygen as its general trait. This bacterium thrives in a hospital setting and flourishes on the skin, particularly in aquatic habitats. Fish can transmit the pathogen to humans, and *Acinetobacter baumannii* has been identified frequently in freshwater (Dekíc, 2018). Another group highly susceptible to this as a blood infection is military members deployed in combat situations. Lice also contain these bacteria; thus, a group at risk that is often ignored is the homeless population. In humans, the bacteria enter through mucus membranes or open skin injuries. The respiratory tract can also be colonized, leading to a high incidence of pneumoniae, or other respiratory diseases. Patients on mechanical ventilation are at a particular risk for *Acinetobacter baumannii* infection development (Howard, 2012). Acinetobacter meningitis has also been observed in post-operative situations. When the bacteria enter the bloodstream, it leads to septicemia or death. OmpA, a membrane protein, is responsible for the virulence of the bacteria as it leads to a dysfunctional mitochondrion that swells and bursts into the infected cells.

Resistance to beta-lactams is observed in *A. baumanii*. When OXA-51 or other OXAs are expressed and the upstream elements, ISAba1 or 9, are present, overexpression occurs. OXAs are carbapenem hydrolyzing oxacillinases which is why overexpression leads to resistance to carbapenem antibiotics (Vázquez-López, 2020). When Rifampicin is used, the use of amino acid substitution to evade active site binding occurs, which leads to much higher amounts of

antibiotics needed for the same effect—the mutation of rpoB in the particular mutation area for *Acinetobacter baumannii*. Tetracycline resistance is this organism is due to the efflux of resistance enzymes and leads to high adeABC expression, which creates resistance. Polymyxin resistance is due to LPS lipid A interactions. A negative charge is gone when adding a residue, which lowers the lipopolysaccharide affinity of the polymyxin antibiotic, creating resistance (Vázquez-López, 2020). These small alterations in *Acinetobacter baumannii* significantly impact antibiotics' effectiveness. The wide variety in first-line defense resistances will continue to grow unless a solution can be found, leaving those concerned about the future with these bacteria.

Pseudomonas aeruginosa

Pseudomonas aeruginosa is a gram-negative bacterium found in freshwater environments, swimming pools, hot tubs, and other community water sources. The bacteria have an extensive genome containing many genes used in the regulation, contributing to the high number of environments it can occupy (Winstanley, 2016). It also is involved in community and hospital infections; however, community infections play a more significant role than in some other bacteria (Wilson, 2022). Examples include puncture wounds, pneumonia, and ear infections. In a hospital, it can be seen in ventilator tubes and catheter-associated urinary tract infections (CAUTI). Immunocompromised individuals with cystic fibrosis, cancer, or AIDS are also at a higher risk for *Pseudomonas aeruginosa* infections.

Antibiotic resistance to most antibiotics, including cephalosporins, fluoroquinolones, and carbapenems, is observed in *P. aeruginosa* (Moradali, 2017). Different intrinsic antibiotic resistance is one element of resistance seen for this bacterium due to the permeability

restriction that the cells possess. The antibiotics mentioned above target bacterial cell walls and work to degrade them in the bacteria. This bacterium being gram-negative inherently has some antibiotic resistance due to phospholipids in a bilayer structure (Pang, 2019). However, *Pseudomonas aeruginosa,* in general, has a high level of restriction on what can enter the cells through porins, much higher than *Escherichia coli*. OprF is the main porin in *Pseudomonas aeruginosa*, and it contains two conformers that fold and restrict what enters. The number of open porins is small, leading to a low level of permeability (Pang, 2019).

Efflux systems are another mechanism of antibiotic resistance that is observed. The type of efflux system in particular for this bacterium is the resistance-nodulation-division (RND) which contains the efflux pumps encoded for by MexAB-OprM, MexCD-OprJ, MexEF-OprN, and MexXY-OprM. Overexpression of these pumps increases resistance as they pump out the antibiotics faster than the antibiotic can work on the organism (Shigemura, 2015). Antibiotic-inactivating enzymes, including beta lactamase encoded by the ampC gene, is a third intrinsic resistance mechanism. When the bond between the amide in the ring is broken, beta-lactam antibiotics lose effectiveness. Class C lactamases hinder cephalosporin function (Pang, 2019). Target modification in *Pseudomonas aeruginosa* is seen through changes in lipid A in lipopolysaccharides which produce resistance to polymyxins (Bassetti, 2018). PmrCAB and arnBCADTEF operons create an and add PEtN and L-Ara4N to the lipid A leading to the excessive expression of lipopolysaccharide modifying operons and this polymyxin resistance (Bassetti, 2018). In combination, these mechanisms lead to the dangers of resistance in *Pseudomonas aeruginosa*, a growing concern in medicine.

Enterobacter spp.

The final bacteria of the ESKAPE pathogens are *Enterobacter spp*., gram-negative and rod-shaped, bacterioa. Primarily these bacteria cause healthcare-associated and nosocomial infections, including urinary tract, respiratory, heart/blood, and wound infections. Thus, those who have invasive medical devices or who have had recent surgeries are more susceptible to *Enterococcus* infection. Various environments can be hosts to *Enterobacter* bacteria, including water, skin, soil, or even food (Ramirez, 2022). They also can be part of the gastrointestinal tract, which is a significant area they can be seen in mammals. Specifically, there are 22 species in this genus; however, not all of them can be transmitted to humans. When these infections form, the lipopolysaccharide capsule causes inflammation, which can lead to sepsis (Ramirez, 2022).

In terms of resistance, the *Enterobacter cloacae* complex has a natural resistance to penicillin and cephalosporins. This natural resistance is due to the expressed ampC gene, which has been mentioned in previous sections. Colistin resistance by *Enterobacter* can be attributed to expression of the mcr, ecr, phoPQ/pmrAB genes, which all lead to a change in the lipid A portion of lipopolysaccharide (LPS) (Aghapour, 2019). When the LPS is changed, and a negative charge is created, resistance can be seen as it decreases affinity of the antibiotic for the bacterium. The Mcr gene is a plasmid-mediated resistance mechanism that can be transferred to different genes leading to an LPS change. The resistance from mcr gene expression includes resistance to beta-lactams, aminoglycosides, quinolones, and more. *Enterobacter* also contains a ramA gene that creates another resistance mechanism when modified. RamA binds to lpxC, lpxO, and lpxL2 genes, affecting the lipid A complex (Aghapour, 2019). Target enzyme

modifications are another reason for antibiotic resistance in E*nterobacter*, as discussed previously. Efflux pumps and other intrinsic mechanisms are also present in *Enterobacter spp*. Many of the mechanisms for antibiotic resistance can be seen throughout many of the ESKAPE pathogens. This leads to the next idea: to decide the best way to combat the growing resistance issue.

Discussion

Developing alternative treatments for antibiotic resistant ESKAPE pathogens are essential in preventing increased mortality rates and healthcare costs worldwide. One way to combat this issue is by prescribing antibiotics in combination to treat these pathogens. Adjuvants may be added, which block the resistance mechanism by blocking efflux pumps and decreasing biofilms. The chance these bacteria are resistant to antibiotics and adjuvants is much lower than one antibiotic on its own. This is not always effective, however, there is the possibility of resistance eventually developing to antibiotics in combinations (Mulani, 2019). A second strategy for treating antibiotic resistance in ESKAPE pathogens is bacteriophage therapy. Phage can be isolated and inserted into cells, sometimes in combination with antibiotics. Phages have been observed to reduce biofilm formation leading to cell lysis. Phage therapy is limited by the stability and administration of the phages (Mulani, 2019).

No one solution will completely fix the antibiotic resistance issue that has become a significant concern in the United States and the world as a whole. The most effective solution is debated, but it is crucial to start correcting this issue before it becomes even more problematic. Having solutions for ESKAPE pathogens when a resistant infection is identified is helpful;

however, combatting the issue at the root is better. One solution includes finding new antibiotics that can be used to treat the infections. Antibiotic production and research have declined rapidly over the years as pharmaceutical companies face financial dilemmas and scientific barriers (Dutescu, 2021). Suppose a new antibiotic was to be created. In that case, it may not be as profitable since the antibiotic may only be used with multi-drug resistant bacteria rather than as a first line of defense (Dutescu, 2021). Another cause of concern is how quickly resistance develops. As mentioned previously, resistant strains were identified relatively quickly. Would these new antibiotics be effective long enough for a profit for these companies to be made? Pharmaceutical companies are heavily focused on profit as a means to motivation for the creation of new drugs. Both of these reasons decrease companies' involvement in creating new antibiotics, leading to this being a questionable solution to the issue. For this to work long-term, there would have to be incentives for companies to continually develop antibiotics so that a consistent stream of antibiotics would be created as resistance develops.

A decline in growth-promoting antibiotic usage among livestock has also been proposed to solve antibiotic resistance. The majority of antibiotics used worldwide are in feed for animals because it increases the growth of the livestock and prevents infection, it has been reported as high as 85 percent of non-organic farms do this (Alliance to Save our Antibiotics). However, this can cause antibiotic-resistant bacteria to be transferred to humans when meat is handled or consumed. Some countries have restricted the use of certain antibiotics in livestock; however, others have little to no regulation of what is being fed to livestock (Metz, 2014). Rather than healthy animals being treated preventatively, they should be tested and treated as infections arise. Companies that produce antibiotics for agricultural and livestock use should have to

submit this data for analysis and regulation. The United States Environmental Protection Agency would be the agency to enforce testing for unnecessary antibiotic use this as they could use the authority of the Federal Insecticide, Fungicide, and Rodenticide Act to require registration of products before marketing (Metz, 2014). These increased regulations and limits on livestock antibiotic use would help decrease the growing antibiotic resistance issue.

Telehealth may also increase the number of antibiotics prescribed for unnecessary situations expediting antibiotic resistance. Telehealth offers very convincing and ease regarding doctors' appointments for both children and adults. Rather than going into an office where someone could continue the spread of infection, appointments can be made from the comfort of their home. Although this sounds incredible beneficially, which it can be, there is evidence that higher amounts of antibiotics are being prescribed without appropriate testing to ensure the correct diagnosis (Kendrick, 2022). One study showed that 52 percent of telehealth visits vs. 31 percent of primary care visits result in antibiotic prescriptions (Sine, 2022). Laboratory tests are frequently bypassed when telehealth is used, and antibiotics are given preemptively based on symptom description. This process can increase a patient's antibiotic use and resistant bacteria exponentially when it does not need to be. Increased regulation for antibiotic prescriptions on telehealth visits could be a possible way to help fight antibiotic-resistant bacteria development.

This is perpetuated by patients giving doctors higher ratings when antibiotics are prescribed (Sine, 2022). Miseducation surrounding antibiotic usage is embedded into our society as people are convinced antibiotics are a fix-all for their illness. Often people would rather feel better fast instead of waiting for the body's natural systems, even if it means a

possible resistance development. In some countries antibiotics are available without prescription at local convenience stores perpetuating this fix all idea. Although it is well known that there is a difference between viruses and bacteria, there is a lack of knowledge that antibiotics cannot cure everything. A survey was presented to 10,000 people, and 64 percent of people believed antibiotics would be appropriate for a cold or flu diagnosis. 33 percent of people believed the antibiotic course should be stopped when symptoms improve (World Health Organization, 2015). A baseline education being taught would give others the tools they need to understand the risks of high antibiotic usage when the appropriate time for antibiotics is, and the importance of following instructions when they are prescribed.

Conclusion

The ESKAPE group of bacteria has added urgency to the issue of antibiotic resistance. The different mechanisms of resistance explored above in the ESKAPE pathogens illustrate the importance of this problem. If nothing is done to help combat this growing problem, infections will become much more deadly and costly to the community. Although one solution will not be enough to fix such a widespread issue, the most crucial step is just starting the process. Companies gaining awareness and increasing regulations, the general population is educated on the issue, and prescribers being more conscious of antibiotic resistance would leave a lasting impact. As the mechanisms behind resistance are continuing to be explored and enhance scientists' understanding of them, more effective solutions can be developed.

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