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The burden of antibiotic resistance of the main microorganisms causing infections in humans – review of the literature

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ABSTRACT

One of the biggest threats to human well-being and public health is antibiotic resistance. If allowed to spread unchecked, it might become a major health risk and trigger another pandemic. This proves the need to develop antibiotic resistance-related global health solutions that take into consideration microdata from various global locations. Establishing positive social norms, guiding individual and group behavioral habits that support global human health, and ultimately raising public awareness of the need for such action could all have a positive impact. Antibiotic resistance is not just a growing clinical concern but also complicates therapy, making adherence to current guidelines for managing antibiotic resistance extremely difficult. Numerous genetic components have been connected to the development of resistance; some of these components have intricate paths of transfer between microorganisms. Beyond this, the subject of antibiotic resistance is becoming increasingly significant in medical microbiology as new mechanisms underpinning its development are identified. In addition to genetic factors, behaviors such as misdiagnosis, exposure to broad-spectrum antibiotics, and delayed diagnosis contribute to the development of resistance. However, advancements in bioinformatics and DNA sequencing technology have completely transformed the diagnostic sector, enabling real-time identification of the components and causes of antibiotic resistance. This information is crucial for developing effective control and prevention strategies to counter the threat.

KEYWORDS: antibiotic resistance, antibiotics, methicillin-resistant *Staphylococcus aureus*, beta-lactamase, carbapenems, vancomycin

ABBREVIATIONS: AOM, acute otitis media; CDC, Centers for Disease Control and Prevention; cIAI, complicated intra-abdominal infection; CRE, carbapenem-resistant Enterobacterales; cUTI, complicated urinary tract infection; ESBL, extended-spectrum beta-lactamase; Hib, *Haemophilus influenzae* type b; LVRE, linezolid/vancomycin -resistant enterococci; MBC, minimum bactericidal concentration; MBL, metallo-beta-lactamases; MDR, multidrug-resistant; MIC, minimum inhibitor concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; PBP, penicillin-binding protein; SCC*mec*, staphylococcal chromosomal cassette *mec*; VRE, vancomycin-resistant enterococci; XDR, extensively drug-resistant

INTRODUCTION

According to the World Health Organization (WHO), antimicrobial resistance is a "serious threat (that) is no longer a prediction for the future, it is happening right now in every region of the world and has the potential to affect anyone, of any age, in any country" [1]. Antibiotics are essential to contemporary medicine, being one of the most important factors in the reduction of infant mortality. Furthermore, they are essential for a wide range of medical procedures, from surgery to chemotherapy, and the treatment of secondary infections and of cancers of infectious origin. However, as multidrug-resis-

tant bacteria become more prevalent worldwide, the threat of incurable diseases is becoming increasingly palpable. A 2022 report by the WHO stated that the world will run out of antibiotics because existing drugs have been developed by modifying existing classes and have been shown to have short cycles of impact [2].

According to a 2019 study, mortality caused by bacterial resistance to antibiotics exceeded 1.2 million over the 1-year study period, surpassing the number of deaths caused by human immunodeficiency virus (HIV) infection and malaria [3]. The same study concluded that over 1.27 million people could have been saved if antibiotic-resistant infections had been replaced by bacterial infections sensitive to common antibiotics [3]. Although the COVID-19 pandemic has captured the attention of the medical world in the last 3 years, antibiotic resistance remains an urgent problem that could lead to the appearance of much more aggressive, even lethal, pathogens in the near future [1].

It was found that mortality caused by increased antibiotic resistance has a higher rate in underdeveloped and developing countries, but remain a priority in developed countries as well [1]. Therefore, a global understanding of this problem is necessary. Deaths resulting from thoraco-abdominal and systemic infections represent 79% of all deaths caused by antibiotic resistance.

One of the most concerning aspects of antibiotic resistance is the occurrence of recurrent infections or secondary infections with saprophytic microorganisms in patients with underlying diseases or limited mobility, which leads in many cases to treatment failure [4,5].

The pathogens most frequently linked to antibiotic resistance-related mortality are *Acinetobacter baumannii*, *Pseudomonas aeruginosa* (*P. aeruginosa*), *Klebsiella pneumoniae* (*K. pneumoniae*), *Staphylococcus aureus* (*S. aureus*), and *Escherichia coli* (*E. coli*). Furthermore, methicillin-resistant *S. aureus* (MRSA), vancomycin-intermediate *S. aureus*, and vancomycin-resistant *S. aureus* were incriminated as a major cause of mortality in a study that examined 88 pathogen–antibiotic combinations [1]. The same study showed that the resistance of bacteria to the first line of antibiotic treatment (used mainly empirically) is responsible for more than 70% of deaths. These antibiotics include fluoroquinolones and beta-lactamases, for example carbapenems, cephalosporins, penicillins, and ciprofloxacin [1].

In response to recent studies, the WHO listed the issue of antibiotic resistance as one of the top ten worldwide dangers to public health, highlighting that the primary reason of the increasing prevalence in antibiotic resistance is improperly delivered therapies (wrong dosages, overuse of antibiotics) [3]. The WHO also cautions that in certain parts of the world, inadequate sanitation and a shortage of drinking water can lead to the spread of bacteria, particularly those that are already resistant to available treatments [3].

ETIOLOGICAL AGENTS OF IMPORTANCE IN THE ERA OF ANTIBIOTIC RESISTANCE

Among Gram-positive pathogens, a global pandemic of resistance of *S. aureus* and *Enterococcus* species currently represent the most significant threat [6,7]. According to studies conducted in the United States, MRSA is responsible for the deaths of more Americans each year than HIV/AIDS, Parkinson's disease, emphysema, and homicide combined [8,9]. In addition, vancomycin-resistant enterococci (VRE) and a growing number of additional pathogens develop resistance to many antibiotics commonly used in medical practice [8]. The global spread of drug resistance of the pathogens most often involved in respiratory infections, *Streptococcus pneumoniae* (*S. pneumoniae*) and *Mycobacterium tuberculosis* (*M. tuberculosis*), has been classified as an epidemic [7].

Gram-negative pathogens represent a particularly alarming problem because they become resistant to almost all available antibiotic options, creating situations reminiscent of the pre-antibiotic era [6–8]. The appearance of Gram-negative multidrug-resistant (MDR) bacilli has affected the entire medical practice [8]. The most severe Gram-negative infections occur in hospital settings and are most commonly caused by Enterobacterales (especially *K. pneumoniae*), *P. aeruginosa*, and *Acinetobacter* [6]. MDR Gram-negative pathogens are also becoming more prevalent in the community and include *E. coli* and *Neisseria gonorrhoeae* (*N. gonorrhoeae*), which produce extended-spectrum beta-lactamases (ESBLs) [7]. These microorganisms are of significant clinical importance in hospitals because infected patients often require care in the intensive care unit (ICU) and are at high risk of morbidity and mortality.

Streptococcus pneumoniae

S. pneumoniae remains the leading pathogen of acute bacterial pneumonia according to US statistics, although after the neonatal period, ~70% of cases of acute pneumonia are caused by viruses with respiratory tropism [10]. *S. pneumoniae* has the potential to produce severe and occasionally fatal infections, and is a major cause of bacterial pneumonia and meningitis, as well as blood, ear, and sinus infections [6,9]. Most cases of antibiotic resistance and deaths in infections with *S. pneumoniae* occur among adults aged 50 years or older, with the highest rates among those aged 65 years or older [6]. Data from vaccine trials for the heptavalent pneumococcal vaccine indicated that a third of radiologically confirmed cases of pneumonia were caused by *S. pneumoniae* [11]. However, a study by the Centers for Disease Control and Prevention (CDC), which investigated pathogens involved in radiologically confirmed pneumonias in hospitalized patients in three US hospitals, found a bacterial pathogen in only 15% of the children, and *S. pneumoniae* was the second most frequent cause of infection, the first being *Mycoplasma pneumoniae* [10].

Complicated pneumonia cases (necrotizing pneumonia, pleural empyema, lung abscess) represent a problem of worldwide importance, even after the introduction of the heptavalent vaccine [12]. Pleural empyema is most commonly determined by serotypes 1, 3, 7A, 18, and 19A, whereas forms with necrosis by serotype 3 of *S. pneumoniae* [12,13]. The rate of these complications has decreased in countries where the 13-valent pneumococcal vaccine was introduced into the vaccination schedule, although serotype 3 continues to be an important etiological agent of pneumonia with pleural empyema [14,15].

Historically, *S. pneumoniae* has been sensitive to penicillins, cephalosporins, macrolides, clindamycin, vancomycin, and trimethoprim-sulfamethoxazole. However, in the late 1990s, and then later in 2002 and 2008, strains of *S. pneumoniae* with a minimum inhibitory concentration (MIC) of >8 μg/ml appeared, changing the definition of pneumococcal sensitivity to penicillins and cephalosporins, from susceptible to intermediate and even resistant [16,17]. Resistance to penicillins correlates directly with resistance to broad-spectrum cephalosporins. After the introduction of the heptavalent vaccine, strains with increased resistance to macrolides were isolated (serotype 19A); the introduction of

the 13-valent vaccine was followed by a decrease in pneumococcal macrolide resistance [18,19]. Linezolid and daptomycin have shown both in laboratory tests and in real-world settings to be effective against *S. pneumoniae*. From 1997 to 2016, 11 strains of invasive *S. pneumoniae* resistant to linezolid were isolated in the United States [20]. Very rarely, resistance to carbapenems has also been observed [21]. In 30% of severe infection with *S. pneumoniae*, the bacteria are completely resistant to one or more clinically relevant antibiotics [6].

After the introduction of the anti-pneumococcal vaccine into the mandatory regimen, a decrease in pneumococcal strains resistant to penicillins and, implicitly, third generation cephalosporins was observed [20,22], caused by a reduction in both pneumococcal colonization and antibiotic use.

Before the use of the heptavalent vaccine, risk factors associated with *S. pneumoniae* antibiotic resistance included being of white race, being a nasopharyngeal carrier or having a pneumococcal infection before the age of 5 years, recent antibiotic treatment, and residence in a community with high antibiotic consumption [23–25]. After the introduction of the heptavalent vaccine, antibiotic resistance to serotypes that were not covered by this vaccine increased [26]. The widespread use of the 13-valent pneumococcal vaccine was associated with an increase in nasopharyngeal carriers of non-vaccine strains, but the proportion of resistant strains isolated from the nasopharynx decreased in most studies [27,28], except for one, which highlighted that after an initial decline in resistance, there was a rebound in resistance, especially of serotype 35B [29].

Streptococcus pyogenes

Streptococcus pyogenes (*S. pyogenes*) is the main bacterial pathogen that affects the pediatric age groups, especially young children and adolescents, and is associated with a range of diseases. It is estimated that there are ~600 million cases of acute *S. pyogenes* pharyngitis and ~700 million cases of *S. pyogenes* pyoderma cases worldwide [30]. Although the conditions generated by *S. pyogenes* are mostly benign, there is a risk of nonsuppurative sequelae such as acute articular rheumatism or acute poststreptococcal glomerulonephritis. Although *S. pyogenes* is still sensitive to penicillins and other antibiotics, it represents a public health problem because of the large number of annual cases, the complications that can occur, and the difficulty of diagnosis. In addition, *S. pyogenes* is an important cause of morbidity and mortality in developing countries, with >500,000 deaths related to acute respiratory failure and invasive infections [30].

In humans, the first step in the pathogenesis of diseases caused by *S. pyogenes* is represented by the colonization of the upper respiratory tract or the skin. The formation of the biofilm facilitates the persistence of the infection [31]. Both M protein and fibronectin contribute to the endocytosis of *S. pyogenes* into respiratory epithelial cells. This intracellular invasion of *S. pyogenes* has been postulated to be responsible for repeated infections after correctly administered antibiotic therapy, and repeated antibiotic courses might not lead to eradication but to the selection of more invasive strains [32].

S. pyogenes is susceptible to beta-lactam agents, but very rarely, strains have been isolated with a mutation of the penicillin-binding protein that confers moderate resistance, needing a higher MIC. Nevertheless, *S. pyogenes* remains susceptible to penicillins [33]. A 2019 study reported that a mutation in the penicillin-binding protein (PBP), *pbp2x*, resulted in enhanced resistance to ampicillin and amoxicillin in two patients with significant invasive infections with *S. pyogenes* subtype *emm43.4*. However, the study found no proof that this mutation is widely distributed [33].

In light of the above, the antibiotic of choice for *S. pyogenes* is penicillin, although amoxicillin and ampicillin are also widely used because of better acceptability by children and parents [34]. Given the resistance of *S. pyogenes* to macrolides, these are reserved for patients who are allergic to beta-lactam antibiotics. Sulfonamides and tetracycline are not effective and should not be used to treat strep throat.

There is evidence that cephalosporins are superior to penicillins and that they may reduce the number of chronic carriers after the end of treatment, but higher costs and the potential risk of developing resistance mean that cephalosporins are used as second-line therapy for patients who are sensitive to beta lactam antibiotics. Erythromycin is an alternative antibiotic for the treatment of certain *S. pyogenes* infections [34].

Some patients do not respond to treatment, which can be classified as bacteriological or clinical failure. When a patient shows symptoms despite a correctly administered treatment, retesting for *S. pyogenes* is necessary. If the culture is positive, then the treatment with beta-lactam antibiotics is resumed. If the culture is negative then the symptoms have another etiology. Bacteriological failure is classified as true or false. In the case of true bacteriological failure, the *emm* type of *S. pyogenes* persists despite correctly conducted treatment. There are several potential causes in the absence of penicillin resistance, such as tolerance to penicillin (the discrepancy between the concentration of penicillin required to inhibit/destroy the bacteria), the presence of pharyngeal flora that increases the colonization and growth of *S. pyogenes* or one that produces beta-lactamases that inactivate penicillin, or the internalization of *S. pyogenes* by the host cells, which protects it from the antibiotic [35,36].

Staphylococcus aureus

One common bacterial pathogen that causes a wide range of clinical symptoms is *S. aureus*. Both community-acquired and hospital-acquired infections are common, and treatment remains difficult to manage owing to the emergence of multidrug-resistant strains such as MRSA [37,38].

MRSA strains carry a *mec* gene on the bacterial chromosome, which is a component of the larger Staphylococcal cassette chromosome *mec* (SCC*mec*) region, more specifically *mecA*, conferring resistance to several antibiotics depending on the type of SCC*mec* [37]. Penicillin-binding protein 2a (PBP-2a) is a protein that is encoded by the *mec* gene. The synthesis of peptidoglycan in the bacterial cell wall is catalyzed by PBP-2a even in the presence of several antibiotics because it has a lesser affinity than other PBPs for binding to beta-lactams and other penicillin-derived antibiotics. Because of this, MRSA strains are resistant to a wide range of antibiotics, and *S. aureus* strains that produce PBP-2a can proliferate in the presence of numerous drugs. Hence, MRSA strains are frequently resistant to methicillin, nafcillin, oxacillin, and cephalosporins [37,38].

MRSA was first discovered five decades ago [39]. Since then, MRSA infections have spread worldwide, occurring with high incidence in many countries in Europe, America, and Asia [7]. MRSA infections can be very severe and are one of the most common infections caused by antibiotic-resistant bacteria [6]. MRSA is resistant to penicillin-like beta-lactam antibiotics [40]. However, a number of antibiotics still retain activity against MRSA, in-

cluding glycopeptides (e.g., vancomycin and teicoplanin), linezolid, tigecycline, daptomycin, and even some newer beta-lactams such as ceftaroline and ceftobiprole [7]. Nevertheless, MRSA has demonstrated exceptional adaptability in its development and dissemination within healthcare facilities, the general population, and more recently among animals. This worsens the prevalence of MRSA infections and poses a difficulty for infection control centers that mainly concentrate on healthcare-associated infections. Furthermore, although resistance to anti-MRSA agents usually occurs through bacterial mutation, there have been reports of transfer of resistance to antibiotics such as linezolid and glycopeptides, which is a major concern [7].

Fortunately, the incidence of MRSA infections associated with nursing seems to be decreasing because aggressive preventive hygiene measures in hospitals have had a positive effect, which confirms that infection control can limit the spread of MRSA [7]. On the other hand, over the past decade, the rate of community-acquired MRSA infections has increased rapidly among the general population. Although there is some evidence that these increases are trending downward, they do not follow the same downward trends observed for hospital-acquired MRSA infections [6].

S. aureus (including MRSA) is found on the skin and mucous membranes, and humans are the major reservoir for these microorganisms [38]. Approximately 50% of all people are thought to be colonized, and around 15% of the population carry *S. aureus* continuously in their nostrils [38]. Some populations tend to have higher rates of *S. aureus* colonization (up to 80%), such as healthcare workers, individuals who use needles regularly (i.e., patients with diabetes and intravenous drug users), hospitalized patients, and immunocompromised individuals. *S. aureus* can spread from person to person by direct contact or through contaminated objects [38,41].

S. aureus infections are regularly seen in primary care providers, internists, and infectious disease specialists. The primary objective of treatment is to ascertain the existence or non-existence of strains that are resistant to drugs. For most infections, it is recommended to limit the duration of antibiotic prescriptions to no more than 7–10 days [41]. The development of resistant bacteria is a consequence of the empirical prescribing of antibiotics [41]. Pharmacists should collaborate with the doctor to focus on antimicrobial therapy, while the nurse can oversee the progress to identify any need for adjustments in the treatment regimen if it proves to be ineffective. Such infections necessitate interprofessional collaboration in order to ensure correct treatment.

Furthermore, it is imperative that a multidisciplinary team of nurses and physicians provide the patient with comprehensive knowledge on hand hygiene to effectively mitigate the spread of illness to others. The treatment of *S. aureus* infections depends largely on the type of infection as well as the presence or absence of drug-resistant strains [41]. In general, penicillin remains the drug of choice for methicillin-susceptible *S. aureus* (MSSA) strains and vancomycin for MRSA strains [38]. Because many MRSA strains are resistant to multiple antibiotics, MRSA infections are increasingly recognized as serious pathogens in both hospital and community settings [38].

A recent study has shown the lethal effect of supernatant isolated from *S. aureus* under the effect of ciprofloxacin on MRSA strains [42]. The study involved the examination of 83 strains of *S. aureus* obtained from hospitals, and the investigation of the minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of MRSA in the presence of ciprofloxacin. The existence of the *mecA* gene in the strains was confirmed through genotyping and phenotyping using PCR testing, revealing that all 83 samples harbored *mecA* genes, indicative of MRSA strains. The average MIC of ciprofloxacin and supernatant for various strains of MRSA were 0.032 mg/ml and 0.02 mg/ml, respectively [42]. Similarly, the average MBC of ciprofloxacin and supernatant for different strains of MRSA were 0.064 mg/ml and 0.04 mg/ml, respectively [42]. The impact of ciprofloxacin and supernatant on the mortality of stressed bacteria was verified, revealing the activation of genes associated with programmed cell death in many MRSA samples following bacterial stress induced by the antibiotic ciprofloxacin. Comparison of the MIC and MBC values for MRSA strains when exposed to ciprofloxacin and the liquid portion of the culture yielded similar outcomes. This suggests that the protein released by cultivated staphylococci has a lethal effect on the bacteria when combined with small quantities of ciprofloxacin [42].

Haemophilus influenzae

Until about 1990, *Haemophilus influenzae* (*H. influenzae*) type b (Hib) was the leading cause of bacterial meningitis in children <5 years of age in the United States, accounting for 8,000–10,000 cases per year [43]. In addition, pyogenic arthritis, pneumonia, pericarditis, and facial cellulitis were all significantly attributed to Hib in young children, and it was also the main cause of epiglottitis [44]. With a peak incidence at 6–7 months of age, approximately 1 in 200 US children suffer from invasive (bacteremic) illness caused by this microorganism before turning 5 years old. Since 1990, the incidence of invasive Hib disease in the United States has decreased by more than 99%, to only 0.8 cases per 100,000 children under 5 years of age, primarily involving children who are not immunized or infants too young for vaccination [44–46]. Globally, Hib deaths decreased by 90% between 2000 and 2015 [47].

Although invasive Hib disease has been successfully reduced in the United States and other developed nations, Hib is still a frequent pathogen in countries in which a significant portion of the population lacks access to routine vaccinations, and continues to be the primary cause of bacterial meningitis and the second cause of bacterial pneumonia in these regions [48]. Roughly 900,000 cases of invasive Hib illness were recorded worldwide in 2008; meningitis and pneumonia accounted for the majority of the 199,000 fatalities [49]. This reflects a large decrease from approximately 371,000 deaths in 2000 [49].

Nontypeable strains of *H. influenzae* are a common cause of localized respiratory tract infections in children and adults, being the primary cause of purulent conjunctivitis, acute otitis media (AOM), otitis media with effusion, and sinusitis in children [50,51]. They are also a prevalent cause of pneumonia and a significant contributor to death in children residing in impoverished nations [50]. Nontypeable *H. influenzae* is also an occasional cause of serious invasive diseases such as septicemia, meningitis, and pyogenic arthritis, especially in neonates, pregnant women, and immunocompromised individuals [52,53]. Following the effective implementation of Hib vaccinations, nontypeable strains of *H. influenzae* currently account for the majority of invasive *H. influenzae* cases in the United States across all age categories. Between 2009 and 2015, the yearly occurrence of nontypeable *H. influenzae* invasive illness was approximately seven instances per 100,000 children aged under 5 years. In Europe, approximately

78% of all reported cases of *H. influenzae* were caused by nontypeable strains between 2007 and 2014 [54].

When considering the treatment of invasive *H. influenzae* infections, it is noteworthy that resistance to ampicillin is common among isolates, with a prevalence of >40% in some communities [55,56]. Consequently, ampicillin should not be used alone as empiric therapy for invasive disease. Resistance to ampicillin is usually related to beta-lactamase production, but is occasionally caused by reduced affinity of certain PBPs (especially PBP3) [57]. Ceftriaxone is the therapy of choice for meningitis caused by *H. influenzae* because of its potent activity against the bacterium (including beta-lactamase-producing isolates and isolates with an altered PBP) and because ceftriaxone reaches high levels in the cerebrospinal fluid ($MIC_{90} \leq 0.03$, with rare isolates having an MIC of 0.25) [58].

Oral medications with efficacy against the strain responsible for otitis media, community-acquired pneumonia, and sinusitis can be used for treatment. Antibiotics that provide a MIC_{90} include cephalexin, cefaclor, cefuroxime, cefixime, amoxicillin-clavulanate, trimethoprim-sulfamethoxazole, clarithromycin, and azithromycin [58].

Moraxella catarrhalis

Moraxella catarrhalis (*M. catarrhalis*) is responsible for up to 30% of AOM cases [59–61], and it is the second most common cause of exacerbation of chronic obstructive pulmonary disease in adults (after *H. influenzae*), being responsible for 2–4 million episodes each year in the United States [62].

Almost all contemporary isolates of *M. catarrhalis* produce beta-lactamase [63]. The bacterium has the ability to create biofilms in laboratory settings and has been found in biofilms in the middle ear of individuals suffering from chronic otitis media. Biofilm production by *S. pneumoniae* and *M. catarrhalis* is considered to be important in the role of these pathogens in recurrent AOM and serous otitis media [64,65]. At the mucosal level of the respiratory tract, *M. catarrhalis* activates a pro-inflammatory response and can also inhibit the inflammatory cascade, leading to the persistent colonization of the mucosal surface [66].

Colonization rates in the upper respiratory tract vary by age, with the highest rates (28–100%) in the first year of life [67]. *M. catarrhalis* can persist for several months, and earlier colonization is associated with higher risks of AOM and relapse [68]. Seasonal peaks of colonization and disease (winter and spring) are similar to several viral respiratory pathogens [69,70].

Between 5–32% of older adults with chronic obstructive pulmonary disease may have, at any time, *M. catarrhalis* colonizing the respiratory tract, with an average carrier duration of 30–40 days [71].

The most frequent diseases caused by *M. catarrhalis* are pneumonia, bronchitis, sinusitis, and AOM [72]. The majority of AOM cases are self-limited [72]. Compared with AOM caused by other pathogens, AOM caused by *M. catarrhalis* is more often a mixed infection and is less often associated with spontaneous perforation and mastoiditis [72]. The bacterium rarely causes suppurative complications of AOM, such as osteomyelitis, meningitis, or brain abscess. In recent years, *M. catarrhalis* has become a more common etiology of AOM, as cases of AOM with *S. pneumoniae* have decreased in frequency because of the routine use of pneumococcal conjugate vaccines (PCV7, PCV13) [61,73].

M. catarrhalis is almost uniformly resistant to penicillin, ampicillin, and amoxicillin owing to the production of beta-lactamases [74–77]. The drug of choice in the treatment of *M. catarrhalis* infections is amoxicillin-clavulanate. Second- or third-generation cephalosporins are alternative therapeutic agents. Strains with resistance to macrolides, tetracycline, trimethoprim-sulfamethoxazole, and quinolones have been reported [75,78].

The importance of *M. catarrhalis* as a respiratory pathogen in the post-PCV13 era and its increasing resistance to antimicrobial agents encourage consideration of a vaccine [79,80]. A combined nontypeable *H. influenzae* and *M. catarrhalis* vaccine candidate using the surface protein UspA2 demonstrated acceptable safety and immunogenicity in a phase 1 study in older adults [81].

Vancomycin-resistant enterococci

The presence of VRE poses a significant treatment challenge. Enterococci are responsible for a wide range of diseases, especially among patients in hospitals or other healthcare institutions, including septicemia of various causes (surgery, urinary tract infections, etc.) [6,40]. VRE infections, often caused by *Enterococcus faecium* (*E. faecium*) and less often by *Enterococcus faecalis* (*E. faecalis*), have a lower worldwide prevalence and epidemiological impact than MRSA, except for the United States and some European countries [7].

The proportion of infections that are resistant to vancomycin depends on the species [6]. Overall, 30% of hospital-acquired enterococcal infections are resistant to vancomycin, resulting in 1,300 deaths per year [6]. The presence of *vanA* and *vanB* genes, responsible for vancomycin resistance, poses a significant risk, with some studies indicating the potential for gene transfer from enterococci to other bacteria, including *S. aureus* [7]. Antibiotic options for the treatment of VRE infections are limited [7]. Antibiotics used against VRE include linezolid and quinupristin–dalfopristin, whereas the role of daptomycin and tigecycline is still under investigation. Unfortunately, VRE remains a major threat. Consequently, there is tremendous interest in the development of new antibiotics that could have bactericidal action against VRE, such as oritavancin [7].

Linezolid-resistant enterococci

The US Food and Drug Administration (FDA) approved linezolid as the first oxazolidinone antibiotic for use in clinical settings in 2000. Oxazolidinones, which are now used in hospital settings, have been regarded as a novel class of antibiotics for the last 40 years [82]. They are very effective against Gram-positive bacteria, including VRE and MRSA, and act through the suppression of protein synthesis by interacting with domain V of the 23S ribosomal RNA (rRNA) [83].

Linezolid is typically used to treat severe infections caused by Gram-positive bacteria that are resistant to many drugs. Currently, linezolid is regarded as a last-resort antibiotic [84]. However, for VRE infections, linezolid is the recommended course of action. Although highly transmissible VRE outbreaks were considered the source of linezolid resistance, it was shown that linezolid therapy in individual patients may also lead to the development of resistance in non-outbreak scenarios [84]. The possibility of VRE epidemics evolving into linezolid/vancomycin-resistant enterococci outbreaks is a significant worry, emphasizing the necessity of genetic surveillance as well as hospital outbreak management and monitoring [84].

Oxazolidinones inhibit the synthesis of bacterial ribosomal proteins and prevent the assembly of the initiation complex [85].

It was believed that resistance would not develop easily, as bacterial species frequently have several copies of the 23S rRNA gene (four alleles in *E. faecalis*, five–six alleles in *E. faecium*) and this would need changes in multiple 23S rRNA copies [86].

Enterococcus strains that are resistant to linezolid have become more common in recent years [87], and the most common causes include mutations in ribosomal proteins L3, L4, and L22, as well as domain V of the 23S rRNA [87,88].

The plasmid-mediated methyltransferase-encoding gene *cfr* was the first known transferable linezolid resistance gene [89]. The phenotype mediated by this gene confers resistance to lincosamides, phenicols, oxazolidinones, streptogramin A, and pleuromutilin [89]. Furthermore, it has been shown that the *cfr* gene is transferred between different bacterial species and genera [90,91]. In reference to enterococci, it was initially revealed that the *cfr* gene was present in animal-origin *E. faecalis*. Several more conjugative plasmids encoding this gene were discovered during additional research on enterococci [92]. In addition, reports of *E. faecium* isolates carrying the *cfr* gene are growing [93]. Since the *cfr* gene was discovered in a bovine *Staphylococcus* isolate in 2000, *Enterococcus* isolates from people and animals, including pigs, cattle, horses, and poultry, have also been shown to have this gene [94].

The ATP-binding cassette (ABC)-F protein encoded by the new transferable oxazolidone-resistance gene (*optrAIt*) in *Enterococcus* spp. was discovered in 2015. This protein confers cross-resistance to oxazolidinones and phenicols while mediating resistance through target protection [95–97]. The *optrAIt* gene is transferable and may be found on plasmids. It confers resistance to streptogramin B, aminoglycosides, macrolides, lincosamides, and phenicols, among other antibiotics. The *optrA* gene was initially identified in human-origin *E. faecalis*, and further investigations have revealed its existence in isolates of *E. faecium* [98–102]. It is more common in enterococci isolated from animals than from humans, according to monitoring studies [103]. The presence of the *optrA* gene was demonstrated in both *E. faecalis* strains isolated from veal meat (2015) and *E. faecium* strains isolated from turkey meat (2012) [104].

Recently, MRSA and enterococci were revealed to harbor *poxtA*, a gene that confers resistance to oxazolidinones [105]. It has been suggested that animal husbandry may be connected to *poxtA* [106]. In 2022, Zarzecka *et al.* reported that 28 strains exhibited phenotypic resistance to linezolid. Two strains (7.1%) were recognised as *E. faecium*, one strain (3.6%) was identified as *E. hirae*, and the majority (89.3%) belonged to the *E. faecalis* strain [82]. In total, 96.4% of the linezolid-resistant isolates were resistant to antibiotics from three or more classes, primarily ansamycins, tetracyclines, and macrolides, with linezolid MICs of 8–32 µg/ml [82]. In eight strains (28.6%), linezolid resistance was caused by the point mutation G2576T in domain V of the 23S rRNA. The *poxtA* gene was found in 64% of *E. faecalis* strains, whereas the *cfr* gene was found in 12% of *E. faecalis* strains and 50% of *E. faecium* strains [82]. The number of linezolid-resistant enterococci that have been identified since the drug was first used in clinical settings is continually rising [107,108]. They have been more prevalent in clinical isolates for a number of years, and lately, they have also been found in food [109–111].

There were fewer isolates of enterococci resistant to linezolid, according to an investigation of antibiotic resistance in foods derived from plants [112], suggesting that selection pressure caused by the use of antibiotics in animal husbandry may be the cause of resistance to linezolid [112].

The most prevalent causes of linezolid resistance are thought to be point mutations in the V domain of 23S rRNA and genes encoding ribosomal proteins L22 (*rplV*), L3 (*rplC*), and L4 (*rplD*) [113].

Zarzecka *et al.* have shown that the primary gene encoding for linezolid resistance is *poxtA* [82]. This gene was found in enterococci strains obtained from food-producing animals and animal-derived foods, and it has been demonstrated that eating certain foods can lead to human contraction of these bacteria [114]. According to Antonelli *et al.*, strains with the *poxtA* gene may spread if oxazolidinones are used excessively in animals raised for food [105].

The available information demonstrates the significance of genotypic characterization of vancomycin and linezolid resistance, which may one day inform treatment decisions. Vancomycin can be used to treat isolates that are sensitive to both linezolid and vancomycin. Linezolid may be used as a monotherapy to treat VRE isolates. In rare cases, linezolid and daptomycin are given together [84]. Nevertheless, oral therapy is not available for linezolid/vancomycin-resistant enterococci isolates, necessitating intravenous antibiotic delivery [84]. Long-term usage of this antibiotic may lead to mutations that decrease resistance to linezolid, according to Smith *et al.* [115].

Antibiotic-resistant *Mycobacterium tuberculosis*

The drug resistance of *Mycobacterium tuberculosis* (*M. tuberculosis*) poses a significant global problem. The WHO reported that in 2012, 170,000 people died from drug-resistant tuberculosis (TB) [9,41]. *M. tuberculosis* is most commonly spread by aerosols. The infections caused by this bacterium can occur anywhere in the body, but most often they are localized in the lungs [6].

The major factors driving TB drug resistance are incomplete, incorrect, or unavailable treatment, as well as the lack of new drugs [6]. Typically, TB infections can be treated and cured with first-line medications such as isoniazid or rifampicin. However, there are instances when *M. tuberculosis* may develop resistance to one or more of these drugs. The management of drug-resistant TB is intricate, necessitating extended treatment durations and the use of costly medications that frequently induce adverse reactions. Extensively drug-resistant TB (XDR-TB) is a form of TB that is resistant to the majority of drugs, including isoniazid, rifampicin, fluoroquinolones, and the three second-line injectable drugs (amikacin, kanamycin, and capreomycin). As a result, there are limited treatment options for patients with XDR-TB, and the effectiveness of available drugs is significantly reduced [6]. Although drug-resistant TB and XDR-TB infections represent a growing threat worldwide, including Romania, in some areas, such as the United States, they are uncommon owing to effective prevention measures [6].

MDR *P. aeruginosa*

P. aeruginosa is a common cause of nosocomial infections, including pneumonia, urinary tract infections, post-surgical infections, and septicemia [6]. Approximately 400 deaths per year are attributed to these infections in the United States [6]. Unfortunately, some strains of MDR *P. aeruginosa* have been shown to be resistant to almost all antibiotics, including aminoglycosides, cephalosporins, fluoroquinolones, and carbapenems [6].

P. aeruginosa infections that have limited treatment choices are frequently observed in ICUs and long-term acute care hospitals. This is likely attributed to the excessive use of antimicrobial

drugs, which facilitates the emergence and dominance of this bacterium [116]. The following are novel treatment options for MDR *P. aeruginosa* infections.

Ceftolozane–tazobactam is a fifth-generation expanded-spectrum cephalosporin paired with a widely recognised beta-lactamase inhibitor. This combination has heightened efficacy against *P. aeruginosa*, encompassing both MDR and XDR strains, owing to its ability to inhibit crucial PBPs. In addition, it demonstrated significant potency, primarily against Enterobacterales, including ESBL strains [117]. However, it is ineffective against *P. aeruginosa* strains that produce carbapenemase, which reduces the available treatment choices for carbapenem-resistant *P. aeruginosa*. Specifically, the presence of metallo-beta-lactamases (MBL) has been associated with the identification of *P. aeruginosa* strains that are not susceptible to ceftolozane–tazobactam [118,119]. Ceftolozane–tazobactam has demonstrated limited efficacy against *P. aeruginosa* in biofilm form in laboratory studies [120]. Ceftolozane–tazobactam is a favorable choice for treating susceptible MDR/XDR *P. aeruginosa* infections. It is considered a primary treatment option for carbapenem-susceptible *P. aeruginosa* strains according to recent European guidelines [121]. In addition, it is recommended for severe infections in the ICU and complex clinical situations, as demonstrated in real-life studies [122,123].

Ceftazidime–avibactam is a unique pairing of a widely used third-generation cephalosporin, recognised for its effectiveness against *Pseudomonas* bacteria, with a newly developed beta-lactamase inhibitor that does not belong to the beta-lactam class of antibiotics. This novel chemical exerts its effects by binding to PBPs found in the cell walls of Gram-negative aerobic pathogens and *P. aeruginosa*, including MDR or XDR strains [124,125]. Real-world observations regarding the treatment of MDR *P. aeruginosa* have shown promising levels of effectiveness. Firstly, in a group of patients with complex medical conditions and severe MDR Gram-negative infections, 31% of which were caused by *P. aeruginosa*, particularly those resistant to carbapenem antibiotics [126]. Secondly, in a retrospective study involving patients with MDR/XDR *P. aeruginosa* infections (61 initial episodes), although not treated immediately [127], it was found to be a viable treatment option. Furthermore, a significant proportion (87.8%) of severe infections caused by MDR and XDR *P. aeruginosa* isolates, which were not resistant to carbapenem, were successfully treated in a group of patients with Gram-negative infections caused by MDR, non-carbapenem-resistant Enterobacterales (CRE). This cohort consisted of 33 out of 41 cases (80.5%) of *P. aeruginosa* infections [128].

Imipenem–cilastatin–relebactam is a novel antibiotic combination that includes imipenem, a carbapenem, and relebactam, a powerful non-beta-lactam bicyclic diazabicyclooctane beta-lactamase inhibitor. Relebactam is chemically similar to avibactam but has an extra piperidine ring [129]. In 2019, the FDA authorized imipenem–cilastatin–relebactam for the treatment of complicated urinary tract infections (cUTI), including pyelonephritis, and complicated intra-abdominal infections (cIAI) in adult patients [129]. In 2020, the European Medicines Agency also approved it for the treatment of infections caused by aerobic Gram-negative bacteria in individuals with limited treatment alternatives [130]. Data obtained from the Study for Monitoring Antimicrobial Resistance Trends (SMART) surveillance program revealed that relebactam enhanced the effectiveness of imipenem in 80.5% of imipenem-resistant *P. aeruginosa* isolates in the United States [131]. Specifically, imipenem–cilastatin–relebactam demonstrated preserved effectiveness against 82.2% of MDR *P. aeruginosa* isolates and 62.2% of XDR *P. aeruginosa* isolates [132]. In another study, the susceptibility of *P. aeruginosa* isolates from intra-abdominal infections and the urinary tract to imipenem–cilastatin–relebactam was found to be 96.7% and 96.4% respectively. In addition, it was observed that imipenem-nonsusceptible and MDR *P. aeruginosa* strains had a susceptibility rate of 85% and 87.3%, respectively [133]. These data align with those from a Canadian study, which showed that imipenem–cilastatin–relebactam had an in vitro activity of 70.8% against MDR *P. aeruginosa* isolates [134].

Meropenem–vaborbactam is an antimicrobial combination that consists of a widely used, powerful carbapenem and a new cyclic boronic acid beta-lactamase inhibitor. The latter has a strong affinity towards serine residues, allowing it to act as a competitive inhibitor by forming a covalent bond with the beta-lactamase without being broken down through hydrolysis [135]. The efficacy of meropenem–vaborbactam against *P. aeruginosa* strains was determined to be generally comparable to that of meropenem alone. A study conducted by Lapuebla *et al.* revealed that 79% of *P. aeruginosa* isolates were sensitive to meropenem, and that the addition of vaborbactam did not alter this rate [136]. The main reason for meropenem resistance in *P. aeruginosa* strains is predominantly caused by mutations in porin or increased activity of efflux pumps. These mechanisms are not counteracted by vaborbactam [137]. However, a separate study indicated that the inclusion of vaborbactam resulted in enhanced eradication of bacteria in a neutropenic mouse thigh infection model, with certain strains of *P. aeruginosa*. This effect was observed despite the fact that the MIC of both agents was the same in laboratory tests. These findings suggest that these strains may possess an inducible beta-lactamase that is effectively inhibited by vaborbactam [138].

A recent study examined the effectiveness of meropenem–vaborbactam in treating pneumonia caused by *P. aeruginosa* and Enterobacterales. The study analyzed data from 3,193 *P. aeruginosa* isolates and 4,790 Enterobacterales isolates collected in US hospitals between 2014 and 2018. The results showed that 89.5% of *P. aeruginosa* isolates were susceptible to meropenem–vaborbactam. Among these isolates, the susceptibility rates for MDR strains and XDR strains were 59.0% and 48.6%, respectively [139].

Carbapenem-resistant Enterobacterales

CRE are a group of bacteria that have become resistant to all or nearly all available antibiotics, including carbapenems, which are usually reserved as a last-resort treatment against pathogens resistant to other drugs [6,9,40]. The enzyme New-Delhi metallo-beta-lactamase-1 (NDM-1) is present in certain Gram-negative Enterobacterales (especially *E. coli* and *K. pneumoniae*), conferring resistance to practically all beta-lactams, including carbapenems [40].

Carbapenems are structurally similar to penicillin and are effective against a wide range of bacteria [140]. In contrast to other beta-lactams, carbapenems possess a carbon atom instead of a sulfone group at the fourth position of the beta-lactam ring. This distinctive architecture significantly contributes to their resistance against beta-lactamases [141]. Carbapenems have limited ability to pass through the cell wall, but they are able to enter bacteria by using outer membrane proteins known as porins. Carbapenems exert their action by breaking down the cell wall through the beta-lactam ring, specifically targeting the PBPs. The mechanism

of action involves the degradation of the glycan backbone in the cell wall by autolysis, leading to the destruction of the cell as a result of osmotic pressure [140–142].

CRE refers to Enterobacterales that exhibit resistance to at least one carbapenem antibiotic, as determined by their antibiotic susceptibility profile (phenotypic definition) [143]. Carbapenem resistance primarily occurs when bacteria undergo certain mechanisms, such as genotypic changes. These mechanisms include acquiring structural alterations in PBPs, exhibiting a decrease or loss of specific outer membrane porins that prevent carbapenems from reaching their target site, activating efflux pumps to eliminate antibiotics and regulate the intramembrane environment, and acquiring beta-lactamases and carbapenemases to break down or hydrolyze carbapenems and other beta-lactam antibiotics (e.g., penicillins and cephalosporins) [140–143].

In general, CRE can develop resistance through genetic changes in the *porin* gene (in non-carbapenemase-producing CRE) or by developing enzymes that can break down carbapenem antibiotics (in carbapenemase-producing CRE) [143]. The existence or manifestation of the gene encoding carbapenemase often confers carbapenem resistance, affecting around 30% of CRE cases. Therefore, carbapenemase-producing CRE is a smaller group that falls inside the larger category of all CRE [143,144]. Although many individuals colonized with CRE do not develop illnesses, they can nevertheless transmit the bacteria [143]. Hence, the Antibiotic Resistance Laboratory Network and CDC laboratories perform regular tests for carbapenemase-producing CRE to proactively prevent and manage their onset and dissemination [143].

Carbapenemases, which are enzymes that break down carbapenem antibiotics, have been categorized into three groups based on the Ambler classification: class A, B, and D beta-lactamases. This classification is based on their ability to hydrolyze and be inhibited by certain substances, using either serine or zinc as catalysts [140,142,145,146].

Class A enzymes, namely serine beta-lactamases, catalyze the hydrolysis of a wide range of beta-lactam antibiotics, such as carbapenems, cephalosporins, penicillin, and aztreonam [146]. The enzymes are classified as chromosomally encoded and plasmid-encoded variants [146]. Chromosomally encoded enzymes include non-metalloenzyme carbapenemase-A (NMC-A), *Serratia marcescens* enzyme (SME), imipenem hydrolyzing beta-lactamase (IMI-1), and *Serratia fonticola* carbapenemase-1 (SFC-1). Plasmid-encoded variants include *K. pneumoniae* carbapenemase (KPC), imipenem-hydrolyzing beta-lactamase (IMI), and Guiana extended spectrum (GES) [140,145]. Of these, the KPC type is the most widespread enzyme and is responsible for epidemics in several Asian, African, North American, and European countries [140,145].

Class B enzymes, sometimes referred to as MBL, use metal ions, typically zinc, as a cofactor to target the active site of the enzyme, namely the beta-lactam ring. There are a total of ten varieties of MBLs, the most significant ones being New Delhi MBL (NDM), Verona integron-encoded MBL (VIM), and imipenemase (IMP) [140,143,145,147]. These enzymes break down all existing beta-lactam antibiotics, with the exception of monobactams such as aztreonam [148].

Class D enzymes, specifically serine beta-lactamases, are a group of enzymes known as oxacillinase (OXA) or oxacillin-hydrolyzing enzymes. There are more than 200 enzymes in this group. OXA exhibits fast mutation and a broad range of action. The most common carbapenem-hydrolyzing enzymes are OXA-48 and OXA-181, which exist in more than 40 different variations [149]. The prevailing forms of OXA-48 and OXA-101 in *K. pneumoniae* have been observed in Turkey, the Middle East, North Africa, and Europe [140,149,150]. Nevertheless, it is important to acknowledge that bacteria that produce OXA enzymes frequently exhibit resistance at a low level as a result of feeble expression. This poses a danger for the detection of false positive results and limits the availability of appropriate treatment alternatives [150].

Aztreonam, a monobactam antibiotic, is effective against bacteria that produce class B and D carbapenemases, when used alone. However, these bacteria frequently harbor ESBL genes, which hydrolyze aztreonam and render it ineffective. As a result, aztreonam has limited therapeutic use when used alone [151,152]. A potential therapeutic option for MBLs is the combination of aztreonam and ceftazidime–avibactam, a new beta-lactam-beta-lactamase inhibitor. Interestingly, aztre-onam is inactive against bacteria that produce class A carbapenemases, including those that produce the widely distributed KPC carbapenemases [151].

While ceftazidime–avibactam by itself is ineffective against MBLs, it exhibits a strong in vitro syn-ergy with aztreonam to act against these isolates [153]. This is especially crucial given that despite its effectiveness against class B carbapenemases, aztreonam is frequently broken down by other beta-lactamases that co-occur with MBLs [154]. Consequently, a recent global assessment revealed that only 29.2% of MBLs were still susceptible to aztreonam monotherapy, but all MBL isolates were inhibited by the combination of aztreonam and avibactam [155]. Six out of ten patients had clinical success after 30 days in a clinical case series assessing this combination treatment for infec-tions caused by NDM-producing MBLs during an outbreak. This suggests that ceftazidime–avibactam plus aztreonam may be a useful clinical option for XDR Enterobacterales infections that contain both class B carbapenemases and ESBL enzymes [156]. Based on these observations, the Infectious Diseases Society of America recommends the use of advises ceftazidime–avibactam alone CRE infections that produce OXA-48 outside of the urinary tract, and in conjunction with aztreonam for CRE infections that produce NDM [157].

Combinations of beta-lactam and beta-lactamase inhibitors have been developed and licensed in recent years with the express purpose of targeting organisms that are resistant to several drugs, such as CRE. The first of these, avibactam, was created in 2011. It is a synthetic diazabicyclooctane non-beta-lactam that exhibits action against class A (KPC) [158,159] and class D (OXA-48-like) carbapenemases, but not MBLs [159–161]. It binds to serine beta-lactamases covalently and re-versibly. Several observational studies have demonstrated that ceftazidime–avibactam is more ef-fective than polymyxin antibiotics in treating CRE infections, including class A carbapenemases, with less toxicity and adverse effects [162–165]. In 2015, the European Medicines Agency and the FDA authorized ceftazidime–avibactam in combination with metronidazole for the treatment of cIAI and cUTI [166]. The approval was based on the results of the RECLAIM trials, which have shown that ceftazidime–avibactam was not inferior to meropenem in the treatment of cIAI [167], and those of the RECAPTURE trial, which demonstrated that doripenem was not inferior to ceftazidime–avibactam in the treatment of cUTI [168]. Following the REPROVE study, a phase 3 trial conducted in 23 countries that demonstrated the noninferiority of ceftazidime–avibactam com-pared to meropenem for the treatment of

nosocomial pneumonia, approval has recently been broad-ened to encompass hospital-acquired and ventilator-associated pneumonia [169]. According to the microbiological investigation, at baseline, a ceftazidime-resistant organism was present in 13.5% of patients in the RECLAIM trials, 19.6% of patients in the RECAPTURE trial, and 28% of patients in the REPROVE study. The rate of MBL infection was only reported by the RECLAIM studies, and it was around 3% [167].

In vitro susceptibility to ceftazidime–avibactam for CRE has remained high in isolates from hospitalized patients worldwide, according to data collected during the INFORM global surveillance survey for antimicrobial resistance; of the 816 non-MBL CRE isolates collected between 2012 and 2014, only 19 (2.3%) were resistant and 97.7% were susceptible to ceftazidime–avibactam [170]. Testing conducted on isolates obtained between 2015 and 2017 revealed a comparably high susceptibility to ceftazidime–avibactam, at 99.8% [171].

Although ceftazidime–avibactam susceptibility rates are still high overall, some mutations that confer resistance have been observed, mostly in carriers of KPC-2 and KPC-3 enzymes. It has been demonstrated that sequence type-258 *K. pneumoniae* with KPC-3 is resistant to ceftazidime–avibactam because KPC-3 was transposed onto a different plasmid, which changed the porin channels OmpK35 and OmpK36 and increased the expression of efflux pumps [172–174]. It is note-worthy that mutations in blaKPC-3 that confer resistance to avibactam have been observed in patients receiving ceftazidime–avibactam therapy. These mutations involve single amino acid substitu-tions at D179Y/T243M, D179Y, and V240G, which alter the Ω-loop in KPC-3. Nevertheless, in certain isolates, these mutations restore susceptibility to meropenem [175]. More recently, a three-amino-acid insertion was shown to confer greater affinity to ceftazidime and reduce the activity of avibactam, leading to resistance [176]. This KPC-3 variation, known as KPC-50, was identified from a *K. pneumoniae* isolate in a Swedish patient [176].

Patients in healthcare settings are increasingly experiencing infections from CRE bacteria that are incurable or challenging to treat. Each year, in the United States, approximately 600 deaths result from infections caused by the two most common types of CRE, carbapenem-resistant *Klebsiella* species and carbapenem-resistant *E. coli* [6].

ESBL-producing Enterobacterales

ESBL-producing Enterobacterales contain a broad-spectrum beta-lactamase enzyme that favors the emergence of resistance to a wide variety of penicillin and cephalosporin antibiotics [6,9]. In the United States, Enterobacterales that produce ESBLs are responsible for 1,700 fatalities and 26,000 nosocomial infections annually [6]. A carbapenem antibiotic is a viable therapeutic option given that a significant fraction of ESBL-producing Enterobacterales are resistant to beta-lactam antibiotics. However, these drugs should be used with caution, as they contribute to the development of resistance [6].

MDR *Acinetobacter*

Acinetobacter is a Gram-negative bacterium that causes pneumonia or bacteremia, particularly in individuals who are severely ill and require mechanical ventilation. Certain strains of *Acinetobacter* have developed resistance to nearly all antibiotics, including carbapenems, which are commonly regarded as the final option for treatment. Approximately 12,000 healthcare-related *Acinetobacter* infections occur in the United States each year, and 63% of these are MDR (resistant to at least three different classes of antibiotics), causing 500 deaths per year [6].

MDR *N. gonorrhoeae*

In recent years, drug-resistant forms of *N. gonorrhoeae* have begun to appear in the United States [8]. Gonorrhea is characterized by discharge and inflammation of the urethra, cervix, pharynx or rectum [6]. Although not normally fatal, gonorrhea spreads easily and can cause severe reproductive complications [9]. The CDC estimates that over 800,000 cases of gonorrhea occur annually, being the second most common infectious disease reported in the United States [6]. If *N. gonorrhoeae* antibiotic resistance continues to spread, it is estimated to cause 75,000 additional cases of pelvic inflammatory disease, 15,000 cases of epididymitis, and 222 additional HIV infections over a projected 10-year period [6].

N. gonorrhoeae resistant to cephalosporins is often resistant to other types of antibiotics, such as fluoroquinolones (e.g. ciprofloxacin, levofloxacin, moxifloxacin, ofloxacin), tetracyclines and penicillins as well [6,7], therefore infections caused by these bacteria will not be able to be cured with empirical treatment regimens [6]. To address this challenge, the CDC has updated its guideline regarding the first-line treatment, recommending ceftriaxone with azithromycin or doxycycline [9].

CAUSES OF ANTIBIOTIC RESISTANCE

Mass use

The overuse of antibiotics is clearly leading to an exponential increase in resistance [6,177]. Epidemiological studies have shown a direct relationship between the use of antibiotics and the emergence and spread of resistant strains [178]. Antibiotics eliminate drug-sensitive microorganisms, leaving resistant bacteria to proliferate as a result of natural selection [178]. Despite warnings, antibiotics continue to be overused globally [178]. For example, in many countries, antibiotics are unregulated and available without a prescription [178]. This lack of regulation makes antibiotics easily available and affordable, thereby promoting overuse [179]. The possibility to purchase these products online further facilitates their availability, even in countries with strict regulations [179].

Improper use

The misuse of antibiotics can also lead to the development of drug-resistant bacteria [6]. Several studies have shown that the indication, drug choice, or duration of antibiotic therapy is incorrect in 30% to 50% of cases [6,180]. Some antibiotics, even if partially effective, should be used with caution, especially in individuals with liver dysfunction, including liver fibrosis and cirrhosis [181]. In addition, 30–60% of antibiotics administered in the ICU have been found to be unnecessary, inappropriate, or suboptimal [180]. The misuse of antibiotics has questionable therapeutic efficacy and exposes patients to potential complications of antibiotic therapy [182]. Antibiotic resistance may arise as a result of subinhibitory and subtherapeutic antibiotic concentrations, as they can induce genetic alterations such as mutagenesis

and altered gene expression. Antibiotic-induced changes in gene expression can increase virulence, whereas increased mutagenesis promotes and spreads antibiotic resistance [183]. The use of antibiotics in low concentrations has been shown to help diversify strains such as *P. aeruginosa*. Subinhibitory concentrations of piperacillin and/or tazobactam were also shown to be responsible for extensive proteome changes in *B. fragilis* [183].

Widely used in agriculture

Antibiotics are used as growth supplements and as a means of preventing infection in animals in both developed and developing regions of the world. Similarly to humans, treating animals with antibiotics can cause bacteria to develop resistance. Antibiotic-resistant bacteria seen in animals can be pathogenic to humans, are easily transmitted to humans through the food chain, and spread widely in ecosystems through animal feces. In humans, this can lead to complex, untreatable long-term infections [184,185]. Antimicrobial products used for hygiene or cleaning purposes may also contribute to this problem as they may limit the development of immunity to environmental antigens in children and adults [179,8]. As a result, the multifunctionality of the immune system may be compromised, potentially increasing morbidity and mortality from normally avirulent infections [179].

Availability of a small number of new antibiotics

The development of new antibiotics, which were previously successful in addressing antibiotic-resistant bacteria, has significantly decelerated owing to technical obstacles, limited understanding, substantial challenges in countering bacterial pathophysiology (such as the complex cell wall of Gram-negative bacteria), and financial and regulatory obstacles. Nevertheless, the widespread distribution of new antibiotics nearly invariably leads to the emergence of resistance, often occurring within a relatively brief timeframe. In an attempt to prevent this development, healthcare specialists frequently restrict the use of latest generation antibiotics, recommending them for the most severe conditions, and continue to administer already well-known antimicrobial agents (often generic drugs) that have demonstrated similar efficacy, thus increasing the likelihood that older agents become ineffective owing to the development of bacterial resistance [184].

Global drug resistance: why antibiotic resistance is important

The economic impact of antibiotic resistance is substantial, being estimated to cost $55 billion annually in the United States [186]. Furthermore, research has shown that an infection caused by ESBL-producing *E. coli* or *Klebsiella* can increase hospital costs by an average of $16,450 and increase the length of stay by an average of 9.7 days [187].

The exorbitant costs associated with antibiotic resistance are not limited to developed countries. Developing countries are disproportionately responsible for the emergence of new antibiotic resistance genes, which have both domestic and international implications [188]. For example, NDM-1 was initially detected in a strain of *K. pneumoniae* from a Swedish patient who had recently traveled to India [189]. MRSA infections were found to result in substantial increases in overall mortality rates, bacterial infection mortality rates, mortality rates attributable to ICU, occurrence of septic shock, and a two-fold increase in the likelihood of long-term care [190]. Consequently, the management of MRSA imposes a considerable financial burden on healthcare organizations, although there is currently insufficient evidence to perform a comprehensive assessment of the economic impact. For example, antibiotics effective against vancomycin-resistant *S. aureus*, such as linezolid, are very expensive in developing or underdeveloped countries (e.g., in Romania, ten tablets of linezolid 600 mg cost approximately €145), significantly contributing to the spread of resistant strains [191]. Additionally, there is a lack of studies examining the economic implications of changes in the epidemiology of MRSA, such as infections acquired from farm animals [190].

According to the European Commission, there are 33,000 deaths caused by antibiotic resistance in the European Union each year, representing approximately €1.5 billion per year in healthcare costs [192]. According to a 2019 report of the CDC on the threat of antibiotic resistance, there are over 2.8 million cases of antibiotic resistance in the United States annually, 35,000 of which result in deaths. The emergence of carbapenem-resistant bacteria is a serious concern because they are classified as 'last resort' antibiotics for treating MDR infections [193].

The CDC's assessment of antibiotic-resistant bacterial infections includes seven different factors, such as the clinical and economic impact of infections, case incidence, and projected incidence over a 10-year period. In addition, transmissibility, availability of effective antibiotics, and barriers to prevention are considered [6]. Based on this assessment, the CDC classified the threat level of each bacterium as 'urgent', 'severe', or 'concerning' (Table 1). Bacteria labeled as 'urgent' or 'severe' require more stringent monitoring and prevention measures, whereas those classified as 'concerning' require less immediate attention [6].

Table 1. The CDC's assessment of antibacterial resistance threats [6]

Urgent	Carbapenem-resistant Enterobacterales Drug-resistant *N. gonorrhoeae*
Severe	Multidrug-resistant *Acinetobacter* ESBL Enterobacterales Vancomycin-resistant enterococci Multidrug-resistant *P. aeruginosa* Methicillin-resistant *S. aureus* Drug-resistant *S. pneumoniae* Drug-resistant *M. tuberculosis*
Concerning	Vancomycin-resistant *S. aureus* Erythromycin-resistant *S. pyogenes*

CONCLUSIONS

Antibiotic resistance is a widespread issue, with bacteria having developed mechanisms to counteract the effectiveness of antibacterial products over many millennia. The rise of antibiotic resistance, coupled with a lack of novel medications, presents a challenging future for antibiotic treatment. Once again, the significance of administering antibiotics in clinical practice cannot be minimized. There is a need for more efficient global regulation of antibiotic usage, even in developed nations. Discontinuing the use of non-prescription antibiotics and providing clinicians with knowledge regarding antimicrobial resistance could additionally

diminish the usage of antibiotics. In order to mitigate insufficient demand, it is imperative to increase worldwide public awareness. The use of antibiotics in agriculture should be restricted to the management of contaminated animals rather than promoting growth. Enhancing the monitoring of antibiotic use and resistance is crucial to facilitate the implementation of antibiotic stewardship. In order to match the rise in antibiotic resistance, substantial global interventions and expenditures are anticipated in the manufacture of new antibiotics, funded by both public and commercial sectors.

Conflict of interest

The authors declare no conflict of interest.

Authorship

A.P.B. and C.B. contributed to conceptualization and wrote the initial draft. G.B. and G.G. edited and revised the manuscript with equal contributions. All authors have read and approved the manuscript before submission.

REFERENCES

1. Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet. 2022 Feb 12;399(10325):629-655. doi: 10.1016/S0140-6736(21)02724-0
2. World Health Organization. Antimicrobial Resistance. Available from: https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance
3. Aljeldah MM. Antimicrobial Resistance and Its Spread Is a Global Threat. Antibiotics (Basel). 2022 Aug 9;11(8):1082. doi: 10.3390/antibiotics11081082
4. Rahimkhani M, Saberian M, Mordadi A, *et al*. Urinary tract infection with Candida glabrata in a patient with spinal cord injury. Acta Medica Iranica. 2015;53(8):516-517
5. Rahimkhani M, Nikfalah A, Saberian M, Mordadi A, Varmazyar S, Tavakoli A. Urinary tract infection in spinal cord injuries. Asian Journal of Pharmaceutical and Clinical Research. 2014;7(2):178-182.
6. Centers for Disease Control and Prevention, Office of Infectious Disease. Antibiotic re-sistance threats in the United States. 2013. Available from: http://www.cdc.gov/drugresistance/threat-report-2013
7. Rossolini GM, Arena F, Pecile P, Pollini S. Update on the antibiotic resistance crisis. Curr Opin Pharmacol. 2014 Oct;18:56-60. doi: 10.1016/j.coph.2014.09.006
8. Golkar Z, Bagasra O, Pace DG. Bacteriophage therapy: a potential solution for the antibiotic resistance crisis. J Infect Dev Ctries. 2014 Feb 13;8(2):129-36. doi: 10.3855/jidc.3573
9. Gross M. Antibiotics in crisis. Curr Biol. 2013 Dec 16;23(24):R1063-5. doi: 10.1016/j.cub.2013.11.057
10. Jain S, Williams DJ, Arnold SR, Ampofo K, Bramley AM, Reed C, *et al*. Community-acquired pneumonia requiring hospitalization among U.S. children. N Engl J Med. 2015;372(9):835-845. doi: 10.1056/NEJMoa1405870
11. Black SB, Shinefield HR, Ling S, Hansen J, Fireman B, Spring D, *et al*. Effectiveness of heptavalent pneumococcal conjugate vaccine in children younger than five years of age for prevention of pneumonia. Pediatr Infect Dis J. 2002 Sep;21(9):810-5. doi: 10.1097/00006454-200209000-00005
12. Byington CL, Korgenski K, Daly J, Ampofo K, Pavia A, Mason EO. Impact of the pneumococcal conjugate vaccine on pneumococcal parapneumonic empyema. Pediatr Infect Dis J. 2006 Mar;25(3):250-4. doi: 10.1097/01.inf.0000202137.37642.ab
13. Li ST, Tancredi DJ. Empyema hospitalizations increased in US children despite pneumococcal conjugate vaccine. Pediatrics. 2010 Jan;125(1):26-33. doi: 10.1542/peds.2009-0184
14. Byington CL, Spencer LY, Johnson TA, Pavia AT, Allen D, Mason EO, *et al*. An epidemiological investigation of a sustained high rate of pediatric parapneumonic empyema: risk factors and microbiological associations. Clin Infect Dis. 2002 Feb 15;34(4):434-40. doi: 10.1086/338460
15. Haggie S, Fitzgerald DA, Pandit C, Selvadurai H, Robinson P, Gunasekera H, *et al*. Increasing Rates of Pediatric Empyema and Disease Severity With Predominance of Serotype 3 S. pneumonia: An Australian Single-center, Retrospective Cohort 2011 to 2018. Pediatr Infect Dis J. 2019 Dec;38(12):e320-e325. doi: 10.1097/INF.0000000000002474
16. Centers for Disease Control and Prevention (CDC). Effect of new susceptibility breakpoints on reporting of resistance in Streptococcus pneumoniae--United States, 2003. MMWR Morb Mortal Wkly Rep. 2004;53(7):152-154.
17. Centers for Disease Control and Prevention (CDC). Effects of new penicillin susceptibility breakpoints for Streptococcus pneumoniae--United States, 2006-2007. MMWR Morb Mortal Wkly Rep. 2008;57(50):1353-1355.
18. Metcalf BJ, Gertz RE Jr, Gladstone RA, Walker H, Sherwood LK, Jackson D, *et al*; Active Bacterial Core surveillance team. Strain features and distributions in pneumococci from children with invasive disease before and after 13-valent conjugate vaccine implementation in the USA. Clin Microbiol Infect. 2016 Jan;22(1):60.e9-60.e29. doi: 10.1016/j.cmi.2015.08.027
19. Schroeder MR, Chancey ST, Thomas S, Kuo WH, Satola SW, Farley MM, Stephens DS. A Population-Based Assessment of the Impact of 7- and 13-Valent Pneumococcal Conjugate Vaccines on Macrolide-Resistant Invasive Pneumococcal Disease: Emergence and Decline of Streptococcus pneumoniae Serotype 19A (CC320) With Dual Macrolide Resistance Mechanisms. Clin Infect Dis. 2017 Sep 15;65(6):990-998. doi: 10.1093/cid/cix446
20. Kim L, McGee L, Tomczyk S, Beall B. Biological and Epidemiological Features of Antibiotic-Resistant Streptococcus pneumoniae in Pre- and Post-Conjugate Vaccine Eras: a United States Perspective. Clin Microbiol Rev. 2016 Jul;29(3):525-52. doi: 10.1128/CMR.00058-15
21. Yamada N, Nakamoto T, Takei H, Shoji T, Takahashi K, Sato J, *et al*. Two cases of bacterial meningitis due to meropenem-resistant Streptococcus pneumoniae: A threat of serotype 35B, ST 558 lineage. J Infect Chemother. 2020 Jul;26(7):745-748. doi: 10.1016/j.jiac.2020.02.013
22. Tomczyk S, Lynfield R, Schaffner W, Reingold A, Miller L, Petit S, *et al*. Prevention of Antibiotic-Nonsusceptible Invasive Pneumococcal Disease With the 13-Valent Pneumococcal Conjugate Vaccine. Clin Infect Dis. 2016 May 1;62(9):1119-25. doi: 10.1093/cid/ciw067
23. Hofmann J, Cetron MS, Farley MM, Baughman WS, Facklam RR, Elliott JA, *et al*. The prevalence of drug-resistant Streptococcus pneumoniae in Atlanta. N Engl J Med. 1995 Aug 24;333(8):481-6. doi: 10.1056/NEJM199508243330803
24. Arnold KE, Leggiadro RJ, Breiman RF, Lipman HB, Schwartz B, Appleton MA, *et al*. Risk factors for carriage of drug-resistant Streptococcus pneumoniae among children in Memphis, Tennessee. J Pediatr. 1996 Jun;128(6):757-64. doi: 10.1016/s0022-3476(96)70326-8
25. Melander E, Ekdahl K, Jönsson G, Mölstad S. Frequency of penicillin-resistant pneumococci in children is correlated to community utilization of antibiotics. Pediatr Infect Dis J. 2000 Dec;19(12):1172-7. doi: 10.1097/00006454-200012000-00011
26. Gertz RE Jr, Li Z, Pimenta FC, Jackson D, Juni BA, Lynfield R, *et al*; Active Bacterial Core Surveillance Team. Increased penicillin nonsusceptibility of nonvaccine-serotype invasive pneumococci other than serotypes 19A and 6A in post-7-valent conjugate vaccine era. J Infect Dis. 2010 Mar;201(5):770-5. doi: 10.1086/650496
27. Dagan R, Juergens C, Trammel J, Patterson S, Greenberg D, Givon-Lavi N, *et al*. Efficacy of 13-valent pneumococcal conjugate vaccine (PCV13) versus that of 7-valent PCV (PCV7) against nasopharyngeal colonization of antibiotic-nonsusceptible Streptococcus pneumoniae. J Infect Dis. 2015 Apr 1;211(7):1144-53. doi: 10.1093/infdis/jiu576
28. Lee GM, Kleinman K, Pelton SI, Hanage W, Huang SS, Lakoma M, *et al*. Impact of 13-Valent Pneumococcal Conjugate Vaccination on Streptococcus pneumoniae Carriage in Young Children in Massachusetts. J Pediatric Infect Dis Soc. 2014 Mar;3(1):23-32. doi: 10.1093/jpids/pit057
29. Lee GM, Kleinman K, Pelton S, Lipsitch M, Huang SS, Lakoma M, *et al*. Immunization, Antibiotic Use, and Pneumococcal Colonization Over a 15-Year Period. Pediatrics. 2017 Nov;140(5):e20170001. doi: 10.1542/peds.2017-0001
30. Carapetis JR, Steer AC, Mulholland EK, Weber M. The global burden of group A streptococcal diseases. Lancet Infect Dis. 2005 Nov;5(11):685-94. doi: 10.1016/S1473-3099(05)70267-X
31. Doern CD, Roberts AL, Hong W, Nelson J, Lukomski S, Swords WE, *et al*. Biofilm formation by group A Streptococcus: a role for the streptococcal regulator of virulence (Srv) and streptococcal cysteine protease (SpeB). Microbiology (Reading). 2009 Jan;155(Pt 1):46-52. doi: 10.1099/mic.0.021048-0
32. Wang B, Cleary PP. Intracellular Invasion by Streptococcus pyogenes: Invasins, host re-ceptors, and relevance to human disease. Microbiol Spectrum. 2018;7(4):GPP3-0049. doi: 10.1128/microbiolspec.GPP3-0049-2018
33. Vannice KS, Ricaldi J, Nanduri S, Fang FC, Lynch JB, Bryson-Cahn C, *et al*. Streptococcus pyogenes pbp2x Mutation Confers Reduced Susceptibility to β-Lactam Antibiotics. Clin Infect Dis. 2020 Jun 24;71(1):201-204. doi: 10.1093/cid/ciz1000
34. Casey JR, Pichichero ME. Meta-analysis of cephalosporin versus penicillin treatment of group A streptococcal tonsillopharyngitis in children. Pediatrics. 2004 Apr;113(4):866-82. doi: 10.1542/peds.113.4.866
35. Martin JM, Green M, Barbadora KA, Wald ER. Group A streptococci among school-aged children: clinical characteristics and the carrier state. Pediatrics. 2004 Nov;114(5):1212-9. doi: 10.1542/peds.2004-0133
36. Gerber MA, Tanz RR, Kabat W, Bell GL, Siddiqui Bp, Lerer TJ, *et al*. Potential mechanisms for failure to eradicate group A streptococci from the pharynx. Pediatrics. 1999 Oct;104(4 Pt 1):911-7. doi: 10.1542/peds.104.4.911
37. Centers for Disease Control and Prevention (CDC). Outbreaks of community-associated methicillin-resistant Staphylococcus aureus skin infections--Los Angeles County, California, 2002-2003. MMWR Morb Mortal Wkly Rep. 2003;Feb 07;52(5):88.
38. Boucher HW, Corey GR. Epidemiology of methicillin-resistant Staphylococcus aureus. Clin Infect Dis. 2008 Jun 1;46 Suppl 5:S344-9. doi: 10.1086/533590
39. Spellberg B, Gilbert DN. The future of antibiotics and resistance: a tribute to a career of leadership by John Bartlett. Clin Infect Dis. 2014 Sep 15;59 Suppl 2(Suppl 2):S71-5. doi: 10.1093/cid/ciu392

40. Sengupta S, Chattopadhyay MK, Grossart HP. The multifaceted roles of antibiotics and antibiotic resistance in nature. Front Microbiol. 2013 Mar 12;4:47. doi: 10.3389/fmicb.2013.00047
41. Tong SY, Davis JS, Eichenberger E, Holland TL, Fowler VG Jr. Staphylococcus aureus infections: epidemiology, pathophysiology, clinical manifestations, and management. Clin Microbiol Rev. 2015 Jul;28(3):603-61. doi: 10.1128/CMR.00134-14
42. Rahimkhani M, Mordadi AR. Survey of the Lethal Effect of Ciprofloxacin and Supernatant Isolated from Staphylococcus Aureus under the Stress of Ciprofloxacin on Methicillin-Resistant Staphylococcus Aureus Strains Isolated from Clinical Specimens. Journal of Payavard Salamat. 2022;15(6):578-584.
43. Cochi SL, Broome CV. Vaccine prevention of Haemophilus influenzae type b disease: past, present and future. Pediatr Infect Dis. 1986 Jan-Feb;5(1):12-9. doi: 10.1097/00006454-198601000-00003
44. Centers for Disease Control and Prevention (CDC). Haemophilus Influenzae Disease (Including Hib). 2014. Available from: http://www.cdc.gov/hi-disease
45. Rosenstein NE, Perkins BA. Update on Haemophilus influenzae serotype b and meningococcal vaccines. Pediatr Clin North Am. 2000 Apr;47(2):337-52, vi. doi: 10.1016/s0031-3955(05)70210-8.
46. Centers for Disease Control and Prevention (CDC). Progress toward elimination of Haemophilus influenzae type b invasive disease among infants and children--United States, 1998−2000. Morb Mortal Wkly Rep. 2002;234-237.
47. Wahl B, O'Brien KL, Greenbaum A, Majumder A, Liu L, Chu Y, *et al*. Burden of Streptococcus pneumoniae and Haemophilus influenzae type b disease in children in the era of conjugate vaccines: global, regional, and national estimates for 2000-15. Lancet Glob Health. 2018 Jul;6(7):e744-e757. doi: 10.1016/S2214-109X(18)30247-X
48. Peltola H. Worldwide Haemophilus influenzae type b disease at the beginning of the 21st century: global analysis of the disease burden 25 years after the use of the polysaccharide vaccine and a decade after the advent of conjugates. Clin Microbiol Rev. 2000 Apr;13(2):302-17. doi: 10.1128/CMR.13.2.302
49. World Health Organization. Haemophilus influenzae type B. Available from: http://www.emro.who.int/health-topics/haemophilus-influenzae-type-b/disease-burden.html
50. Van Eldere J, Slack MP, Ladhani S, Cripps AW. Non-typeable Haemophilus influenzae, an under-recognised pathogen. Lancet Infect Dis. 2014 Dec;14(12):1281-92. doi: 10.1016/S1473-3099(14)70734-0
51. Murphy TF. Haemophilus influenzae in chronic bronchitis. Semin Respir Infect. 2000 Mar;15(1):41-51. doi: 10.1053/srin.2000.0150041
52. Campos J, Hernando M, Román F, Pérez-Vázquez M, Aracil B, Oteo J, *et al*; Group of Invasive Haemophilus Infections of the Autonomous Community of Madrid, Spain. Analysis of invasive Haemophilus influenzae infections after extensive vaccination against H. influenzae type b. J Clin Microbiol. 2004 Feb;42(2):524-9. doi: 10.1128/JCM.42.2.524-529.2004
53. O'Neill JM, St Geme JW 3rd, Cutter D, Adderson EE, Anyanwu J, Jacobs RF, *et al*. Invasive disease due to nontypeable Haemophilus influenzae among children in Arkansas. J Clin Microbiol. 2003 Jul;41(7):3064-9. doi: 10.1128/JCM.41.7.3064-3069.2003
54. Whittaker R, Economopoulou A, Dias JG, Bancroft E, Ramliden M, Celentano LP; European Centre for Disease Prevention and Control Country Experts for Invasive Haemophilus influenzae Disease. Epidemiology of Invasive Haemophilus influenzae Disease, Europe, 2007-2014. Emerg Infect Dis. 2017 Mar;23(3):396-404. doi: 10.3201/eid2303.161552
55. Yanagihara K, Matsumoto T, Tokimatsu I, Tsukada H, Fujikura Y, Miki M, *et al*. Nationwide surveillance of bacterial respiratory pathogens conducted by the surveillance committee of Japanese Society of Chemotherapy, the Japanese Association for Infectious Diseases, and the Japanese Society for Clinical Microbiology in 2010: general view of the pathogens' antibacterial susceptibility. J Infect Chemother. 2015;21:410-420. doi: 10.1016/j.jiac.2020.05.006
56. Zhu H, Wang A, Tong J, Yuan L, Gao W, Shi W, *et al*. Nasopharyngeal carriage and antimicrobial susceptibility of Haemophilus influenzae among children younger than 5 years of age in Beijing, China. BMC Microbiol. 2015 Feb 4;15:6. doi: 10.1186/s12866-015-0350-7
57. Kishii K, Chiba N, Morozumi M, Hamano-Hasegawa K, Kurokawa I, Masaki J, *et al*. Diverse mutations in the ftsI gene in ampicillin-resistant Haemophilus influenzae isolates from pediatric patients with acute otitis media. J Infect Chemother. 2010 Apr;16(2):87-93. doi: 10.1007/s10156-009-0011-6
58. Long SS, Prober CG, Fischer M, Kimberlin DW. Principles and Practice of Pediatric Infectious Diseases. 6th ed. Amsterdam: Elsevier; 2023.
59. Vergison A. Microbiology of otitis media: a moving target. Vaccine. 2008 Dec 23;26 Suppl 7:G5-10. doi: 10.1016/j.vaccine.2008.11.006
60. Arguedas A, Kvaerner K, Liese J, Schilder AG, Pelton SI. Otitis media across nine countries: disease burden and management. Int J Pediatr Otorhinolaryngol. 2010 Dec;74(12):1419-24. doi: 10.1016/j.ijporl.2010.09.022
61. Marchisio P, Esposito S, Picca M, Baggi E, Terranova L, Orenti A, *et al*.; Milan AOM Study Group. Prospective evaluation of the aetiology of acute otitis media with spontaneous tympanic membrane perforation. Clin Microbiol Infect. 2017 Jul;23(7):486.e1-486.e6. doi: 10.1016/j.cmi.2017.01.010
62. Sethi S, Murphy TF. Infection in the pathogenesis and course of chronic obstructive pulmonary disease. N Engl J Med. 2008 Nov 27;359(22):2355-65. doi: 10.1056/NEJMra0800353
63. Schmitz FJ, Beeck A, Perdikouli M, Boos M, Mayer S, Scheuring S, *et al*. Production of BRO beta-lactamases and resistance to complement in European Moraxella catarrhalis isolates. J Clin Microbiol. 2002 Apr;40(4):1546-8. doi: 10.1128/JCM.40.4.1546-1548.2002
64. Pearson MM, Laurence CA, Guinn SE, Hansen EJ. Biofilm formation by Moraxella catarrhalis in vitro: roles of the UspA1 adhesin and the Hag hemagglutinin. Infect Immun. 2006 Mar;74(3):1588-96. doi: 10.1128/IAI.74.3.1588-1596.2006
65. Hall-Stoodley L, Hu FZ, Gieseke A, Nistico L, Nguyen D, Hayes J, *et al*. Direct detection of bacterial biofilms on the middle-ear mucosa of children with chronic otitis media. JAMA. 2006 Jul 12;296(2):202-11. doi: 10.1001/jama.296.2.202
66. Slevogt H, Seybold J, Tiwari KN, Hocke AC, Jonatat C, Dietel S, *et al*. Moraxella catarrhalis is internalized in respiratory epithelial cells by a trigger-like mechanism and initiates a TLR2- and partly NOD1-dependent inflammatory immune response. Cell Microbiol. 2007 Mar;9(3):694-707. doi: 10.1111/j.1462-5822.2006.00821.x
67. Faden H, Harabuchi Y, Hong JJ. Epidemiology of Moraxella catarrhalis in children during the first 2 years of life: relationship to otitis media. J Infect Dis. 1994 Jun;169(6):1312-7. doi: 10.1093/infdis/169.6.1312
68. Faden H, Duffy L, Wasielewski R, Wolf J, Krystofik D, Tung Y. Relationship between nasopharyngeal colonization and the development of otitis media in children. Tonawanda/Williamsville Pediatrics. J Infect Dis. 1997 Jun;175(6):1440-5. doi: 10.1086/516477
69. Sarubbi FA, Myers JW, Williams JJ, Shell CG. Respiratory infections caused by Branhamella catarrhalis. Selected epidemiologic features. Am J Med. 1990 May 14;88(5A):9S-14S. doi: 10.1016/0002-9343(90)90254-b
70. Duppenthaler A, Gorgievski-Hrisoho M, Frey U, Aebi C. Two-year periodicity of respiratory syncytial virus epidemics in Switzerland. Infection. 2003 Mar;31(2):75-80. doi: 10.1007/s15010-002-3124-8
71. Murphy TF, Brauer AL, Grant BJ, Sethi S. Moraxella catarrhalis in chronic obstructive pulmonary disease: burden of disease and immune response. Am J Respir Crit Care Med. 2005 Jul 15;172(2):195-9. doi: 10.1164/rccm.200412-1747OC
72. Broides A, Dagan R, Greenberg D, Givon-Lavi N, Leibovitz E. Acute otitis media caused by Moraxella catarrhalis: epidemiologic and clinical characteristics. Clin Infect Dis. 2009 Dec 1;49(11):1641-7. doi: 10.1086/647933
73. Kaur R, Morris M, Pichichero ME. Epidemiology of Acute Otitis Media in the Postpneumococcal Conjugate Vaccine Era. Pediatrics. 2017 Sep;140(3):e20170181. doi: 10.1542/peds.2017-0181
74. Schreckenberger PC, Daneshvar MI, Hollis DG. Acinetobacter, Achromobacter, Chrys-eobacterium, Moraxella, and other nonfermentative Gram-negative rods. In: Murray PR, Baron EJ, Jorgensen JH, *et al*., eds. Manual of Clinical Microbiology. 9th ed. Washington, DC: ASM Press; 2003. p. 770-802.
75. Yamada K, Arai K, Saito R. Antimicrobial susceptibility to β-lactam antibiotics and production of BRO β-lactamase in clinical isolates of Moraxella catarrhalis from a Japanese hospital. J Microbiol Immunol Infect. 2017 Jun;50(3):386-389. doi: 10.1016/j.jmii.2016.08.003
76. Goto H, Shimada K, Ikemoto H, Oguri T; Study Group on Antimicrobial Susceptibility of Pathogens Isolated from Respiratory Infections. Antimicrobial susceptibility of pathogens isolated from more than 10,000 patients with infectious respiratory diseases: a 25-year longitudinal study. J Infect Chemother. 2009 Dec;15(6):347-60. doi: 10.1007/s10156-009-0719-3
77. Saito R, Nonaka S, Fujinami Y, Matsuoka S, Nakajima S, Nishiyama H, *et al*. The frequency of BRO β-lactamase and its relationship to antimicrobial susceptibility and serum resistance in Moraxella catarrhalis. J Infect Chemother. 2014 Jan;20(1):6-8. doi: 10.1016/j.jiac.2013.06.003
78. Król-Turmińska K, Olender A, Bogut A. Tetracycline resistance in Moraxella catarrhalis clinical strains isolated in Poland. New Mi-crobiol. 2020;43(3):103-106.
79. Felmingham D, White AR, Jacobs MR, Appelbaum PC, Poupard J, Miller LA, *et al*. The Alexander Project: the benefits from a decade of surveillance. J Antimicrob Chemother. 2005 Oct;56 Suppl 2:ii3-ii21. doi: 10.1093/jac/dki297
80. de Vries SP, Bootsma HJ, Hays JP, Hermans PW. Molecular aspects of Moraxella catarrhalis pathogenesis. Microbiol Mol Biol Rev. 2009 Sep;73(3):389-406. doi: 10.1128/MMBR.00007-09
81. Van Damme P, Leroux-Roels G, Vandermeulen C, De Ryck I, Tasciotti A, Dozot M, *et al*. Safety and immunogenicity of non-typeable Haemophilus influenzae-Moraxella catarrhalis vaccine. Vaccine. 2019 May 21;37(23):3113-3122. doi: 10.1016/j.vaccine.2019.04.041
82. Zarzecka U, Zakrzewski AJ, Chajęcka-Wierzchowska W, Zadernowska A. Linezolid-Resistant Enterococcus spp. Isolates from Foods of Animal Origin-The Genetic Basis of Acquired Resistance. Foods. 2022 Mar 28;11(7):975. doi: 10.3390/foods11070975
83. Na SH, Moon DC, Choi MJ, Oh SJ, Jung DY, Kang HY, *et al*. Detection of oxazolidinone and phenicol resistant enterococcal isolates from duck feces and carcasses. Int J Food Microbiol. 2019 Mar 16;293:53-59. doi: 10.1016/j.ijfoodmicro.2019.01.002
84. Misiakou MA, Hertz FB, Schønning K, Häussler S, Nielsen KL. Emergence of linezolid-resistant Enterococcus faecium in a tertiary hospital in Copenhagen. Microb Genom. 2023 Jul;9(7):mgen001055. doi: 10.1099/mgen.0.001055
85. Swaney SM, Aoki H, Ganoza MC, Shinabarger DL. The oxazolidinone linezolid inhibits initiation of protein synthesis in bacteria. Antimicrob Agents Chemother. 1998 Dec;42(12):3251-5. doi: 10.1128/AAC.42.12.3251
86. Xiong YQ, Yeaman MR, Bayer AS. Linezolid: a new antibiotic. Drugs Today (Barc). 2000 Sep;36(9):631-9. doi: 10.1358/dot.2000.36.9.593780

87. Hashemian SMR, Farhadi T, Ganjparvar M. Linezolid: a review of its properties, function, and use in critical care. Drug Des Devel Ther. 2018 Jun 18;12:1759-1767. doi: 10.2147/DDDT.S164515
88. Aoki H, Ke L, Poppe SM, Poel TJ, Weaver EA, Gadwood RC, *et al*. Oxazolidinone antibiotics target the P site on Escherichia coli ribosomes. Antimicrob Agents Chemother. 2002 Apr;46(4):1080-5. doi: 10.1128/AAC.46.4.1080-1085.2002
89. Long KS, Vester B. Resistance to linezolid caused by modifications at its binding site on the ribosome. Antimicrob Agents Chemother. 2012 Feb;56(2):603-12. doi: 10.1128/AAC.05702-11
90. Bender JK, Fleige C, Klare I, Fiedler S, Mischnik A, Mutters NT, *et al*. Detection of a cfr(B) Variant in German Enterococcus faecium Clinical Isolates and the Impact on Linezolid Resistance in Enterococcus spp. PLoS One. 2016 Nov 28;11(11):e0167042. doi: 10.1371/journal.pone.0167042
91. Cafini F, Nguyen le TT, Higashide M, Román F, Prieto J, Morikawa K. Horizontal gene transmission of the cfr gene to MRSA and Enterococcus: role of Staphylococcus epidermidis as a reservoir and alternative pathway for the spread of linezolid resistance. J Antimicrob Chemother. 2016 Mar;71(3):587-92. doi: 10.1093/jac/dkv391
92. Liu Y, Wang Y, Wu C, Shen Z, Schwarz S, Du XD, *et al*. First report of the multidrug resistance gene cfr in Enterococcus faecalis of animal origin. Antimicrob Agents Chemother. 2012 Mar;56(3):1650-4. doi: 10.1128/AAC.06091-11
93. Diaz L, Kiratisin P, Mendes RE, Panesso D, Singh KV, Arias CA. Transferable plasmid-mediated resistance to linezolid due to cfr in a human clinical isolate of Enterococcus faecalis. Antimicrob Agents Chemother. 2012 Jul;56(7):3917-22. doi: 10.1128/AAC.00419-12
94. LaMarre JM, Howden BP, Mankin AS. Inactivation of the indigenous methyltransferase RlmN in Staphylococcus aureus increases linezolid resistance. Antimicrob Agents Chemother. 2011 Jun;55(6):2989-91. doi: 10.1128/AAC.00183-11
95. Sharkey LKR, O'Neill AJ. Antibiotic Resistance ABC-F Proteins: Bringing Target Protection into the Limelight. ACS Infect Dis. 2018 Mar 9;4(3):239-246. doi: 10.1021/acsinfecdis.7b00251
96. Wang Y, Zou Y, Xie J, Wang T, Zheng X, He H, *et al*. Linezolid versus vancomycin for the treatment of suspected methicillin-resistant Staphylococcus aureus nosocomial pneumonia: a systematic review employing meta-analysis. Eur J Clin Pharmacol. 2015 Jan;71(1):107-15. doi: 10.1007/s00228-014-1775-x
97. Brenciani A, Morroni G, Vincenzi C, Manso E, Mingoia M, Giovanetti E, *et al*. Detection in Italy of two clinical Enterococcus faecium isolates carrying both the oxazolidinone and phenicol resistance gene optrA and a silent multiresistance gene cfr. J Antimicrob Chemother. 2016 Apr;71(4):1118-9. doi: 10.1093/jac/dkv438
98. Cai J, Wang Y, Schwarz S, Lv H, Li Y, Liao K, *et al*. Enterococcal isolates carrying the novel oxazolidinone resistance gene optrA from hospitals in Zhejiang, Guangdong, and Henan, China, 2010-2014. Clin Microbiol Infect. 2015 Dec;21(12):1095.e1-4. doi: 10.1016/j.cmi.2015.08.007
99. Cui L, Wang Y, Lv Y, Wang S, Song Y, Li Y, *et al*. Nationwide Surveillance of Novel Oxazolidinone Resistance Gene optrA in Enterococcus Isolates in China from 2004 to 2014. Antimicrob Agents Chemother. 2016 Nov 21;60(12):7490-7493. doi: 10.1128/AAC.01256-16
100. He T, Shen Y, Schwarz S, Cai J, Lv Y, Li J, *et al*. Genetic environment of the transferable oxazolidinone/phenicol resistance gene optrA in Enterococcus faecalis isolates of human and animal origin. J Antimicrob Chemother. 2016 Jun;71(6):1466-73. doi: 10.1093/jac/dkw016
101. Huang J, Chen L, Wu Z, Wang L. Retrospective analysis of genome sequences revealed the wide dissemination of optrA in Gram-positive bacteria. J Antimicrob Chemother. 2017 Feb;72(2):614-616. doi: 10.1093/jac/dkw488
102. Li D, Wang Y, Schwarz S, Cai J, Fan R, Li J, *et al*. Co-location of the oxazolidinone resistance genes optrA and cfr on a multiresistance plasmid from Staphylococcus sciuri. J Antimicrob Chemother. 2016 Jun;71(6):1474-8. doi: 10.1093/jac/dkw040
103. Wang Y, Lv Y, Cai J, Schwarz S, Cui L, Hu Z, *et al*. A novel gene, optrA, that confers transferable resistance to oxazolidinones and phenicols and its presence in Enterococcus faecalis and Enterococcus faecium of human and animal origin. J Antimicrob Chemother. 2015 Aug;70(8):2182-90. doi: 10.1093/jac/dkv116
104. Cavaco LM, Korsgaard H, Kaas RS, Seyfarth AM, Leekitcharoenphon P, Hendriksen RS. First detection of linezolid resistance due to the optrA gene in enterococci isolated from food products in Denmark. J Glob Antimicrob Resist. 2017 Jun;9:128-129. doi: 10.1016/j.jgar.2017.04.001
105. Antonelli A, D'Andrea MM, Brenciani A, Galeotti CL, Morroni G, Pollini S, *et al*. Characterization of poxtA, a novel phenicol-oxazolidinone-tetracycline resistance gene from an MRSA of clinical origin. J Antimicrob Chemother. 2018 Jul 1;73(7):1763-1769. doi: 10.1093/jac/dky088
106. Dejoies L, Sassi M, Schutz S, Moreaux J, Zouari A, Potrel S, *et al*. Genetic features of the poxtA linezolid resistance gene in human enterococci from France. J Antimicrob Chemother. 2021 Jul 15;76(8):1978-1985. doi: 10.1093/jac/dkab116
107. Kehrenberg C, Schwarz S. Distribution of florfenicol resistance genes fexA and cfr among chloramphenicol-resistant Staphylococcus isolates. Antimicrob Agents Chemother. 2006 Apr;50(4):1156-63. doi: 10.1128/AAC.50.4.1156-1163.2006
108. Gawryszewska I, Żabicka D, Hryniewicz W, Sadowy E. Linezolid-resistant enterococci in Polish hospitals: species, clonality and determinants of linezolid resistance. Eur J Clin Microbiol Infect Dis. 2017 Jul;36(7):1279-1286. doi: 10.1007/s10096-017-2934-7
109. Zahedi Bialvaei A, Rahbar M, Yousefi M, Asgharzadeh M, Samadi Kafil H. Linezolid: a promising option in the treatment of Gram-positives. J Antimicrob Chemother. 2017 Feb;72(2):354-364. doi: 10.1093/jac/dkw450
110. Chajęcka-Wierzchowska W, Zadernowska A, García-Solache M. Ready-to-eat dairy products as a source of multidrug-resistant Enterococcus strains: Phenotypic and genotypic characteristics. J Dairy Sci. 2020 May;103(5):4068-4077. doi: 10.3168/jds.2019-17395
111. Chajęcka-Wierzchowska W, Zadernowska A, Zarzecka U, Zakrzewski A, Gajewska J. Enterococci from ready-to-eat food - horizontal gene transfer of antibiotic resistance genes and genotypic characterization by PCR melting profile. J Sci Food Agric. 2019 Feb;99(3):1172-1179. doi: 10.1002/jsfa.9285
112. Chajęcka-Wierzchowska W, Zadernowska A, Łaniewska-Trokenheim Ł. Diversity of Antibiotic Resistance Genes in Enterococcus Strains Isolated from Ready-to-Eat Meat Products. J Food Sci. 2016 Nov;81(11):M2799-M2807. doi: 10.1111/1750-3841.13523
113. Fioriti S, Morroni G, Coccitto SN, Brenciani A, Antonelli A, Di Pilato V, *et al*. Detection of Oxazolidinone Resistance Genes and Characterization of Genetic Environments in Enterococci of Swine Origin, Italy. Microorganisms. 2020 Dec 17;8(12):2021. doi: 10.3390/microorganisms8122021
114. Lei CW, Kang ZZ, Wu SK, Chen YP, Kong LH, Wang HN. Detection of the phenicol-oxazolidinone-tetracycline resistance gene poxtA in Enterococcus faecium and Enterococcus faecalis of food-producing animal origin in China. J Antimicrob Chemother. 2019 Aug 1;74(8):2459-2461. doi: 10.1093/jac/dkz198
115. Smith TT, Tamma PD, Do TB, Dzintars KE, Zhao Y, Cosgrove SE, *et al*. Prolonged linezolid use is associated with the development of linezolid-resistant Enterococcus faecium. Diagn Microbiol Infect Dis. 2018 Jun;91(2):161-163. doi: 10.1016/j.diagmicrobio.2018.01.027
116. Centers for Disease Control and Prevention (CDC). Antibiotic Resistance & Patient Safety Portal. Available from: https://arpsp.cdc.gov/profile/antibiotic-resistance/mdr-pseudomonas-aeruginosa
117. Giacobbe DR, Bassetti M, De Rosa FG, Del Bono V, Grossi PA, Menichetti F, *et al*; ISGRI-SITA (Italian Study Group on Resistant Infections of the Società Italiana Terapia Antinfettiva). Ceftolozane/tazobactam: place in therapy. Expert Rev Anti Infect Ther. 2018 Apr;16(4):307-320. doi: 10.1080/14787210.2018.1447381
118. Del Barrio-Tofiño E, López-Causapé C, Oliver A. Pseudomonas aeruginosa epidemic high-risk clones and their association with horizontally-acquired β-lactamases: 2020 update. Int J Antimicrob Agents. 2020 Dec;56(6):106196. doi: 10.1016/j.ijantimicag.2020.106196
119. Livermore DM, Mushtaq S, Meunier D, Hopkins KL, Hill R, Adkin R, *et al*.; BSAC Resistance Surveillance Standing Committee. Activity of ceftolozane/tazobactam against surveillance and 'problem' Enterobacteriaceae, Pseudomonas aeruginosa and non-fermenters from the British Isles. J Antimicrob Chemother. 2017 Aug 1;72(8):2278-2289. doi: 10.1093/jac/dkx136
120. Velez Perez AL, Schmidt-Malan SM, Kohner PC, Karau MJ, Greenwood-Quaintance KE, Patel R. In vitro activity of ceftolozane/tazobactam against clinical isolates of Pseudomonas aeruginosa in the planktonic and biofilm states. Diagn Microbiol Infect Dis. 2016 Jul;85(3):356-359. doi: 10.1016/j.diagmicrobio.2016.02.014
121. Pogue JM, Kaye KS, Veve MP, Patel TS, Gerlach AT, Davis SL, *et al*. Ceftolozane/Tazobactam vs Polymyxin or Aminoglycoside-based Regimens for the Treatment of Drug-resistant Pseudomonas aeruginosa. Clin Infect Dis. 2020 Jul 11;71(2):304-310. doi: 10.1093/cid/ciz816
122. Balandin B, Ballesteros D, Ruiz de Luna R, López-Vergara L, Pintado V, Sancho-González M, *et al*. Multicenter study of ceftolozane/tazobactam for treatment of Pseudomonas aeruginosa infections in critically ill patients. Int J Antimicrob Agents. 2021 Mar;57(3):106270. doi: 10.1016/j.ijantimicag.2020.106270
123. Fernández-Cruz A, Alba N, Semiglia-Chong MA, Padilla B, Rodríguez-Macías G, Kwon M, *et al*. A Case-Control Study of Real-Life Experience with Ceftolozane-Tazobactam in Patients with Hematologic Malignancy and Pseudomonas aeruginosa Infection. Antimicrob Agents Chemother. 2019 Jan 29;63(2):e02340-18. doi: 10.1128/AAC.02340-18
124. Daikos GL, da Cunha CA, Rossolini GM, Stone GG, Baillon-Plot N, Tawadrous M, *et al*. Review of Ceftazidime-Avibactam for the Treatment of Infections Caused by Pseudomonas aeruginosa. Antibiotics (Basel). 2021 Sep 18;10(9):1126. doi: 10.3390/antibiotics10091126
125. Yahav D, Giske CG, Grāmatniece A, Abodakpi H, Tam VH, Leibovici L. New β-Lactam-β-Lactamase Inhibitor Combinations. Clin Microbiol Rev. 2020 Nov 11;34(1):e00115-20. doi: 10.1128/CMR.00115-20
126. Jorgensen SCJ, Trinh TD, Zasowski EJ, Lagnf AM, Bhatia S, Melvin SM, *et al*. Real-World Experience With Ceftazidime-Avibactam for Multidrug-Resistant Gram-Negative Bacterial Infections. Open Forum Infect Dis. 2019 Dec 6;6(12):ofz522. doi: 10.1093/ofid/ofz522
127. Corbella L, Boán J, San-Juan R, Fernández-Ruiz M, Carretero O, Lora D, *et al*. Effectiveness of ceftazidime-avibactam for the treatment of infections due to Pseudomonas aeruginosa. Int J Antimicrob Agents. 2022 Feb;59(2):106517. doi: 10.1016/j.ijantimicag.2021.106517
128. Vena A, Giacobbe DR, Castaldo N, Cattelan A, Mussini C, Luzzati R, *et al*. Clinical Experience with Ceftazidime-Avibactam for the Treatment of Infections due to Multidrug-Resistant Gram-Negative Bacteria Other than Carbapenem-Resistant Enterobacterales. Antibiotics (Basel). 2020 Feb 9;9(2):71. doi: 10.3390/antibiotics9020071
129. U.S. Food and Drug Administration. FDA Approves New Treatment for Complicated Urinary Tract and Complicated Intra-abdominal Infections. Available from: https://www.fda.gov/news-events/press-announcements/fda-approves-newtreatment-complicated-urinary-tract-and-complicated-intra-abdominal-infections

130. European Medicines Agency. Recarbrio: EPAR-Product Information. Available from: https://www.ema.europa.eu/en/ documents/product-information/recarbrio-epar-product-information_en.pdf
131. Lob SH, Hackel MA, Kazmierczak KM, Young K, Motyl MR, Karlowsky JA, *et al.* In Vitro Activity of Imipenem-Relebactam against Gram-Negative ESKAPE Pathogens Isolated by Clinical Laboratories in the United States in 2015 (Results from the SMART Global Surveillance Program). Antimicrob Agents Chemother. 2017 May 24;61(6):e02209-16. doi: 10.1128/AAC.02209-16
132. Karlowsky JA, Lob SH, Raddatz J, DePestel DD, Young K, Motyl MR, *et al.* In Vitro Activity of Imipenem/Relebactam and Ceftolozane/Tazobactam Against Clinical Isolates of Gram-negative Bacilli With Difficult-to-Treat Resistance and Multidrug-resistant Phenotypes-Study for Monitoring Antimicrobial Resistance Trends, United States 2015-2017. Clin Infect Dis. 2021 Jun 15;72(12):2112-2120. doi: 10.1093/cid/ciaa381
133. Karlowsky JA, Lob SH, Kazmierczak KM, Young K, Motyl MR, Sahm DF. In vitro activity of imipenem/relebactam against Enterobacteriaceae and Pseudomonas aeruginosa isolated from intraabdominal and urinary tract infection samples: SMART Surveillance United States 2015-2017. J Glob Antimicrob Resist. 2020 Jun;21:223-228. doi: 10.1016/j.jgar.2019.10.028
134. Walkty A, Karlowsky JA, Baxter MR, Adam HJ, Golden A, Lagace-Wiens P, *et al*; Canadian Antimicrobial Resistance Alliance (CARA). In vitro activity of imipenem-relebactam against various resistance phenotypes/genotypes of Enterobacterales and Pseudomonas aeruginosa isolated from patients across Canada as part of the CANWARD study, 2016-2019. Diagn Microbiol Infect Dis. 2021 Sep;101(1):115418. doi: 10.1016/j.diagmicrobio.2021.115418
135. Noval M, Banoub M, Claeys KC, Heil E. The Battle Is on: New Beta-Lactams for the Treatment of Multidrug-Resistant Gram-Negative Organisms. Curr Infect Dis Rep. 2020 Jan 13;22(1):1. doi: 10.1007/s11908-020-0710-9
136. Lapuebla A, Abdallah M, Olafisoye O, Cortes C, Urban C, Quale J, *et al.* Activity of Meropenem Combined with RPX7009, a Novel β-Lactamase Inhibitor, against Gram-Negative Clinical Isolates in New York City. Antimicrob Agents Chemother. 2015 Aug;59(8):4856-60. doi: 10.1128/AAC.00843-15
137. Novelli A, Del Giacomo P, Rossolini GM, Tumbarello M. Meropenem/vaborbactam: a next generation β-lactam β-lactamase inhibitor combination. Expert Rev Anti Infect Ther. 2020 Jul;18(7):643-655. doi: 10.1080/14787210.2020.1756775
138. Sabet M, Tarazi Z, Griffith DC. Activity of Meropenem-Vaborbactam against Pseudomonas aeruginosa and Acinetobacter baumannii in a Neutropenic Mouse Thigh Infection Model. Antimicrob Agents Chemother. 2018 Dec 21;63(1):e01665-18. doi: 10.1128/AAC.01665-18
139. Carvalhaes CG, Shortridge D, Sader HS, Castanheira M. Activity of Meropenem-Vaborbactam against Bacterial Isolates Causing Pneumonia in Patients in U.S. Hospitals during 2014 to 2018. Antimicrob Agents Chemother. 2020 Feb 21;64(3):e02177-19. doi: 10.1128/AAC.02177-19
140. Codjoe FS, Donkor ES. Carbapenem Resistance: A Review. Med Sci (Basel). 2017 Dec 21;6(1):1. doi: 10.3390/medsci6010001
141. Papp-Wallace KM, Endimiani A, Taracila MA, Bonomo RA. Carbapenems: past, present, and future. Antimicrob Agents Chemother. 2011 Nov;55(11):4943-60. doi: 10.1128/AAC.00296-11
142. Smith HZ, Hollingshead CM, Kendall B. Carbapenem-Resistant Enterobacterales. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024. Available from: https://www.ncbi.nlm.nih.gov/books/NBK551704
143. Centers for Disease Control and Prevention (CDC). Healthcare-Associated Infections (HAIs): CRE Technical Information. 2019. Available from: https://www.cdc.gov/hai/organisms/cre/technical-info.html
144. Dankittipong N, Fischer EAJ, Swanenburg M, Wagenaar JA, Stegeman AJ, de Vos CJ. Quantitative Risk Assessment for the Introduction of Carbapenem-Resistant Enterobacteriaceae (CPE) into Dutch Livestock Farms. Antibiotics (Basel). 2022 Feb 21;11(2):281. doi: 10.3390/antibiotics11020281
145. Taggar G, Attiq Rheman M, Boerlin P, Diarra MS. Molecular Epidemiology of Carbapenemases in Enterobacteriales from Humans, Animals, Food and the Environment. Antibiotics (Basel). 2020 Oct 13;9(10):693. doi: 10.3390/antibiotics9100693
146. Queenan AM, Bush K. Carbapenemases: the versatile beta-lactamases. Clin Microbiol Rev. 2007 Jul;20(3):440-58. doi: 10.1128/CMR.00001-07
147. Farhat N, Khan AU. Evolving trends of New Delhi Metallo-betalactamse (NDM) variants: A threat to antimicrobial resistance. Infect Genet Evol. 2020 Dec;86:104588. doi: 10.1016/j.meegid.2020.104588
148. Boyd SE, Livermore DM, Hooper DC, Hope WW. Metallo-β-Lactamases: Structure, Function, Epidemiology, Treatment Options, and the Development Pipeline. Antimicrob Agents Chemother. 2020 Sep 21;64(10):e00397-20. doi: 10.1128/AAC.00397-20
149. Kopotsa K, Osei Sekyere J, Mbelle NM. Plasmid evolution in carbapenemase-producing Enterobacteriaceae: a review. Ann N Y Acad Sci. 2019 Dec;1457(1):61-91. doi: 10.1111/nyas.14223
150. Boyd SE, Holmes A, Peck R, Livermore DM, Hope W. OXA-48-Like β-Lactamases: Global Epidemiology, Treatment Options, and Development Pipeline. Antimicrob Agents Chemother. 2022 Aug 16;66(8):e0021622. doi: 10.1128/aac.00216-22
151. Jean SS, Lee WS, Lam C, Hsu CW, Chen RJ, Hsueh PR. Carbapenemase-producing Gram-negative bacteria: current epidemics, antimicrobial susceptibility and treatment options. Future Microbiol. 2015;10(3):407-25. doi: 10.2217/fmb.14.135
152. Ract P, Compain F, Robin F, Decre D, Gallah S, Podglajen I. Synergistic in vitro activity between aztreonam and amoxicillin-clavulanate against Enterobacteriaceae-producing class B and/or class D carbapenemases with or without extended-spectrum β-lactamases. J Med Microbiol. 2019 Sep;68(9):1292-1298. doi: 10.1099/jmm.0.001052
153. Maraki S, Mavromanolaki VE, Moraitis P, Stafylaki D, Kasimati A, Magkafouraki E, *et al.* Ceftazidime-avibactam, meropenen-vaborbactam, and imipenem-relebactam in combination with aztreonam against multidrug-resistant, metallo-β-lactamase-producing Klebsiella pneumoniae. Eur J Clin Microbiol Infect Dis. 2021 Aug;40(8):1755-1759. doi: 10.1007/s10096-021-04197-3.
154. Shields RK, Doi Y. Aztreonam Combination Therapy: An Answer to Metallo-β-Lactamase-Producing Gram-Negative Bacteria? Clin Infect Dis. 2020 Aug 14;71(4):1099-1101. doi: 10.1093/cid/ciz1159
155. Karlowsky JA, Kazmierczak KM, de Jonge BLM, Hackel MA, Sahm DF, Bradford PA. In Vitro Activity of Aztreonam-Avibactam against Enterobacteriaceae and Pseudomonas aeruginosa Isolated by Clinical Laboratories in 40 Countries from 2012 to 2015. Antimicrob Agents Chemother. 2017 Aug 24;61(9):e00472-17. doi: 10.1128/AAC.00472-17
156. Shaw E, Rombauts A, Tubau F, Padullés A, Càmara J, Lozano T, *et al.* Clinical outcomes after combination treatment with ceftazidime/avibactam and aztreonam for NDM-1/OXA-48/CTX-M-15-producing Klebsiella pneumoniae infection. J Antimicrob Chemother. 2018 Apr 1;73(4):1104-1106. doi: 10.1093/jac/dkx496
157. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious Diseases Society of America Guidance on the Treatment of Extended-Spectrum β-lactamase Producing Enterobacterales (ESBL-E), Carbapenem-Resistant Enterobacterales (CRE), and Pseudomonas aeruginosa with Difficult-to-Treat Resistance (DTR-P. aeruginosa). Clin Infect Dis. 2021 Apr 8;72(7):e169-e183. doi: 10.1093/cid/ciaa1478
158. Zhanel GG, Lawson CD, Adam H, Schweizer F, Zelenitsky S, Lagacé-Wiens PR, *et al.* Ceftazidime-avibactam: a novel cephalosporin/β-lactamase inhibitor combination. Drugs. 2013 Feb;73(2):159-77. doi: 10.1007/s40265-013-0013-7
159. Ehmann DE, Jahić H, Ross PL, Gu RF, Hu J, Kern G, *et al.* Avibactam is a covalent, reversible, non-β-lactam β-lactamase inhibitor. Proc Natl Acad Sci U S A. 2012 Jul 17;109(29):11663-8. doi: 10.1073/pnas.1205073109
160. Sousa A, Pérez-Rodríguez MT, Soto A, Rodríguez L, Pérez-Landeiro A, Martínez-Lamas L, *et al.* Effectiveness of ceftazidime/avibactam as salvage therapy for treatment of infections due to OXA-48 carbapenemase-producing Enterobacteriaceae. J Antimicrob Chemother. 2018 Nov 1;73(11):3170-3175. doi: 10.1093/jac/dky295
161. De la Calle C, Rodríguez O, Morata L, Marco F, Cardozo C, García-Vidal C, *et al.* Clinical characteristics and prognosis of infections caused by OXA-48 carbapenemase-producing Enterobacteriaceae in patients treated with ceftazidime-avibactam. Int J Antimicrob Agents. 2019 Apr;53(4):520-524. doi: 10.1016/j.ijantimicag.2018.11.015
162. van Duin D, Lok JJ, Earley M, Cober E, Richter SS, Perez F, *et al.*; Antibacterial Resistance Leadership Group. Colistin Versus Ceftazidime-Avibactam in the Treatment of Infections Due to Carbapenem-Resistant Enterobacteriaceae. Clin Infect Dis. 2018 Jan 6;66(2):163-171. doi: 10.1093/cid/cix783
163. Shields RK, Nguyen MH, Chen L, Press EG, Potoski BA, Marini RV, *et al.* Ceftazidime-Avibactam Is Superior to Other Treatment Regimens against Carbapenem-Resistant Klebsiella pneumoniae Bacteremia. Antimicrob Agents Chemother. 2017 Jul 25;61(8):e00883-17. doi: 10.1128/AAC.00883-17
164. Tumbarello M, Raffaelli F, Giannella M, Mantengoli E, Mularoni A, Venditti M, *et al.* Ceftazidime-Avibactam Use for Klebsiella pneumoniae Carbapenemase-Producing K. pneumoniae Infections: A Retrospective Observational Multicenter Study. Clin Infect Dis. 2021 Nov 2;73(9):1664-1676. doi: 10.1093/cid/ciab176
165. Wilson GM, Fitzpatrick M, Walding K, Gonzalez B, Schweizer ML, Suda KJ, *et al.* Meta-analysis of Clinical Outcomes Using Ceftazidime/Avibactam, Ceftolozane/Tazobactam, and Meropenem/Vaborbactam for the Treatment of Multidrug-Resistant Gram-Negative Infections. Open Forum Infect Dis. 2021 Jan 5;8(2):ofaa651. doi: 10.1093/ofid/ofaa651
166. United States Food and Drug Administration. AVYCAZ safely and effectively. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/206494s005,s006lbl.pdf.
167. Mazuski JE, Gasink LB, Armstrong J, Broadhurst H, Stone GG, Rank D, *et al.* Efficacy and Safety of Ceftazidime-Avibactam Plus Metronidazole Versus Meropenem in the Treatment of Complicated Intra-abdominal Infection: Results From a Randomized, Controlled, Double-Blind, Phase 3 Program. Clin Infect Dis. 2016 Jun 1;62(11):1380-1389. doi: 10.1093/cid/ciw133
168. Wagenlehner FM, Sobel JD, Newell P, Armstrong J, Huang X, Stone GG, *et al.* Ceftazidime-avibactam Versus Doripenem for the Treatment of Complicated Urinary Tract Infections, Including Acute Pyelonephritis: RECAPTURE, a Phase 3 Randomized Trial Program. Clin Infect Dis. 2016 Sep 15;63(6):754-762. doi: 10.1093/cid/ciw378
169. Torres A, Zhong N, Pachl J, Timsit JF, Kollef M, Chen Z, *et al.* Ceftazidime-avibactam versus meropenem in nosocomial pneumonia, including ventilator-associated pneumonia (REPROVE): a randomised, double-blind, phase 3 non-inferiority trial. Lancet Infect Dis. 2018 Mar;18(3):285-295. doi: 10.1016/S1473-3099(17)30747-8
170. de Jonge BL, Karlowsky JA, Kazmierczak KM, Biedenbach DJ, Sahm DF, Nichols WW. In Vitro Susceptibility to Ceftazidime-Avibactam of Carbapenem-Nonsusceptible Enterobacteriaceae Isolates Collected during the INFORM Global Surveillance Study (2012 to 2014). Antimicrob Agents Chemother. 2016 Apr 22;60(5):3163-9. doi: 10.1128/AAC.03042-15

171. Spiliopoulou I, Kazmierczak K, Stone GG. In vitro activity of ceftazidime/avibactam against isolates of carbapenem-non-susceptible Enterobacteriaceae collected during the INFORM global surveillance programme (2015-17). J Antimicrob Chemother. 2020 Feb 1;75(2):384-391. doi: 10.1093/jac/dkz456
172. Nelson K, Hemarajata P, Sun D, Rubio-Aparicio D, Tsivkovski R, Yang S, *et al.* Resistance to Ceftazidime-Avibactam Is Due to Transposition of KPC in a Porin-Deficient Strain of Klebsiella pneumoniae with Increased Efflux Activity. Antimicrob Agents Chemother. 2017 Sep 22;61(10):e00989-17. doi: 10.1128/AAC.00989-17
173. Humphries RM, Hemarajata P. Resistance to Ceftazidime-Avibactam in Klebsiella pneumoniae Due to Porin Mutations and the Increased Expression of KPC-3. Antimicrob Agents Chemother. 2017 May 24;61(6):e00537-17. doi: 10.1128/AAC.00537-17
174. Humphries RM, Yang S, Hemarajata P, Ward KW, Hindler JA, Miller SA, *et al.* First Report of Ceftazidime-Avibactam Resistance in a KPC-3-Expressing Klebsiella pneumoniae Isolate. Antimicrob Agents Chemother. 2015 Oct;59(10):6605-7. doi: 10.1128/AAC.01165-15
175. Shields RK, Chen L, Cheng S, Chavda KD, Press EG, Snyder A, *et al.* Emergence of Ceftazidime-Avibactam Resistance Due to Plasmid-Borne blaKPC-3 Mutations during Treatment of Carbapenem-Resistant Klebsiella pneumoniae Infections. Antimicrob Agents Chemother. 2017 Feb 23;61(3):e02097-16. doi: 10.1128/AAC.02097-16
176. Poirel L, Vuillemin X, Juhas M, Masseron A, Bechtel-Grosch U, Tiziani S, *et al.* KPC-50 Confers Resistance to Ceftazidime-Avibactam Associated with Reduced Carbapenemase Activity. Antimicrob Agents Chemother. 2020 Jul 22;64(8):e00321-20. doi: 10.1128/AAC.00321-20
177. Read AF, Woods RJ. Antibiotic resistance management. Evol Med Public Health. 2014 Oct 28;2014(1):147. doi: 10.1093/emph/eou024
178. The antibiotic alarm. Nature. 2013 Mar 14;495(7440):141. doi: 10.1038/495141a
179. Michael CA, Dominey-Howes D, Labbate M. The antimicrobial resistance crisis: causes, consequences, and management. Front Public Health. 2014 Sep 16;2:145. doi: 10.3389/fpubh.2014.00145
180. Luyt CE, Bréchot N, Trouillet JL, Chastre J. Antibiotic stewardship in the intensive care unit. Crit Care. 2014 Aug 13;18(5):480. doi: 10.1186/s13054-014-0480-6
181. Rahimkhani M, Ghofrani H. Helicobacter pylori and peptic ulcer in cirrhotic patients. Pakistan Journal of Medical Sciences. 2008;24(6):849-852.
182. Lushniak BD. Antibiotic resistance: a public health crisis. Public Health Rep. 2014 Jul-Aug;129(4):314-6. doi: 10.1177/003335491412900402
183. Viswanathan VK. Off-label abuse of antibiotics by bacteria. Gut Microbes. 2014 Jan-Feb;5(1):3-4. doi: 10.4161/gmic.28027
184. Sreeja MK, Gowrishankar NL, Adisha S, Divya KC. Antibiotic resistance-reasons and the most common resistant pathogens - a review. Res J Pharm Technol. 2017;10:1886-1890. doi: 10.5958/0974-360X.2017.00331.6
185. Manyi-Loh C, Mamphweli S, Meyer E, Okoh A. Antibiotic Use in Agriculture and Its Consequential Resistance in Environmental Sources: Potential Public Health Implications. Molecules. 2018 Mar 30;23(4):795. doi: 10.3390/molecules23040795
186. Smith R, Coast J. The true cost of antimicrobial resistance. BMJ. 2013 Mar 11;346:f1493. doi: 10.1136/bmj.f1493
187. Lee SY, Kotapati S, Kuti JL, Nightingale CH, Nicolau DP. Impact of extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella species on clinical outcomes and hospital costs: a matched cohort study. Infect Control Hosp Epidemiol. 2006 Nov;27(11):1226-32. doi: 10.1086/507962
188. Kariuki S, Revathi G, Kiiru J, Mengo DM, Mwituria J, Muyodi J, *et al.* Typhoid in Kenya is associated with a dominant multidrug-resistant Salmonella enterica serovar Typhi haplotype that is also widespread in Southeast Asia. J Clin Microbiol. 2010 Jun;48(6):2171-6. doi: 10.1128/JCM.01983-09
189. Walsh TR, Weeks J, Livermore DM, Toleman MA. Dissemination of NDM-1 positive bacteria in the New Delhi environment and its implications for human health: an environmental point prevalence study. Lancet Infect Dis. 2011 May;11(5):355-62. doi: 10.1016/S1473-3099(11)70059-7
190. Antonanzas F, Lozano C, Torres C. Economic features of antibiotic resistance: the case of methicillin-resistant Staphylococcus aureus. Pharmacoeconomics. 2015 Apr;33(4):285-325. doi: 10.1007/s40273-014-0242-y
191. Linezolid price in Romania. Available from: https://comenzi.farmaciatei.ro/medicamente-cu-reteta/medicamente/linezolid-600-mg-10-comprimate-filmate-krka-p356273
192. European Commission Public Health. EU Action on Antimicrobial Resistance. Available from: https://ec.europa.eu/health/antimicrobial-resistance/eu-action-antimicrobial-resistance_en
193. University of Oxford New Resistance-Busting Antibiotic Combination Could Extend the Use of 'Last-Resort' Antibiotics. Dec 14, 2021. Available from: https://www.ox.ac.uk/news/2021-12-14-new-resistance-busting-antibiotic-combination-could-extend-use-last-resort