AMERICAN SOCIETY FOR MICROBIOLOGY | Clinical Microbiology Reviews®

REVIEW

Antimicrobial Resistance in ESKAPE Pathogens

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Citation De Oliveira DMP, Forde BM, Kidd TJ, Harris PNA, Schembri MA, Beatson SA, Paterson DL, Walker MJ. 2020. Antimicrobial resistance in ESKAPE pathogens. Clin Microbiol Rev 33:e00181-19. https://doi.org/10.1128/CMR.00181-19.

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Published 13 May 2020

SUMMARY Antimicrobial-resistant ESKAPE (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species) pathogens represent a global threat to human health. The acquisition of antimicrobial resistance genes by ESKAPE pathogens has reduced the treatment options for serious infections, increased the burden of disease, and increased death rates due to treatment failure and requires a coordinated global response for antimicrobial resistance surveillance. This looming health threat has restimulated interest in the development of new antimicrobial therapies, has demanded the need for better patient care, and has facilitated heightened governance over stewardship practices.

KEYWORDS *Acinetobacter*, *Enterobacter*, *Enterobacterales*, *Enterococcus*, *Klebsiella*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, antibiotic resistance, multidrug resistance

INTRODUCTION

The emergence of multidrug-resistant (MDR) bacteria (bacteria resistant to more than three antibiotic classes) (1) has been paralleled by a waning antibiotic development pipeline (2). The U.S. Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) categorize antimicrobial-resistant (AMR) pathogens as a looming threat to human health (3, 4). Currently, no systematic international surveillance of AMR exists (3), but available reports estimate that more than 2 million AMR infections with a death toll of 29,000 occur in the United States per annum, at an attributable health care cost of more than $4.7 billion (4). In Europe, over 33,000 deaths and 874,000 disability-adjusted life years are attributed to hospital-acquired (HA) and community-acquired (CA) AMR infections each year, accounting for $1.5 billion in direct and indirect costs (5, 6). In developing nations, where economic loss estimates are not available, communicable diseases remain the leading cause of death, and these are now heightened by emerging and reemerging infectious diseases (7–9). While AMR genes occur naturally in the environment, the use of antibiotics has selected for the presence of AMR genes. The lack of rapid diagnostic methods to identify bacterial pathogens and AMR genes in clinical settings has resulted in the often unnecessary use of broad-spectrum antibiotics (10).

In February 2017, to focus and guide research and development related to new antibiotics, the WHO published its list of pathogens for which new antimicrobial development is urgently needed. Within this broad list, ESKAPE (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species) pathogens (11) were designated "priority status" (12).

Through genetic mutation and the acquisition of mobile genetic elements (MGEs) (13), ESKAPE pathogens have developed resistance mechanisms against oxazolidinones, lipopeptides, macrolides, fluoroquinolones, tetracyclines, β-lactams, β-lactam–β-lactamase inhibitor combinations, and antibiotics that are the last line of defense, including carbapenems, glycopeptides, and clinically unfavorable polymyxins (14–19). Comparatively, resistance to lipoglycopeptides is rare and has only recently been documented (20). This may be potentially attributed to the dual action of lipoglycopeptides in inhibiting both peptidoglycan synthesis and destabilizing the bacterial cell membrane. Overall, the constitutive and/or inducible expression of these drug resistance mechanisms has resulted in the increased representation of bacterial species with these mechanisms in hospital-acquired infections (12).

Since the turn of the 1990s, the development and commercialization of novel antibiotics have slowed. Between 2017 and 2019, 11 new antimicrobial therapies were approved by the U.S. Food and Drug Administration (U.S. FDA) (21). Of these 11 antimicrobials, 4 were approved by the European Union European Medicines Agency (E.U. EMA): the meropenem-vaborbactam combination (Vaborem), eravacycline (Xerava), delafloxacin (Baxdela/Quofenix), and the imipenem-cilastatin-relebactam combination (Recarbrio; a positive opinion toward the granting of marketing authorization

was recommended in December 2019, and approval was provided in February 2020) (22–25). Apart from these antimicrobials, during this time frame, the E.U. EMA additionally approved ceftobiprole (Zeftera; also approved by the Australian Therapeutic Goods Agency in 2016 and by Health Canada in 2015), whereas the Japanese Pharmaceutical and Medical Devices Agency (PMDA) approved lascufloxacin (Lasvic) (26–29). Global initiatives to deliver new stand-alone antibacterial therapies or complementing alternative therapies are urgently needed. In this review, we assess the current state of AMR in ESKAPE pathogens, with a focus on current and emerging drug development avenues in the response against AMR.

VANCOMYCIN-RESISTANT ENTEROCOCCI

Enterococcus faecium is a prominent cause of health care-associated infections, and hospital-adapted lineages are increasingly resistant to vancomycin (30) (Table 1). The dissemination of *Enterococcus* in the United States occurred in two separate waves. The first wave began in the 1980s and was associated with the introduction of third-generation cephalosporins driving the emergence of vancomycin- and ampicillin-resistant *Enterococcus faecalis* (31). The second wave, dominated by vancomycin-resistant *E. faecium* (VRE*fm*), was hypothesized to have spread from the United States to other parts of the world. Several European countries have now reported increases in VRE*fm* prevalence in hospitalized patients (32, 33). In Australia, 47% of *E. faecium* blood culture isolates are VRE*fm*, contributing to an incidence rate of vancomycin-resistant enterococci (VRE) which surpasses that of many other high-income nations (34, 35). VRE*fm* multilocus sequence types (ST) pertaining to clonal complex 17 (CC17) are currently responsible for a significant burden of hospital-acquired infection (36). Highly prevalent in the gut microbiome of wild and domesticated animals (37, 38), CC17 strains have been associated with outbreaks in Europe, Asia, South America, and Australia (34, 39–42). Although the zoonotic transfer of CC17 strains from animals to humans is largely attributed to the spread of this complex, fresh food has also been found to be a significant reservoir (36). Despite spread in the community appearing high, community-associated infections caused by CC17 strains are uncommon.

Compared to the durations of outbreaks caused by the other ESKAPE pathogens, VRE*fm* outbreaks have a long duration, approximating 11 months, on average (43, 44). The entry of VRE*fm* into the bloodstream of hospitalized patients is typically preceded by antibiotic exposure, enabling VRE*fm* to become the predominant species in the gastrointestinal tract (45, 46). The duration of prior antibiotic exposure is strongly associated with a subsequent risk of VRE infection (47). In a 2016 national survey of 1,058 bloodstream infections caused by *Enterococcus* in Australia, almost 50% of *E. faecium* isolates were vancomycin resistant (48). In the United States, the incidence of hospital- and community-acquired VRE infection between 2012 and 2017 significantly decreased (4). The management of patients infected with VRE is complicated by the excess cost and disruption resulting from the need for isolation rooms, contact precautions, and dedicated room cleaning. The treatment of significant infection relies upon second-line antibiotic therapies (e.g., tigecycline and daptomycin), which are often associated with increased cost, diminished efficacy, and a greater risk of toxicity compared with the cost, efficacy, and risk of toxicity of first-line antibiotic therapies (Table 1) (49, 50). Defining the additional risk of a poor outcome attributable to vancomycin resistance in enterococci has been challenging, largely because of the confounding effects of comorbidity (51). Most studies have demonstrated an association of VRE infection with excess mortality, the duration of hospital admission, and treatment costs (52, 53), especially when VRE cause a bloodstream infection (54).

METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS*

Methicillin resistance was first identified in *Staphylococcus aureus* in 1961 as a consequence of widespread penicillin usage (55). The introduction of penicillin also heightened the emergence of penicillinase-producing *S. aureus*. Although methicillin-resistant *S. aureus* (MRSA) is still a significant burden in U.S. health care settings, the

TABLE 1 Clinical characteristics of ESKAPE pathogens[a]

Species	Resistances	Clinical manifestations	Major ST/CC	Mortality rates	Treatments	Key characteristics
Vancomycin-resistant *Enterococcus*	Vancomycin (184, 471), ampicillin (472), linezolid (35), teicoplanin (473), piperacillin (474), cephalosporins (64), multidrug resistant (184)	Catheter-associated-UTI, vascular catheter-associated bacteremia, intra-abdominal and pelvic infection, endocarditis (51)	*E. faecium* ST17 (CC17) (35), ST203 (CC17) (475), ST796 (476), ST1421 (35), and CC17 (36); *E. faecalis* CC2 (477), CC9 (477), ST6 (478), and ST16 (479)	Over 30% for bacteremia (35, 480); 2.5-fold increase in mortality from bacteremia caused by VRE compared to that from bacteremia caused by vancomycin-sensitive bacteria (473)	Nitrofurantoin[b] (481), fosfomycin (482), linezolid (480), daptomycin (18), chloramphenicol (483), doxycycline (483), high-dose ampicillin and sulbactam (483), omadacycline (396)	10% of all HA bloodstream infections (484, 485); tolerant to heat, chlorine, and alcohol preparations (486); *E. faecium* demonstrates significantly higher levels of resistance than *E. faecalis* (35); commonly encountered as asymptomatic colonization (487)
Methicillin-resistant *S. aureus*	Aminoglycosides (488), β-lactams (489), chloramphenicol (488), trimethoprim (313), macrolides (313), tetracycline (313), fluoroquinolones (64), multidrug resistant (488)	Acute bacterial skin and skin structure infection (490), bacteremia (488), pneumonia (491), osteoarticular infection (492), endocarditis (488)	ST5 (65), ST8 (493), ST22 (35), ST30 (494), ST59 (495), ST72 (CC8) (496), ST80 (70), ST398 (livestock associated) (71, 497)	Greater than 20% for bloodstream infection (76, 77); overall mortality ranges from 15–50% (498)	Vancomycin (488), clindamycin (499), daptomycin (500), linezolid (501), tedizolid (502), dalbavancin (503), tigecycline (504), trimethoprim and sulfamethoxazole (505), pristinamycin (506), omadacycline (396), lefamulin (403)	In Asia, 50% of all *S. aureus* bloodstream infections are caused by MRSA (507); in USA, HA-MRSA infections have decreased by 54% (508); in Europe, the total proportion of reported MRSA infections among *S. aureus* infections decreased from 19.6% in 2014 to 16.4% in 2018 (64); 20–40% of the population carries *S. aureus* as a commensal organism (488)
K. pneumoniae	Polymyxins (276), carbapenems (509), fluoroquinolones (64), third-generation cephalosporins (64), aminoglycosides (64), tetracyclines (276), pandrug resistant (276)	Pneumonia (510), pyogenic liver abscesses (511), necrotizing and soft tissue infection (92), bloodstream infection, meningitis (512), endophthalmitis (512), UTI (513)	ST11 (82, 514), ST15 (82, 515), ST17 (516), ST37 (516), ST101 (82, 517), ST147 (518), ST258 (148, 519), ST307 (88, 89), ST405 (520), ST512 (82)	40% to 70% for CRKP bloodstream infection (509, 521); 40% for CRKP pulmonary infection (521, 522); 25% to 47% for hvKP necrotizing and soft tissue infection (90, 92)	Aminoglycosides (523), polymyxin combination therapy (524), tigecycline (79), meropenem (523), meropenem-vaborbactam (525), ertapenem and meropenem (526), imipenem-cilastatin-relebactam (24), ceftazidime-avibactam (527), plazomicin (393), eravacycline (394)	USA has more than 7,000 HA-CRKP infections per year (80); in Taiwan, 80% of pyogenic liver abscess cases are attributed to hvKP (511)
A. baumannii	Carbapenems (103), polymyxins (108), β-lactams (103), tigecycline (103), ceftazidime (103), fourth-generation cephalosporins (103), multidrug resistant (101, 103)	Ventilator-associated pneumonia (528), central line bloodstream infections (528), nosocomial meningitis (529), skin and soft tissue infection (530), catheter-associated UTI (528)	ST195 (CC92) (531), ST457 (CC92) (531), pan-European epidemic clones I, II, and III (532)	35% for ventilator-associated pneumonia and bloodstream infections (533)	Colistin (534), tigecycline (102), cefiderocol (412), eravacycline (394)	2% of all HA-infections in USA and Europe (100, 101); high mutation frequency upon desiccation (535); persistence in biofilms during soft tissue infection (536); tolerance to low-ethanol environments and resistance to chlorhexidine-based disinfectants (537, 538)
P. aeruginosa	First- and second-generation cephalosporins (110), piperacillin-tazobactam (35, 110), aminoglycosides (110), quinolones (110), carbapenems (35, 110), polymyxins (110), multidrug resistant (539)	UTI (540), bloodstream infection (539), ventilator-associated pneumonia (64), chronic respiratory infection (541), skin and soft tissue infection (542), endocarditis (543)	ST111 (544), ST175 (112, 544), ST233 (544), ST235 (111, 545), ST253 (544), ST292 (114), ST1725 (544)	67% for MDR bacteremia (539); 33.9% for UTI (540)	Piperacillin-tazobactam (35), ceftolozane-tazobactam (546), ceftazidime (35), meropenem (35), ciprofloxacin (35), ceftazidime-avibactam (527), cefiderocol (412), imipenem-cilastatin-relebactam (24)	High incidence of infection in burn victims (542); 51,000 HA infections in USA per year (547–550)
Enterobacter species	Carbapenems (3), fourth-generation cephalosporins (102), fluoroquinolones (102), β-lactams (157), polymyxins (130), multidrug resistant (102), pandrug resistant (130)	UTI (551), bloodstream infection (552), neonatal pneumonia (553), skin and soft tissue infection (554), intra-abdominal infection (555), endocarditis (556), septic arthritis (556)	In *K. aerogenes*, ST4 (127) and ST93 (127); in *E. cloacae*, ST66 (557), ST78 (557), ST108 (557), ST144 (557), and ST171 (128)	Exceeds 40% for *E. cloacae* bloodstream infection (552, 558)	Nitrofurantoin[b] (35), cefepime (35), ceftriaxone (35), ciprofloxacin (35), gentamicin (35), meropenem (35), piperacillin-tazobactam (35), trimethoprim with or without sulfamethoxazole (35), imipenem-cilastatin-relebactam (24)	*E. cloacae* is the 3rd most frequent *Enterobacterales* species causing bloodstream infection (552); infections are prevalent in neonates and elderly individuals (556, 559); clinically relevant *E. hormaechei* is an important emerging pathogen within the *E. cloacae* complex (125, 126)

[a]Abbreviations: ST, sequence type; CC, clonal complex; UTI, urinary tract infection; HA, hospital acquired; CRKP, carbapenem-resistant *K. pneumoniae*; hvKP, hypervirulent *K. pneumoniae*.
[b]Nitrofurantoin is prescribed only for uncomplicated urinary tract infections.

incidence of hospital-acquired MRSA (HA-MRSA) is declining (4, 56) (Table 1). Opposite this finding, the incidence of community-acquired MRSA (CA-MRSA) infections in the same region has significantly increased (56). CA-MRSA infections emerged among the indigenous population of Australia in the 1980s (57) and in otherwise healthy communities of the United States and Canada in the 1990s (58). In North America, where CA-MRSA is prevalent, MRSA epidemics are largely attributed to the emergence of either of two unrelated MRSA clones (59, 60). The MRSA clone USA400, isolated from the pediatric population, initiated the first epidemic wave and remains a common cause of community-onset disease among indigenous populations in Alaska and the Pacific Northwest (61). Since 2001, USA400 has been superseded by an epidemic caused by MRSA USA300 (61, 62) and closely related variants, which are now the most prevalent CA-MRSA isolates in North America and northern parts of South America.

Today, the burden of MRSA across the world varies substantially (4, 63, 64). In China, the prevalence of HA- and CA-MRSA infections wavered remarkably between 2007 and 2018. The prevalence of HA-MRSA clones ST239-t030 and ST239-t037 was significantly reduced (from 20.3% to 1% and 18.4% to 0.5%, respectively), and these have now been replaced by the ST5-t2460 clone (from 0% to 17.3%), which has seen a rapid emergence. Furthermore, the incidence of CA-MRSA clones ST59 and ST398 also increased over the same period (from 1.0% to 5.8% and 1.8% to 10.5%, respectively) (65). In Northern Europe (i.e., the United Kingdom and France), a steady decrease in the prevalence of HA-MRSA was observed between 2015 and 2018 and was largely attributed to improved national infection control programs (64, 66, 67). In comparison, the rates of HA-MRSA in Southern Europe (i.e., Portugal, Spain, Italy, and Greece) remain high (5, 64).

CA-MRSA strains have typically been associated with skin and soft tissue infections, whereas HA-MRSA strains are associated with severe pneumonia and bloodstream infections (68). The division between CA- and HA-MRSA strains is becoming indistinct, with CA-MRSA strains now identified to be a causative agent of bloodstream infections in nosocomial settings. MRSA ST80 is a well-defined agent of CA-MRSA in Europe. Although it is now becoming less prevalent in select European countries (69), CA-MRSA ST80 is now a major contributor of infection in defined health care settings (70). Furthermore, examples of CA-MRSA (e.g., ST398) have been shown to be associated with exposure to livestock (particularly pigs) in Europe (71) (Table 1). Although individuals with direct exposure to livestock are the most at risk from livestock-associated MRSA (LA-MRSA), it has now been reported that LA-MRSA substantially contributes to the burden of nosocomial infection in Europe (72). One of the less-defined and neglected subgroups of *S. aureus* is borderline oxacillin-resistant *S. aureus* (BORSA). Found both in community settings and in hospital settings, BORSA is characterized by intermediate resistance to penicillinase-resistant penicillins, with oxacillin MICs being between 1 and 8 μg/ml (73). Lacking the *mecA* gene, BORSA is not truly either methicillin resistant or methicillin sensitive, and frequent misidentification poses a significant threat to patient treatment and outcome, as severe BORSA infections may be nonresponsive to high doses of oxacillin (74). Overall, MRSA infections carry additional health care burdens in terms of morbidity, length of hospital stay, health care costs, and quality of life (75). The rate of mortality following *S. aureus* bloodstream infection exceeds 20%, and the presence of methicillin resistance is independently associated with increased mortality (76, 77).

KLEBSIELLA PNEUMONIAE

Cephalosporin- and carbapenem-class antibiotics have been a mainstay of treatment for serious infections caused by *Enterobacterales*, such as *K. pneumoniae*, but efficacy has been compromised by the widespread acquisition of genes encoding enzymes, such as extended-spectrum β-lactamases (ESBLs) and carbapenemases, which mediate the respective resistance to these critical drugs (19). High rates of mortality, often exceeding 40%, have been associated with severe infections caused by carbapenem-resistant *Enterobacterales* (CRE) (78). Effective antimicrobial options are

often lacking, and treatment typically requires reliance on drugs with a risk of toxicity (e.g., aminoglycosides, polymyxins) or other safety concerns (e.g., tigecycline) (79) (Table 1). Carbapenem-resistant *K. pneumoniae* (CRKP) strains are the most clinically prominent CRE (64, 80). In the United States, carbapenemases carried by *K. pneumoniae* were originally reported in 2001 (81). Since then, the genes encoding these β-lactamases have spread among several Gram-negative bacterial species. Between 2005 and 2010, an increase in CRKP isolates causing invasive infections was reported across Europe (64). The spread of CRKP in Europe has been driven by direct and indirect patient-to-patient transmission in nosocomial settings, largely attributed to ST11, ST15, ST101, and ST258 strains, along with the ST258 derivative ST512 (82) (Table 1). The global burden of CRKP has now been further exacerbated by successive waves of CRKP emerging from several locations across the Indian Ocean rim, the United States, and China (83–87). The global dissemination of CRKP is exemplified by the CRKP clone ST307. The ST307 clone has successfully disseminated across every major continent (88), demonstrating extremely high transmission rates in health care settings (89).

Recent reports suggest that AMR hypervirulent *K. pneumoniae* (hvKP) strains are also emerging. In Taiwan, hvKP causes as many cases of necrotizing fasciitis as *Streptococcus pyogenes* and is associated with a higher mortality rate (47% versus 19%) (90). The detection of hvKP is now being reported around the world in both high- and low-income settings (87, 91, 92). An important laboratory feature frequently seen in hvKP strains is the presence of a hypermucoviscous phenotype (in association with the K1 and K2 capsular serotypes) (93).

ACINETOBACTER BAUMANNII

A. baumannii infections typically occur in hospitalized patients or patients with significant contact with the health care system (94). Historically, *A. baumannii* has been associated with hot and/or humid geographic climates (95, 96). Between 1987 and 1996, the frequency of both community- and hospital-acquired infections across the United States was observed to rise by 50% between the months of July and October (97). Since the 1970s, *A. baumannii* has become increasingly common in temperate climates, a shift largely attributed to improved environmental persistence mechanisms and MDR development (98). Community-acquired pneumonia due to *A. baumannii* has been described in tropical regions of Asia and Australia among individuals with a history of alcohol abuse (99). Although *A. baumannii* infection rates are comparatively low compared to those of other ESKAPE pathogens (100, 101), approximately 45% of all global *A. baumannii* isolates are considered MDR, with rates exceeding 60% in the United States (4, 101), Latin America, and the Middle East (102). Turkey and Greece have reported MDR rates exceeding 90% (103). These levels of MDR for *A. baumannii* are over four times higher than those observed in *K. pneumoniae* and *P. aeruginosa* (3). A key aspect of *A. baumannii* physiology is the propensity to develop rapid resistance. From 2011 to 2016, the rate of identification of *A. baumannii* isolates resistant to carbapenem- and β-lactam-class antibiotics has increased by over 30% globally (103). The spread of MDR and carbapenem-resistant *A. baumannii* (CRAB) isolates is largely associated with three international clonal lineages: CC1, CC2, and CC3 (104, 105). CC1 is prevalent worldwide, while CC2 and CC3 are highly prevalent in Europe and North America. CC15 and CC79 are also predominant in Central and South America (106, 107). With the emergence of pandrug-resistant isolates, last-resort carbapenem- and polymyxin-class antibiotics are no longer effective (103, 108) (Table 1). Without adequate action via improved epidemiological surveillance and therapeutic development, *A. baumannii* has the capacity to potentiate a global epidemic.

PSEUDOMONAS AERUGINOSA

Widely present in aquatic environments, *P. aeruginosa* is a Gram-negative opportunistic human pathogen commonly associated with severe respiratory infections in patients with impaired immunity. While *P. aeruginosa* is responsible for 10% of all

nosocomial infections, there is also increasing acknowledgment of *P. aeruginosa* as a cause of community-acquired infection.

The plasticity and adaptability of the *P. aeruginosa* genome, conferred by a repertoire of regulatory genes (>8% of the 6-Mb genome), are key features in the pathogen's ability to chronically persist in the host and evade antibiotic treatment (109). Intrinsically resistant to a wide array of antimicrobial agents, *P. aeruginosa* currently displays resistance to multiple classes of antibiotics (6, 110) (Table 1). In the United States, although AMR rates remain high, surveillance suggests a trend toward declining rates of resistance (4). Globally, patterns of *P. aeruginosa* AMR vary substantially. Today, the highest rates of AMR in *P. aeruginosa* occur in North, Central, and South America, Western and Central Europe, China, India, and Southeast Asia (7). With an enhanced capacity to acquire and maintain foreign antibiotic resistance elements, *P. aeruginosa* lineages ST235 and ST175 have emerged as high-risk globally dispersed clones and remain a major contributor of hospital-acquired infection (111, 112). Furthermore, the widespread distribution of *P. aeruginosa* nosocomial isolates resistant to last-resort polymyxin- and carbapenem-class antibiotics is well documented (7, 113, 114).

Patients with chronic or inherited lung disease, such as bronchiectasis and cystic fibrosis (CF), are highly susceptible to persistent pulmonary infection, with episodic exacerbations requiring hospitalization and intravenous antibiotics, with a subsequent risk of selection for MDR (115). *P. aeruginosa* has been shown to remain viable in the lungs of patients diagnosed with CF for over a decade (116). *P. aeruginosa* colonizes moist environments and therefore can be found in many health care settings, especially in the context of chronic wounds, respiratory support, or urinary tract devices, where biofilm formation predisposes for persistence, immune evasion, and antimicrobial resistance (117, 118).

ENTEROBACTER SPECIES

Over the last 35 years, *Enterobacter aerogenes* (now renamed *Klebsiella aerogenes*) and *Enterobacter cloacae* species have presented as significant threats to neonatal wards and patients in intensive care units, particularly those dependent on mechanical ventilation (119). The emergence of these two *Enterobacter* species as clinically significant MDR pathogens has occurred in concurrent epidemic waves. From the early 1990s to 2003, *E. aerogenes* was the most clinically prevalent cause of *Enterobacter* nosocomial infection (119). During this period, the hospital-acquired *E. aerogenes* infection incidence was high in Western Europe (120, 121), largely attributed to the dispersion of a single epidemic clone (122, 123). In about 2010, *E. aerogenes* was superseded by *E. cloacae* as the most common clinically isolated species of the genus (124). It is worth noting that other members of the *E. cloacae* complex, especially *Enterococcus hormaechei*, are clinically relevant and are often difficult to discriminate at the species level based on standard phenotypic assays (125, 126).

MDR *Enterobacter* species are an increasing cause of hospital-acquired infection. In the United States, *E. aerogenes* ST4 and ST93 currently represent prevalent lineages associated with nosocomial infection (127). For the *E. cloacae* complex, recent data suggest that carbapenem resistance has directionally spread across the United States due to the dissemination of hospital-associated carbapenem-resistant *E. cloacae* ST178 and ST78 isolates (128). Prior to 2005, an estimated 99.9% of *Enterobacter* strains were sensitive to carbapenems (129). Carbapenem resistance is now reported in all WHO health regions (3). Moreover, pandrug-resistant *E. aerogenes* has also emerged, displaying resistance to the last-resort antibiotic colistin (130) (Table 1). To complicate the treatment of bacterial infections further, *E. aerogenes* is capable of harboring subpopulations of colistin-resistant bacteria which are undetectable using current diagnostic testing strategies (131).

ESCHERICHIA COLI

Although not formally recognized as part of the ESKAPE group of pathogens, AMR *Escherichia coli* is identified as a major cause of bloodstream and urinary tract infection

(UTI) in both community and health care settings globally (5, 35, 64). Sepsis is one of the most common manifestations of *E. coli* UTI. In Australian inpatient and emergency department settings, *E. coli* is the most prevalent Gram-negative bacterial species isolated from both blood and urine cultures (35). Over the past decade, several pandemic clones of MDR uropathogenic *E. coli* (e.g., ST131 and ST95) have disseminated worldwide (132, 133). Through horizontal gene transfer, *E. coli* typically acquires resistance genes from other members of the *Enterobacterales*. High rates of resistance to aminopenicillins, fluoroquinolones, aminoglycosides, and third-generation cephalosporins are noted across Europe (64). Although carbapenem resistance is rare in invasive *E. coli* strains, the general situation in Europe for CRE, including *E. coli*, was shown to worsen between 2010 and 2018 (134). Furthermore, in 2016, resistance to the last-resort polymyxin, colistin, was identified in *E. coli* strains isolated from pig farms in China (135). Although not discussed further in this review, AMR *E. coli* is currently one of the largest clinical burdens facing both human and animal health. In order not to exacerbate these challenges further, organizations involved in AMR policy, research and development (R&D), and surveillance need to consider this pathogen as a critical public health concern.

ESKAPE PATHOGEN MECHANISMS OF ANTIBIOTIC RESISTANCE

Given the frequency at which ESKAPE organisms are encountered in the clinical setting, it is not surprising that numerous different AMR mechanisms are observed in these pathogens. These can be broadly categorized into four groups, comprising (i) inactivation or alteration of the antimicrobial molecule, (ii) bacterial target site modifications, (iii) reduced antibiotic penetration/accumulation, and (iv) the formation of bacterial biofilms (Fig. 1). Here we explore the most important AMR determinants that have contributed to the success of ESKAPE pathogens in the modern-day clinical setting.

Antibiotic Inactivation/Alteration

One of the most common AMR mechanisms employed by ESKAPE pathogens involves the production of enzymes that irreversibly destroy or neutralize antibiotics. Such enzymes are particularly prevalent among the Gram-negative pathogens and comprise those (i) that destroy the active antibiotic site (e.g., hydrolytic cleavage of the β-lactam ring by β-lactamases) or (ii) that covalently modify key structural elements of the drug to hinder bacterial target site interaction (e.g., aminoglycoside-modifying enzymes [AMEs] that catalyze hydroxyl/amino group modifications).

***β*-Lactamases.** β-Lactamase enzymes were first identified soon after the initial discovery and purification of penicillin (136). Since then, >2,600 unique β-lactamases enabling resistance to one or more β-lactams (i.e., penicillins, cephalosporins, monobactams, and carbapenems) have been described (137). β-Lactamases remain the most important resistance mechanism among Gram-negative ESKAPE pathogens, where they are concentrated within the periplasm, thus hydrolyzing the β-lactam agents prior to reaching the penicillin-binding protein (PBP) target in the cell wall.

β-Lactamase enzymes are typically classified according to their primary molecular structure (i.e., the Ambler scheme [138]) or combined hydrolytic and inhibition functional properties (i.e., the Bush-Jacoby system [139]). Ambler class A enzymes contain serine in their active site and comprise penicillinases, cephalosporinases, narrow- and broad-spectrum β-lactamases, extended-spectrum β-lactamases (ESBLs), and carbapenemases. Overall, they represent the largest cluster of β-lactamase enzymes and collectively are capable of inactivating most β-lactam classes, including the penicillins, early cephalosporins, third-generation oxyimino-cephalosporins, monobactams, cephamycins, and carbapenems. Their susceptibility to inhibition by clavulanic acid and tazobactam is variable, though all are inhibited by novel β-lactamase inhibitor agents, including avibactam, relebactam, and vaborbactam (139, 140).

Ambler class A enzymes comprise various important β-lactamases that are frequently observed in Gram-negative (e.g., TEM, SHV, CTX-M, and KPC) and Gram-positive

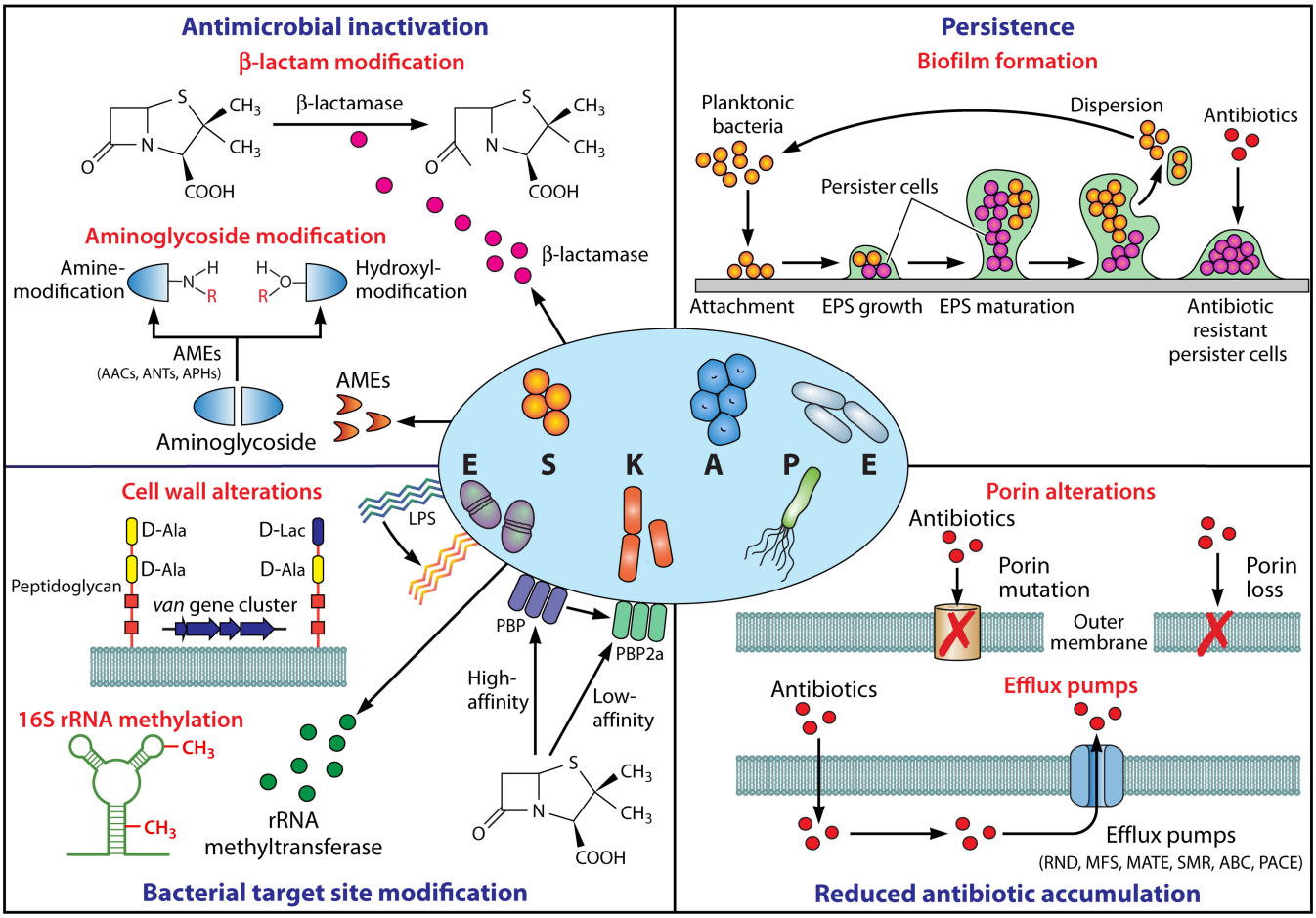

FIG 1 Mediators of ESKAPE pathogen antimicrobial resistance. Mechanisms facilitating antimicrobial resistance in ESKAPE pathogens can be broadly categorized into four groups: (i) enzyme-mediated antimicrobial inactivation, which either irreversibly destroys the active antibiotic site (e.g., hydrolytic cleavage of the β-lactam ring by β-lactamases) or covalently modifies key structural elements of the drug to hinder the bacterial target site interaction (e.g., aminoglycoside-modifying enzymes that catalyze hydroxyl/amino group modifications); (ii) bacterial target site modification, which prevents the binding or which reduces the affinity of the antibiotic molecule at the cell surface (e.g., LPS modification, PBP2a expression with reduced β-lactam affinity, and *van* gene cluster-mediated peptidoglycan modification) or intracellularly (e.g., 16S RNA methylation); (iii) reduced antibiotic accumulation through the mutation or loss of outer membrane channels (e.g., OprD in *P. aeruginosa*, CarO in *A. baumannii*, and OmpK36 in *K. pneumoniae*) and expression of efflux systems to actively extrude drugs out of the cell (e.g., RND, MFS, MATE, SMR, ABC, and PACE); and (iv) persistence through biofilm-embedded cells which demonstrate a markedly higher tolerance to antimicrobial agents than planktonic bacteria. AMEs, aminoglycoside-modifying enzymes; AACs, aminoglycoside acetyltransferases; ANTs, aminoglycoside nucleotidyltransferases; APHs, aminoglycoside phosphotransferases; LPS, lipopolysaccharide; PBP, penicillin-binding protein; RND, resistance-nodulation-division; MFS, major facilitator superfamily; MATE, multidrug and toxic compound extrusion; SMR, small multidrug resistance; ABC, ATP-binding cassette; PACE, proteobacterial antimicrobial compound efflux; EPS, extracellular polymeric substance.

(e.g., penicillinase) ESKAPE pathogens. Indeed, *blaZ*-encoded penicillinases that emerged widely and soon after the introduction of penicillin are now detectable in ~85% of clinically significant *S. aureus* isolates and some *Enterococcus* spp. (141–144). Likewise, the narrow-spectrum TEM-type β-lactamases, which readily hydrolyze early cephalosporins and penicillins, are frequently encountered in *K. pneumoniae* and *Enterobacter* spp. but have also been reported in *A. baumannii* and *P. aeruginosa*. SHV-1, which has a substrate and inhibition profile similar to that of TEM-1, is almost universally found in the progenitor species, *K. pneumoniae* (144, 145).

Due to a combination of strong selection pressures and the frequency at which AMR determinants are mobilized between organisms, both TEM- and SHV-type enzymes have undergone extensive evolution in recent decades (145). This has resulted in the proliferation and dissemination of numerous plasmid-encoded ESBL variants that can also hydrolyze oxyimino-β-lactams and aztreonam (139, 145). Other class A ESBLs, namely, enzymes of the CTX-M, PER, GES, and VEB families, have also been reported across all Gram-negative ESKAPE pathogens. Characteristically, most class A ESBL

enzymes remain susceptible to clavulanic acid, though Bush-Jacoby subgroup 2br and 2ber ESBLs (e.g., TEM-30, SHV-10, and TEM-50) show reduced susceptibility to various β-lactamase inhibitors (146). Concerningly, inhibitor-resistant β-lactamases have also been reported in *K. pneumoniae* strains harboring KPC serine carbapenemase enzymes (147). Plasmid-encoded KPCs have been associated with major outbreaks worldwide (e.g., the outbreak caused by *K. pneumoniae* ST258) and hydrolyze virtually all β-lactams, including carbapenems (148). Despite this, there is emerging evidence that infections with KPC-producing organisms can be successfully targeted with various new β-lactamase–β-lactamase inhibitor combinations, including imipenem-cilastatin-relebactam, meropenem-vaborbactam, and ceftazidime-avibactam (149). Unfortunately, the rapid evolution of ceftazidime-avibactam resistance has already been reported in *K. pneumoniae* ST258 bla_{KPC-3}-harboring isolates and in non-ST258 clonal backgrounds and additional bla_{KPC} variants (17, 150, 151).

Ambler class B metallo-β-lactamases (MBLs) represent another clinically important group of enzymes capable of hydrolyzing most β-lactams, including carbapenems. However, in contrast to other β-lactamases, they require Zn^{2+} at their active site, display a low affinity for aztreonam, and are inhibited by EDTA (139). The most prominent MBLs encountered in the Gram-negative ESKAPE pathogens (e.g., MBLs of the IMP, VIM, and NDM families) are encoded on conjugative plasmids. IMP- and VIM-type MBLs were first detected in clinical *P. aeruginosa* isolates (152, 153) but have since been identified in *K. pneumoniae*, *E. cloacae* complex isolates, and *Acinetobacter* spp. (154–157). NDM-type enzymes have also been detected across all Gram-negative ESKAPE bacteria and are of particular concern due to the fact that they are incorporated into transferable genetic elements that also encode determinants for resistance to other antibiotic classes (157, 158).

Group C β-lactamases comprise chromosomally encoded cephalosporinases, such as AmpC, that are found in many *Enterobacterales* (including *Enterobacter* spp.), *P. aeruginosa*, and *Acinetobacter* spp. (159). They are most active on narrow- to intermediate-spectrum cephalosporins plus aztreonam and are usually resistant to clavulanic acid. The rate of constitutive expression of AmpC is usually low, but clinically relevant resistance is inducible during therapy (139). Plasmid-mediated resistance involving group C enzymes has also been reported widely, including reports of plasmids in organisms, such as *K. pneumoniae*, that do not normally contain genes encoding these enzymes on their chromosome (159).

β-Lactamases belonging to Ambler class D primarily consist of oxacillin-hydrolyzing enzymes (OXA), which are able to hydrolyze oxacillin and its derivatives, which display ESBL-like substrate properties, and which show variable resistance to β-lactam inhibitors (139). Importantly, some OXA-type β-lactamases, such as OXA-48 and its derivatives, also confer carbapenem resistance. OXA-type enzymes are most frequently found in *Acinetobacter* spp., where they are often located on the chromosome. However, plasmid-borne OXA-48-like enzymes are now widely distributed in many *Enterobacterales* species, including *K. pneumoniae* and *Enterobacter* spp. (160), many of which express other ESBLs, such as CTX-M-15, and thus provide resistance to most β-lactam agents (161).

Aminoglycoside-modifying enzymes. The most common aminoglycoside resistance mechanism encountered among ESKAPE pathogens occurs through the production of AMEs. During transportation of the drug across the cytoplasmic membrane, these enzymes covalently catalyze specific hydroxyl or amino group modifications of the aminoglycoside molecule, thus reducing antibacterial activity through diminished bacterial ribosomal subunit binding. Based on their biochemical activity, there are three classes of AMEs (i.e., aminoglycoside acetyltransferases [AACs], aminoglycoside phosphotransferases [APHs], and aminoglycoside nucleotidyltransferases [ANTs]). Enzymes within each class are then further subdivided according to the position of the modification site, resistance profile, and specific protein designation (162). Earlier work has shown that the global distribution of AMEs varies with respect to geography, antibiotic selection pressure, and bacterial species (163, 164). Depending on the specific enzyme

and the host organism, genes coding for AMEs are located on plasmids, on transposons, or in the chromosome (162), though the high frequency of these resistance determinants among ESKAPE pathogens is largely attributable to acquisition via horizontal gene transfer (165).

AACs encompass the largest AME class and in an acetyl coenzyme A-dependent manner catalyze the acetylation of specific amino groups present on the antibiotic acceptor molecule. Of the four AAC subclasses, the AAC(1) and AAC(3) enzymes target amino group positions 1 and 3 of the central 2-deoxystreptamine ring, respectively, whereas the AAC(2′) and AAC(6′) subclasses modify the respective 2′ and 6′ amino group positions of the 2,6-dideoxy-2,6-diamino-glucose ring (166). While comprehensive analyses of global AAC epidemiology remain relatively scarce, recent investigations conducted in the United States, Europe, and Asia indicate that Gram-negative ESKAPE pathogens most frequently encode AAC(3) and AAC(6′) enzymes, which collectively confer resistance to gentamicin, tobramycin, and amikacin (165, 167, 168).

APHs comprise the second most abundant class of AMEs, which decrease aminoglycoside binding affinity by catalyzing ATP-dependent phosphorylation of —OH groups on the antibiotic molecule. Of the seven different APH subclasses [i.e., APH(4), APH(6), APH(9), APH(3′), APH(2″), APH(3″), and APH(7″)], APH(3′) is the most widely distributed among clinical isolates, with the *aph(3′)-IIIa* gene being recognized as a key determinant of plasmid-mediated amikacin resistance in both *S. aureus* and *Enterococcus* spp. (165).

The final class of AMEs encompasses the ANTs, which reduce aminoglycoside toxicity via the magnesium-dependent transfer of a nucleoside monophosphate to —OH groups on the antibiotic molecule. Overall, there are five subclasses of ANTs [i.e., ANT(6), ANT(9), ANT(4′), ANT(2″), and ANT(3″)], of which ANT(4′) and ANT(2″) are the most clinically relevant. ANT(4′) enzymes conferring resistance to amikacin and tobramycin have been detected in *S. aureus*, *Enterococcus* spp., *K. pneumoniae*, and *P. aeruginosa*. ANT(2″), encoded by the *ant(2″)-Ia* (or *aadB*) gene, is frequently associated with gentamicin and tobramycin resistance across all the Gram-negative ESKAPE organisms (165).

Most importantly, broad-spectrum aminoglycoside resistance in the ESKAPE pathogens is often conferred through the presence of multiple or bifunctional AMEs. This frequently occurs among Gram-negative organisms, where multiple AMEs result in significantly increased aminoglycoside resistance (169–171). Likewise, expression of the bifunctional AAC(6′)-APH(2″) enzyme, which resides on the common Tn*4001* transposon, accounts for high-level gentamicin resistance in both *S. aureus* and *Enterococcus* spp. (including MRSA and VRE strains) worldwide (152). More recently, a variant enzyme termed AAC(6′)-Ib-cr, which confers low-level plasmid-mediated aminoglycoside and ciprofloxacin resistance, has been described in *K. pneumoniae*, *Enterobacter* spp., *A. baumannii*, and *P. aeruginosa* (172–175).

Target Site Modifications

Another common AMR strategy employed by the ESKAPE pathogens is to modify the antibiotic target site, thereby reducing the affinity or preventing the binding of the antibiotic molecule. Specifically, these mechanisms include (i) target enzyme modification, (ii) ribosomal target site alterations, and (iii) cell wall precursor alterations.

Target enzyme modifications. β-Lactam antibiotics inhibit bacteria by binding to PBP enzymes anchored in the cell wall. In MRSA, resistance to methicillin and other β-lactam antibiotics is mediated through expression of the foreign *mecA* gene. *mecA* codes for PBP2a, a modified PBP with a low affinity for β-lactams, which renders most β-lactam agents completely ineffective against MRSA (176). *mecA* is located within the staphylococcal cassette chromosome *mec* (SCC*mec*), which also encodes a two-component regulatory system (TCRS; designated MecI and MecR1), site-specific *ccr* recombinase genes, as well as three joining (J) regions that can contain additional resistance determinants, mobile genetic elements (MGEs), and regulators (176). Cryptic or low-level *mecA*-positive MRSA strains displaying oxacillin MICs of $\leq$2 μg/ml are often

misidentified as methicillin-sensitive *S. aureus*, proving a particular problem in the accurate identification of CA- and LA-MRSA (177, 178).

Thirteen distinct SCC*mec* types of various sizes and with various genetic contents have been identified thus far in *S. aureus* (179). Isolates possessing multidrug resistance and larger SCC*mec* types are typically associated with hospital-acquired MRSA (HA-MRSA) strains (e.g., SCC*mec* types I to III), whereas community-acquired strains expressing predominantly β-lactam resistance alone are more often associated with smaller SCC*mec* cassettes (e.g., types IV and V). Interestingly, two other *mec* gene homologues (designated *mecB* and *mecC*) have been recently identified in MRSA (180, 181). Though the frequency of strains expressing *mecB* is unclear at present, recent studies indicate that *mecC*-encoding *S. aureus* strains are predominantly found across the United Kingdom and Europe at a low but variable prevalence across several host species, including livestock and humans (176, 182, 183).

Both *E. faecalis* and *E. faecium* also express PBP5, a low-affinity chromosomally encoded ortholog of PBP2a in MRSA, which confers intrinsic low- to moderate-level β-lactam resistance (penicillin MICs are 2 to 8 μg/ml for *E. faecalis* and 16 to 32 μg/ml for *E. faecium*). In addition, up to 90% of hospital-associated *E. faecium* strains show high-level ampicillin resistance (MICs, $>$128 μg/ml), arising through the overproduction of PBP5 or polymorphisms in PBP5, which further decrease the affinity for β-lactam agents (184, 185). Although uncommonly reported, alterations in *A. baumannii* PBPs can also contribute to carbapenem resistance (186).

Another important example in which AMR arises in ESKAPE pathogens through modification of enzyme targets is fluoroquinolone resistance. Fluoroquinolones, such as ciprofloxacin and norfloxacin, represent some of the most widely prescribed antimicrobial agents worldwide. These are active against most ESKAPE organisms and target the DNA gyrase and topoisomerase IV enzymes, necessary for bacterial DNA repair and replication. Each of these heterotetrameric topoisomerases consists of two pairs of subunits (A and B) encoded by the *gyrA* and *gyrB* genes, respectively (or the *parC* and *parE* topoisomerase IV homologues, respectively) (187). Fluoroquinolone resistance most commonly occurs through spontaneous *gyrA* and *parC* mutations that give rise to amino acid changes clustered in the 5′ quinolone-binding region of the enzyme (188–190), though there is some evidence to suggest that B-subunit alterations also contribute to reduced susceptibility (191, 192). The level of resistance achieved by single-target mutations is dependent on both the specific agent and the bacterial species (187), while the accumulation of multiple mutations across both target enzymes often leads to the evolution of a high-level fluoroquinolone resistance phenotype (193).

Plasmid-mediated quinolone resistance (PMQR) conferred by Qnr-family proteins represents another fluoroquinolone resistance mechanism in *K. pneumoniae* and *Enterobacter* spp. (194, 195). *qnr*-encoded proteins (e.g., QnrA, QnrB, QnrS) bind directly to the DNA gyrase antibiotic target, thereby providing low-level fluoroquinolone resistance. PMQR is common among ESBL-producing organisms and can augment fluoroquinolone resistance levels arising through other mechanisms (194, 195).

Ribosomal target site alterations. A major mechanism of resistance to macrolide-lincosamide-streptogramin B (MLS_B) antibiotics in *S. aureus* and *Enterococcus* spp. is mediated by the *erm*-encoded rRNA methyltransferases. These enzymes mono- or dimethylate the A2058 residue within the 23S rRNA of the bacterial 50S ribosomal subunit, thus impairing MLS_B target binding (196, 197). Expression of *erm* can be either constitutive or inducible. Constitutively expressing strains display cross-resistance to all MLS_B agents. In contrast, inducibly resistant strains show resistance to 14- and 15-member inducer macrolides (e.g., erythromycin, clarithromycin, and azithromycin) but remain susceptible to lincosamides and streptogramin. There are 42 currently described classes of *erm* genes, many of which are located on mobile genetic elements (MGEs). *erm*(A) resides on transposon Tn*554* as part of the SCC*mec* II cassette found predominantly in HA-MRSA strains. *erm*(C) is primarily associated with plasmid-mediated resistance in methicillin-susceptible *S. aureus*, whereas *erm*(B) is more commonly found in enterococci (198, 199).

ESKAPE organism resistance to linezolid and aminoglycosides is also mediated at the ribosomal level. Indeed, linezolid resistance in both *S. aureus* and *Enterococcus* spp. can arise through mutations in genes encoding 23S rRNA and/or 50S ribosomal subunit proteins or via Cfr-mediated methylation of 23S rRNA at residue A2503 (200). The *cfr* gene is transferable within MGEs, often in association with other AMR determinants (e.g., *erm*) (201, 202), and has been detected in staphylococcal strains possessing other linezolid resistance mechanisms (203). The enzymatic methylation of 16S rRNA conferring high-level aminoglycoside resistance (to all aminoglycosides, including plazomicin [described below]) has also recently emerged as an important acquired AMR mechanism in the Gram-negative ESKAPE pathogens (204, 205). To date, 10 different classes of 16S rRNA methyltransferases have been documented worldwide (e.g., ArnA, RmfA to RmfH, and NmpA). Concerningly, these enzymes are often located on plasmids that harbor the genes for other MDR determinants (e.g., $bla_{\text{OXA-23}}$ and bla_{NDM}), thus further reducing the available treatment options (205).

Cell wall precursor alterations. One of the most important AMR mechanisms that has emerged in Gram-positive ESKAPE organisms in recent decades has been the development of glycopeptide resistance. In susceptible Gram-positive organisms, bacterial cell wall biosynthesis is inhibited by glycopeptides that target outer cell wall D-Ala–D-Ala peptidoglycan precursor residues. Glycopeptide resistance in enterococci involves the acquisition of *van* gene clusters which coordinate (i) the synthesis of modified peptidoglycan precursors that exhibit subdued glycopeptide binding (i.e., the natural D-Ala–D-Ala termini are replaced with either D-Ala-D-lactate or D-Ala–D-serine) and (ii) the production of D,D-carboxypeptidases that eliminate residual natural D-Ala–D-Ala precursors from the host cell (184, 206). To date, nine distinct *van* gene clusters have been classified, with the majority of human VRE infections being attributed to *E. faecium* and *E. faecalis* isolates carrying *vanA* and *vanB* gene clusters. *vanA*-mediated resistance occurs most frequently and is characterized by high-level resistance to both vancomycin and teicoplanin (206). The *vanA* gene cluster is typically associated with Tn*1546* and related transposons, which can be localized on both plasmids and chromosomal DNA (207). In contrast, the *vanB* gene cluster confers resistance to only vancomycin and is most often carried by Tn*1547*/Tn*5382* transposons that localize to the chromosome (208, 209).

Since 2002, sporadic cases of vancomycin-resistant *S. aureus* (termed VRSA) infection have also been reported. This form of vancomycin resistance (MIC, $\geq$16 μg/ml) is conferred by the *vanA* gene cluster on Tn*1546*, which is acquired via conjugative transfer of enterococcal plasmids (210, 211). In such instances, vancomycin resistance is maintained either by retention of the donor enterococcal plasmid within the *S. aureus* recipient or through transposition of the incoming Tn*1546* element onto an endogenous staphylococcal plasmid. Most cases of VRSA infection have been observed among patients with prior/current VRE infections, though the frequency of such detections is low, with less than 20 cases being reported across North America, South America, and Europe to date (212–215). This most likely reflects several factors, including plasmid instability, the relatively low prevalence of donor *Enterococcus* strains containing compatible plasmids carrying *vanA*, robust *S. aureus* restriction modification systems which restrict unmodified DNA from entering the cell, as well as VanA-associated fitness costs (216–219).

A much more commonly encountered issue is the detection of *S. aureus* isolates that exhibit intermediate resistance to vancomycin (i.e., MICs, 4 to 8 μg/ml; termed vancomycin-intermediate *S. aureus* [VISA] strains). This form of AMR typically emerges through prolonged exposure to vancomycin, giving rise to an initial heterogeneous VISA (hVISA) phenotype, in which a small subpopulation of cells demonstrates MICs of $\geq$4 μg/ml (220). The precise mechanisms underlying the hVISA/VISA phenotypes are incompletely understood, though various studies indicate the role of genetic modifications to regulatory genes and global epigenetic changes which lead to cell wall thickening, decreased peptidoglycan cross-linking, and autolytic activity, as well as an excess of D-Ala–D-Ala residues (198, 221–225). As opposed to person-to-person trans-

mission, the vast majority of hVISA and VISA infections arise via *in vivo* evolution within individual patients and typically involve pandemic HA-MRSA lineages (e.g., ST239 and ST5). However, it should be noted that CA-MRSA clones, including the USA300 clone, can also exhibit this resistance phenotype (146, 226).

Resistance to daptomycin, an agent that has activity against Gram-positive bacteria and that is related to host cationic antimicrobial peptides (AMPs), has also been observed in both *S. aureus* and enterococci in recent years. The precise mechanisms of resistance are yet to be fully elucidated, but it has been postulated that alterations in cell surface charge, phospholipid composition/metabolism, and membrane stress responses are involved (227). Recent studies also highlight the emergence of acquired polymyxin (another cationic AMP) resistance in *K. pneumoniae*, *A. baumannii*, and *P. aeruginosa* arising from remodeling of outer membrane (OM) lipopolysaccharide (LPS) lipid A structures. These modifications contribute to reduce the net negative charge of the LPS, thus reducing its polymyxin binding efficiency. In *K. pneumoniae*, loss-of-function mutations of the *mgrB* gene (a negative feedback regulator of the PhoPQ TCRS), mutations driving the expression of the PhoPQ, PmrAB, and CrrAB TCRS, as well as the acquisition of the plasmid-mediated *mcr* gene all give rise to resistance-associated lipid A modifications (e.g., addition of 4-amino-4-deoxy-L-arabinose [Ara4N], phosphoethanolamine [PEtN], and 2-hydroxymyristate through increased expression of the *pmrHFIJKLM* operon, *pmrC*, and *lpxO*, respectively) (135, 228–230). Of these, *mgrB* inactivation has been reported the most frequently and, interestingly, also gives rise to other modifications that collectively promote virulence and that attenuate early host defense responses (228). The primary mechanisms of polymyxin resistance in *A. baumannii* comprise mutations in the PmrAB TCRS leading to PEtN synthesis and the loss of LPS through inactivation of the *lpxA*, *lpxC*, and *lpxD* lipid A biosynthesis genes (229). Polymyxin resistance in *P. aeruginosa* is conveyed by five TCRS, including PmrAB, PhoPQ, ParRS, ColRS, and CpsRS, most frequently resulting in the constitutive expression of *pmrHFIJKLM* and the addition of Ara4N (229).

Reduced Antibiotic Penetration and Accumulation

Porins. Mutations leading to the downregulation, balance, function, and/or loss of the outer membrane protein channels (porins) also represent important mediators of AMR among Gram-negative ESKAPE pathogens. Hydrophilic agents, such as the β-lactams (including carbapenems) and some fluoroquinolones which rely on porins to penetrate the outer membrane barrier, are particularly affected. Moreover, these mutations can arise during treatment (231, 232) and, importantly, enhance the influence of other resistance mechanisms, such as efflux pumps and degradative enzymes (198). For example, the loss or modification of the *P. aeruginosa* OprD porin is linked to reduced carbapenem susceptibility (233). Likewise, the loss or inactivation of CarO in *A. baumannii* is associated with imipenem resistance (234). During antibiotic therapy, it is also recognized that *K. pneumoniae* and some *Enterobacter* spp. can sequentially alter the balance of different porins. In some cases, the sorbitol-sensitive Omp35 porin is replaced with Omp36, which has a smaller channel size. These Omp35-deficient, Omp36-producing strains typically exhibit intermediate carbapenem susceptibility profiles, while those lacking both porins show carbapenem resistance (233, 235, 236). Overexpression of the LamB porin in association with strains showing porin deficiency or reduced porin expression can also contribute to reduce β-lactam susceptibility (235, 236). Mutations leading to conformational changes in the eyelet region of the *E. aerogenes* Omp36 lumen with reduced β-lactam permeability have also been reported (235).

Efflux pumps. The expression of bacterial efflux pumps, which actively extrude drugs out of the cell, also greatly contributes to AMR. Genes encoding efflux pumps can be located on the chromosome or within MGEs. To date, six major families of efflux pumps have been characterized, comprising the (i) resistance-nodulation-division (RND), major facilitator superfamily (MFS), multidrug and toxic compound extrusion (MATE), small multidrug resistance (SMR), ATP-binding cassette (ABC), and proteobac-

terial antimicrobial compound efflux (PACE) families (234, 237). All six families are represented within the ESKAPE group, with individual exporters varying in terms of their substrate specificity. Of note, RND-type efflux pump-mediated resistance is of particular concern with respect to AMR among Gram-negative bacteria. For example, the chromosomally encoded MexAB-OprM efflux system in *P. aeruginosa* exhibits broad substrate specificity and when overexpressed confers fluoroquinolone, aminoglycoside, and β-lactam resistance. Likewise, the overproduction of AcrAB-TolC is characteristic of multidrug-resistant *K. pneumoniae* and *Enterobacter* strains. The *A. baumannii* AdeABC, AdeFGH, and AdeIJK RND-type efflux pumps are also associated with broad-range AMR (234, 238–240). More recently, the chromosomally encoded OqxAB efflux pump, which contributes to reduced quinolone and chloramphenicol susceptibility, has been identified in *K. pneumoniae* (195, 241). OqxAB homologues have also been observed in some *Enterobacter* spp., though, aside from tigecycline (242), these elements are not thought to contribute to clinically relevant drug resistance under *in vitro* conditions (241).

Other Mechanisms and Survival Strategies

Biofilms. In addition to the aforementioned classical AMR mechanisms, it is now also recognized that growth within biofilms can further impede antimicrobial activity. Biofilms are structured, surface-attached microbial communities encased in an extracellular matrix (ECM) which demonstrate a markedly higher tolerance to antimicrobial agents than nonadherent planktonic cells (118, 243, 244). Most notably, biofilms play a prominent role in chronic infections, such as those involving *P. aeruginosa* in the airways of patients with cystic fibrosis and indwelling medical device infections caused by *S. aureus* and *A. baumannii* (118, 245). The reduced antibiotic susceptibility exhibited by biofilm-embedded cells is thought to be multifactorial and can vary according to the species and genetic makeup of the organism(s), the nature of the antimicrobial agent, the developmental stage of the biofilm, and the environmental conditions (118, 246). More recently, it has been recognized that bacterial aggregation can also give rise to reduced antibiotic susceptibility independent of growth on a surface. Some of the factors attributable to the increased antibiotic recalcitrance of biofilms include (i) restriction of antibiotic penetration by the ECM, (ii) the secretion of antibiotic-modifying enzymes, extracellular DNA, and other macromolecules into the ECM, (iii) the accumulation of filamentous bacteriophages which promote the formation of liquid crystalline structures, (iv) differential metabolic activity, (v) the emergence of persister cells (see below), (vi) biofilm-associated upregulation of bacterial efflux, (vii) enhanced horizontal gene transfer and mutation frequency, and (viii) interactions between different bacterial species within mixed-species biofilms (246–249). A classic example of the last two factors was reported by Weigel and colleagues, who observed that a plasmid carrying a *vanA* vancomycin resistance gene in a VRSA strain arose from a VRE strain present within the same multispecies biofilm (250).

Antibiotic tolerance and persistence. Aside from antibiotic resistance, which is characterized by the presence of inheritable resistance-encoding genes or mutations that give rise to an increased MIC, there is increasing evidence that some ESKAPE pathogens are able to overcome treatment through antibiotic tolerance. Antibiotic tolerance enables an entire bacterial population to withstand transient exposures to high doses of bactericidal antibiotics (e.g., β-lactams and quinolones) without a change in the MIC. This occurs in the absence of any genetic resistance factor and is typically associated with an arrested (or dormant) growth state which is reversed upon removal of the antibiotic exposure (251, 252). Antibiotic tolerance can arise from genetic mutations but may also be conferred by stressful external conditions, including nutrient limitation, host factors, temperature, and antibiotic treatment (251). Concerningly, recent studies of MRSA infections in humans also indicate that the evolution of antibiotic tolerance can facilitate the emergence of mutational resistance (253). Quantitative assessment of antibiotic tolerance can be reliably achieved by the minimum duration for killing of 99% of a bacterial population (MDK_{99}), which evaluates the time

that it takes to eradicate 99% of a bacterial population at antibiotic concentrations that substantially exceed the MIC (252, 254). In a related phenomenon, antibiotic tolerance can also be observed among subpopulations of bacterial cells termed "persisters." Antibiotic persistence is frequently associated with biofilm infections and is characterized by a biphasic $MDK_{99,99}$ killing curve which displays the emergence of a clonal persister subpopulation over time. Persister bacterial cells do not respond to antibiotics, and although they fail to divide in the presence of bactericidal antimicrobials, they are not killed. Upon treatment cessation, these persistent subpopulations are then able to resume growth, thus contributing to relapsing or chronic infection (252, 255, 256).

Intracellular survival. Another possible factor contributing to AMR among ESKAPE pathogens is the observation that some species can be internalized and then survive for extended periods within host cells. Indeed, recent *in vitro* studies show that upon engulfment by alveolar macrophages, both *K. pneumoniae* and *E. faecalis* are able to survive and persist within unique intracellular vacuolar compartments (257, 258). Likewise, there is accumulating evidence that *S. aureus* has the capacity to adhere to, enter, and survive within both professional and nonprofessional phagocytes, including macrophages; epithelial, endothelial, and mammary cells; keratinocytes; osteoblasts; and fibroblasts (259, 260). In such instances, it is thus plausible that the microbes are able to not only evade many of the hosts' immune defenses but also remain insulated from the activity of cell-impermeant antibiotics, thus providing a reservoir for disseminated and/or latent infection. Such a scenario was recently illustrated by Lehar and colleagues, who showed that, compared to extracellular planktonic bacteria, intracellular MRSA isolates exhibit a 100-fold increase in the vancomycin MIC, as well as an enhanced propensity for systemic dissemination in an antibiotic-treated mouse infection model (261).

MOBILE GENETIC ELEMENTS CONFERRING ANTIMICROBIAL RESISTANCE

While bacteria can be intrinsically resistant to certain antibiotics, they may also accumulate AMR genes on MGEs. MGEs are segments of DNA that are capable of capturing genes and mediating their movement within the genome (intracellular mobility) or between different cells (intercellular mobility). In this fashion, MGEs are responsible for much of the observed phenotypic variability in AMR both within and between bacterial species. The association of AMR and MGEs has been extensively reviewed recently (262). Thus, here we summarize those elements most relevant to the ESKAPE pathogens, mainly, plasmids, insertion sequences (IS) and transposons (Tn), integrative and conjugative elements (ICE), and other genomic islands (GI) (Table 2).

Insertion Sequences and Transposons

IS are small elements (typically, $<$3 kb) that are capable of self-transposition. The canonical IS unit is composed of one or two genes required for mobility, flanked by terminal inverted repeats (IRs) (263, 264). IS are capable of mobilizing neighboring genes (cargo genes) in structures called composite/compound transposons, where two copies of an identical or related IS mobilize the region between them (265, 266). Classic examples of composite transposons associated with the carriage of AMR genes include Tn*9* (IS*1*; chloramphenicol resistance), Tn*10* (IS*10*; tetracycline resistance), Tn*5* (IS*50*; aminoglycoside and bleomycin resistance) (262, 265), and, more recently, Tn*6330* (IS*Apl1*), which is responsible for mobilizing the colistin resistance gene *mcr-1* (135, 262, 267). More complex unit transposons can also be found in both Gram-negative and Gram-positive bacteria. Unit transposons are large IS-like elements flanked by terminal IRs with genes (for example, *tnpA* [transposase] and *tnpR* [resolvase] in Tn*3*) that facilitate replicative transposition. In the ESKAPE pathogens, AMR genes are frequently associated with the Tn*3* family (Tn*1*, Tn*2*, and Tn*3*) (207, 268, 269), Tn*7*-like unit transposons (270, 271), and Tn*552*-like elements (272) (Table 2).

In some cases, single IS elements can also mobilize neighboring genes. IS*Ecp1* is commonly associated with the β-lactamase genes $bla_{CTX\text{-}M}$ (e.g., $bla_{CTX\text{-}M\text{-}1}$, $bla_{CTX\text{-}M\text{-}9}$, $bla_{CTX\text{-}M\text{-}15}$), $bla_{CMY\text{-}2}$, and bla_{ACC} and, more recently, with the $bla_{OXA\text{-}181}$ carbapen-

TABLE 2 MGEs associated with carriage of antimicrobial resistance genes in ESKAPE pathogens[a]

Species	Resistance(s)	MGE type	MGE	Key characteristics	Reference(s)
Vancomycin-resistant *Enterococcus*	Vancomycin	Tn	Tn*1546*	A composite transposon (IS*16*) responsible for dissemination of vancomycin resistance in both enterococci and staphylococci	560, 561
	Vancomycin	ICE	Tn*1549*-like	*vanB* is typically associated with Tn*1549*-like and Tn*5382*-like transposons, which are closely related; significant role in the global spread of vancomycin resistance	334, 335
	Chloramphenicol, aminoglycosides, tetracycline, kanamycin, MLS, chloramphenicol, streptomycin, vancomycin	Plasmid	Inc18-type (e.g., pR23 and pEF-01), RepA_N plasmids (e.g., pRUM-like)	Conjugative; broad host range, allowing for transfer into a variety of bacterial species; responsible for introducing vancomycin resistance into MRSA	262, 562, 563, 564, 565
Methicillin-resistant *S. aureus*	β-Lactams	Tn	Tn*552*-like elements	Tn*552* is a complex unit transposon responsible for mobilization and dissemination of β-lactam resistance in staphylococci; associated with a pSK1-like and pSK41-like plasmid	272
	Vancomycin	Tn	Tn*1546*	A composite transposon (IS*16*) responsible for dissemination of vancomycin resistance in both enterococci and staphylococci	
	Tetracycline, chloramphenicol, erythromycin	Plasmid	Small (1- to 10-kb) multicopy plasmids	Typically carries a single resistance gene	314–316
	β-Lactams, aminoglycosides, trimethoprim, antiseptics	Plasmid	pSK1-like plasmids	Associated with carriage of the Tn*552*-like β-lactam resistance transposons	317
	Aminoglycosides, β-lactams, vancomycin	Plasmid	pSK41-like plasmids (e.g., pSK41, pGO1, and pLW103)	Conjugative; associated with carriage of the Tn*552*-like β-lactam resistance transposons; associated with carriage of *vanA* on the Tn*1546* glycopeptide resistance transposon	318–321
	Methicillin, penicillin, β-lactams	GI	SCC*mec* element	SCC*mec* has a limited distribution and is restricted to 11 major clonal lineages of *S. aureus* from 5 clonal complexes	336–338
	Methicillin, glycopeptides	IS	IS*1182*, IS*256*	Insertional deactivation, resulting in increased resistance	566, 567
Enterobacterales (*K. pneumoniae* and *Enterobacter* spp.)	Multidrug: β-lactams, carbapenems, trimethoprim, chloramphenicol, fluoroquinolones	IS	IS*Ecp1*, IS*CR*	Typically encodes a promiscuous transposase which can mobilize adjacent genes when they fail to identify terminal repeat sequences; IS*Ecp1* elements are commonly associated with mobilization of β-lactamase genes; IS*CR* elements are commonly associated with complex class 1 integrons	273–276, 280, 568, 569
	Carbapenems, colistin	IS	Various IS, including IS*Ecp1*	Insertional deactivation resulting in increased resistance	276, 281, 282, 570
	Multidrug: β-lactams, aminoglycosides, trimethoprim, antiseptics, carbapenems, colistin, cephalosporins	Plasmid	IncF-type, IncI, IncH (HiI1 and HI2), IncL, IncC, IncN, IncH, IncX3	Typically, low-copy-number plasmids; broad and narrow host ranges; can act as vehicles for carriage of other mobile resistance elements, e.g., transposons and integrons	293, 294, 571
A. baumannii	Multidrug: β-lactams, aminoglycosides chloramphenicol, tetracycline, sulfonamide	Tn	AbaR, AbGR11	Tn7-like unit transposons	270, 271
	Carbapenems	Tn	Tn*2006*	The Tn*2006* composite transposon (IS*Ab1*) is responsible for mobilization of the bla_{OXA-23} carbapenemase	
	Carbapenems	IS	IS*Ab825*, IS*Ab125*	Insertional deactivation of the outer membrane protein *carO* results in elevated carbapenem MICs	223
	Carbapenems	IS	IS*Aba1*	IS insertion upstream of bla_{OXA-53} drives expression of the gene; IS-mediated constitutive expression of bla_{OXA-53} confers high-level carbapenem resistance	283
	Gentamicin, tobramycin	Plasmid	pRAY-like plasmids	Small (6- to 10-kb), widely distributed plasmids	303, 304
	Multidrug: carbapenems and kanamycin	Plasmid	RepAci6-like plasmids (e.g., pAB-G7-2 and pACICU2), pNDM-BJ01-like plasmids	Kanamycin resistance is associated with carriage of the Tn*aphA6* transposon; carbapenem resistance is associated with carriage of the Tn*2006* transposon; pNDM-BJ01-like plasmids from *A. lwoffii* carry the bla_{NDM-1} carbapenemase genes	302, 305, 306
P. aeruginosa	Carbapenems, β-lactams	IS	IS*21*, IS*PA26*	Insertional deactivation, resulting in increased resistance	572, 573
	Carbapenems	Plasmid	IncP-2 plasmids	Carbapenemases associated with class 1 integrons carried on IncP-2-type plasmids	309–311
	Carbapenems, aminoglycosides	ICE	*P. aeruginosa* pathogenicity island (e.g., PAPI-1, PAGI-2/PAGI-3-like)	Multidrug resistance is associated with carriage of antimicrobial resistance genes on Tn*6162* and Tn*6163* elements in a genomic island	333

[a]Abbreviations: MGEs, mobile genetic elements; ICE, integrative and conjugative elements; Tn, transposon; IS, insertion sequence; GI, genomic island; MLS, macrolide lincosamide sulfonamides; SCC*mec*, staphylococcal cassette chromosome *mec*.

emase gene (273–276). IS*Ecp1* elements encode promiscuous transposases that can recognize a variety of different sequences as right IRs (IR_r), thereby allowing them to capture adjacent genes. Related IS (IS*1247*, IS*Kpn23*, and IS*Enca1*) have also been associated with the mobilization of adjacent resistance genes in a manner similar to that for IS*Ecp1* (277, 278). Recently, it has been demonstrated that IS*26* can produce a circular intermediate consisting of a single copy of IS*26* and a DNA segment immediately adjacent to it. This structure, termed a translocatable unit (TU), can then move by a replicative mechanism (279). IS*CR* elements also form circular intermediates. They move and can capture adjacent genes by rolling-circle replication (280).

IS elements can also impact the evolution of AMR in the host by the transpositional deactivation of genes and by modulating the expression of adjacent genes through the delivery of promoter or terminator sequences (reviewed in reference 264). The insertional deactivation of uptake systems is a common mechanism by which IS elements can affect antibiotic susceptibilities. For example, IS-mediated deactivation of the *ompK36* porin in *K. pneumoniae* results in elevated carbapenem MICs (281). Similarly, insertional inactivation of the *mgrB* regulatory gene in *K. pneumoniae* drives the overexpression of the *pmrHFIJKLM* operon, conferring colistin resistance (276, 282).

Many IS carry strong promoter sequences, and their insertion upstream of chromosomal genes can drive the expression of that gene and influence AMR. This mechanism is clearly evident in *A. baumannii*, where insertion of an IS*Aba1* element upstream of the bla_{OXA-51} gene confers carbapenem resistance (283). Similar mechanisms of IS-mediated constitutive expression of resistance genes have been observed in *K. pneumoniae* and *P. aeruginosa* (284, 285). Alternatively, an IS may provide only the −35 region promoter component, which, together with a −10 region donated by an adjacent gene, forms a hybrid promoter to drive the expression of neighboring genes. Hybrid IS promoters have been identified in at least 17 different bacterial species (286), including *A. baumannii*, *K. pneumoniae*, and *P. aeruginosa* (283, 287, 288).

Plasmids

Plasmids are an important vehicle for gene transfer in both Gram-negative and Gram-positive bacteria (289). Typically, plasmids are circular, double-stranded, and self-replicating DNA molecules that are readily vertically inherited in a growing population (290). While it is clear that the MGEs described thus far (IS elements, transposons, etc.) are primarily responsible for mobilizing resistance genes, the dissemination of these genes is mainly attributed to conjugative plasmids. Plasmids are rich in IS and other MGEs carrying AMR genes and facilitate the intra- and interspecies horizontal transfer of these elements (135, 291–293).

MDR *Enterobacterales* (*K. pneumoniae* and *Enterobacter* species) carry plasmids from a wide variety of different incompatibility (Inc) groups (294) (Table 2), but those from Inc group types F (multiple F-type replicons can be found together in multireplicon plasmids), I, H (HI1 and HI2), L, C, and N are most frequently associated with multidrug resistance (293, 294). Of particular concern among the *Enterobacterales* is the role that these plasmids continue to play in the emergence and dissemination of ESBLs, particularly those of the bla_{CTX-M} type (19, 295, 296); AmpC-type cephalosporinases (bla_{CMY-2} and bla_{DHA-1}) (297–299); carbapenemase-encoding genes (bla_{VIM}, bla_{KPC}, bla_{NDM}, and bla_{OXA-48}) (161, 300, 301); and plasmid-mediated colistin resistance (*mcr*) (229). Comparatively little is known about plasmids from *A. baumannii* compared to what is known about plasmids from the *Enterobacterales*. However, in 2011, a Europe-wide study of clinical *A. baumannii* isolates found that resistance plasmids were mainly associated with carriage of the bla_{OXA} (bla_{OXA-23}, bla_{OXA-58}-like, and bla_{OXA-40}) carbapenemase genes (302), kanamycin and amikacin resistance, and gentamicin and tobramycin resistance (303–306). Additionally, plasmids related to pNDM-BJ01 from *Acinetobacter lwoffii* carry the globally distributed bla_{NDM-1} carbapenemase gene (307).

In *P. aeruginosa*, resistance genes are typically found on chromosomal resistance islands rather than plasmids. However, *P. aeruginosa* may carry large (~300- to 500-kb), transferable IncP-2 plasmids (308) associated with the carriage of carbapenemase

genes, specifically, bla_{IMP} (bla_{IMP-9} and bla_{IMP-45}) (309, 310) and bla_{VIM} (bla_{VIM-2}) (311) carbapenemases, on class 1 integrons.

AMR plasmids are frequently found in clinical staphylococcal isolates (312, 313). These include small (1- to 10-kb) multicopy plasmids typically encoding a single resistance gene (314–316) and larger (>15-kb) multiresistance plasmids, such as the prototype pSK1 family of multiresistance plasmids (317) (Table 2). A single family of larger (>30-kb) conjugative multiresistance plasmids, including pSK41, pGO1, and pLW1043 (318, 319), can also be found in clinical strains of staphylococci and are credited with the emergence of aminoglycoside, β-lactam, and vancomycin resistance in *S. aureus* populations (267, 320–326).

In the enterococci, AMR is largely encoded on Inc18 and RepA_N plasmids (262). Both Inc18 and RepA_N plasmids have a broad host range, allowing for their transfer into a variety of bacterial species, and are responsible for introducing vancomycin resistance into MRSA (218).

Genomic Islands and Integrative Conjugative Elements

Genomic islands (GIs) are discrete genomic loci that have been acquired through horizontal gene transfer (HGT) (327). Many different types of GIs exist (328–330), and describing them all is beyond the scope of this review. Here, we only briefly describe the integrative conjugative elements (ICE) and the SCC*mec* element.

ICE are conjugative elements that integrate into the host chromosome and that are passively replicated along with the host genome during cell division (331, 332). In *P. aeruginosa* ICE, specifically, the *P. aeruginosa* pathogenicity/genomic island-type ICE (PAPI-1, PAGI-2/PAGI-3-like), are the most important for acquired AMR genes (333) (Table 2). ICE are also important carriers of AMR genes in enterococci (334). Of particular note is the *vanB*-associated Tn*1549*, which has played a significant role in the global spread of vancomycin resistance (335).

In staphylococci, SCC*mec* is a genomic island carried in the chromosome of MRSA isolates (336). The SCC*mec* element carries the *mecA* gene, encoding a low-affinity penicillin-binding protein, PBP2a, that confers resistance to methicillin, penicillin, and other β-lactam antibiotics. Horizontal transfer of the SCC*mec* element facilitates the movement of the *mecA* gene and methicillin resistance among the staphylococci. However, despite this capacity for mobility, SCC*mec* has a limited distribution and appears to be restricted to 11 major clonal lineages of *S. aureus* from 5 clonal complexes (337, 338).

Contribution of Horizontal Gene Transfer to the Spread of Mobile Genetic Elements

HGT facilitates the movement of MGEs between bacteria and is considered the primary mechanism for the emergence and spread of AMR among pathogenic bacteria (339). Of the three primary mechanisms of HGT, conjugation, transduction, and transformation, the dissemination of MGEs that carry AMR genes is mostly by conjugation. Conjugative plasmids and ICE facilitate the rapid dissemination of AMR genes among bacteria of diverse origins (19, 340–343). Additionally, conjugative plasmids can also mobilize nonconjugative plasmids, including those with broad host ranges (344). Although it has been less well studied, there is currently indirect evidence that transduction can contribute to the spread of AMR genes between members of the same bacterial species. Bacteriophages isolated from hospital-acquired MRSA, *Pseudomonas*, and *Acinetobacter* strains have been shown to transduce AMR genes to recipient strains under laboratory conditions (345–348). There is currently no substantial direct evidence to suggest that transformation contributes to the spread of AMR among the ESKAPE pathogens. However, *Acinetobacter*, *Pseudomonas*, and *Staphylococcus* strains are all capable of DNA uptake and natural transformation (349). and the *Enterobacterales* are predicted to be naturally competent (350, 351). Additionally, natural transformation can facilitate the transfer of transposons and integrons between

bacterial species (352). Consequently, the potential role that transformation plays in the spread of AMR genes cannot be overlooked.

Coselection of Antimicrobial Resistance with Detergents and Biocides

Due to the fitness cost imposed by plasmid carriage, plasmids tend to be lost from bacterial populations under conditions in which they provide no selective advantage (353, 354). However, antibiotic stewardship programs and the restricted use of key antibiotics have not been successful in controlling the emergence and spread of AMR. One mechanism which promotes the persistence of AMR genes in bacterial populations is coselection with genes that confer resistance to metals and antimicrobial biocides (355–358). Coselection can result when antibiotic resistance and biocide resistance share a mechanism, for example, modification of the cell wall/membrane preventing entry into the cell or upregulation of efflux pumps to remove unwanted compounds from the cell (359–361). Coselection can also occur when the bacteria carry genes that promote resistance or decreased susceptibility to both types of antimicrobial compounds. The colocation of AMR and biocide resistance genes on plasmids and other MGEs (296–298) is particularly problematic, as exposure to the latter can facilitate the spread of AMR genes by HGT. In 2015, a large-scale study on coselection potential that examined 2,522 bacterial genomes and 4,582 plasmids found that among plasmids carrying genes for AMR and biocide resistance, 57% were conjugative, whereas only 18% of plasmids carrying either AMR or biocide resistance genes were conjugative (357).

Although many different mechanisms of coselection exist, of particular concern in clinical environments is the *qac* family of biocide resistance genes, specifically, *qacEΔ1*, a truncated version of the *qacE* gene associated with low-level resistance to quaternary ammonium compounds (QACs) and other biocides (e.g., biguanides, diamidines, and xanthenes) (362, 363). *qacEΔ1* is frequently found as a component of AMR gene cassettes on class 1 integrons, which are more prevalent in bacteria exposed to detergent and other biocides than in bacteria not exposed to these compounds (362, 364, 365). Biocides, such as quaternary ammonium compounds, are heavily used as cleaning agents in hospitals. Consequently, intertwined AMR and QAC resistance mechanisms can represent a long-term selection pressure for the maintenance and spread of AMR in clinical environments (366–369).

Antibiotic stewardship programs are designed to limit the use of key antibiotics to prevent the spread of AMR. However, in order for these programs to be successful, it is also important to consider measures which prevent the accumulation of biocides and other antimicrobial toxicants that can promote coselection.

THERAPEUTIC ADVANCES AGAINST ESKAPE PATHOGENS

Antimicrobial drug discovery is highly challenging, and the current rise in AMR is eroding the efficacy of available antibiotics (370). Since the early 1960s, only 4 new classes of antibiotics have been introduced: quinolones, lincosamides, oxazolidinones, and cyclic lipopeptides. The global financial antibiotic market, estimated at $30 billion, is still dominated by classes of antibiotics discovered over half a century ago (371). Frequently, "novel antibiotics" is a term often used for successive compounds derived from established antibiotic classes (371). The reserved use of such novel drugs as last-resort measures has constrained the profit margins of the pharmaceutical industry, leading organizations to withdraw their research effort from antimicrobial drug discovery (370). Economic barriers surrounding the R&D of antimicrobial drug design are largely instigated by the large operational cost of clinical trials, estimated to be upwards of $130 million, with postapproval follow-on trials amounting to an added $146 million (372). Antimicrobial drug candidates targeting more than one clinical indication require significantly more financial support, further exacerbating the financial hurdle (373). The financial justification for the development and commercialization of new therapies often fails to outweigh the value to public health and foregoing investment (374). Limited by stewardship practices, the net value of an R&D project has

been estimated to be €31.5 million, which in turn considerably weakens the economic incentive (375). Today, the majority of pharmaceutical companies which do undertake R&D have few antimicrobial products on the market aimed at the WHO's priority pathogen list (376). Due to the absence of revenue from sales, these companies are largely dependent on external partnering funding sources, such as the U.S. Biomedical Advanced Research and Development Authority (BARDA), Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X), the Wellcome Trust, the National Institute of Allergy and Infectious Diseases (NIAID), and the Innovative Medicines Initiative (IMI; a joint undertaking between the European Union and the European Pharmaceutical Industry), initiatives funded solely and/or in partnership (376–379). Identifying antibiotic-related health priorities, defining appropriate stewardship practices, and developing new sustainable economic models to stimulate antibiotic innovation are key intersecting themes currently requiring a cooperative restructure. Funded by IMI, Driving Reinvestment in Research and Development and Responsible Antibiotic Use (DRIVE-AB) is a pioneering project composed of 15 public and 7 private partners from 12 countries aiming to tackle this issue (380). Through the use of surveillance systems data, antibiotic prescription databases, and published literature, DRIVE-AB aims to develop models which transform the way in which policy makers stimulate and financially incentivize antibiotic innovation (380, 381). Despite collaborative projects like these, the majority of new R&D programs aimed at tackling AMR are currently funded by public and nonprofit partnerships (374). This approach often neglects obstacles, such as licensing, affordability, and stewardship, which affect access to new antimicrobials in low- and middle-income countries. Even though antibiotic drug discovery has reduced and investment from the pharmaceutical industry has receded, promising antimicrobial strategies are still being developed (Table 3) (371, 382–389).

Recently Approved Drugs

In 2018, three new antibiotics with the potential to treat serious bacterial infections successfully emerged through clinical trials with either U.S. FDA or E.U. EMA approval (390) (Table 3). All three drug compounds target the 30S subunit of the bacterial ribosome. The aminoglycoside class analog plazomicin (Zemdri; Achaogen Inc.) was approved by the U.S. FDA in June 2018 for the treatment of patients 18 years of age or older for complicated UTI including pyelonephritis. Plazomicin was not approved by the U.S. FDA for the treatment of bloodstream infections due to a lack of effectiveness (390–392). From a randomized trial involving 609 patients, once-daily treatment with plazomicin was shown to be noninferior to treatment with meropenem (treatment every 8 h) for use against complicated UTIs and acute pyelonephritis caused by *Enterobacterales*, including MDR strains (393). Plazomicin also demonstrated efficacy better than that of meropenem for eradication of aminoglycoside-resistant and ESBL-producing *Enterobacterales* (393).

Eravacycline (Xerava; Tetraphase Pharmaceuticals Inc.) is a tetracycline analog approved by the U.S. FDA in August 2018 and the E.U. EMA in September 2018 (22, 390, 394) (Table 3). Eravacycline has been developed solely for the treatment of complicated intra-abdominal infections caused by Gram-negative and Gram-positive ESKAPE pathogens, including CRE and CRAB (394). In the IGNITE4 clinical trial, eravacycline was shown to be noninferior to meropenem for the treatment of complicated intra-abdominal infections caused by ESBL-producing *Enterobacterales* (395). Furthermore, patients treated with eravacycline experienced relatively low rates (3 to 5%) of adverse events, such as nausea, vomiting, and diarrhea (395).

Omadacycline (Nuzyra; Paratek Pharmaceuticals Inc.), a tetracycline-class drug active against Gram-negative and Gram-positive ESKAPE pathogens, was approved by the U.S. FDA in October 2018 for the treatment of CA bacterial pneumonia, acute bacterial skin and skin structure infection (ABSSSI), and complicated and uncomplicated UTI (390, 396) (Table 3). In a recent clinical trial, once-daily administration through interchanging intravenous and oral administration demonstrated that omadacycline was noninferior

TABLE 3 Antimicrobial drugs in the clinical pipeline as of February 2020[a]

Drug name	Drug class	Drug target	Development stage	Company	Pathogen target	Application[b]	Information of note[b]
Plazomicin (Zemdri)	Aminoglycoside	30S subunit of bacterial ribosome	U.S. FDA approved on 26 June 2018	Achaogen Inc.	*E. coli*, *K. pneumoniae*, *Proteus mirabilis*, *E. cloacae*, and CRE	cUTI including acute pyelonephritis	Nephrotoxicity has been reported
Cefiderocol (Fetroja)	Siderophore–β-lactam (cephalosporin)	PBP	U.S. FDA approved on 14 November 2019	Shionogi & Co. Ltd.	CRE, CRAB, and CRPA	cUTI	
Imipenem + cilastatin + relebactam (Recarbrio)	β-Lactam (carbapenem) + β-lactamase inhibitor (diazabicyclooctane)	PBP, β-lactamase	U.S. FDA approved on 17 July 2019; E.U. EMA approved on 13 February 2020	Merck & Co., Inc.	CRE and CRPA	cUTI including pyelonephritis, cIAI, and HA and VA bacterial pneumonia	
Meropenem- vaborbactam (Vabomere/Vaborem)	β-Lactam (carbapenem) + β-lactamase inhibitor (cyclic boronate)	PBP, β-lactamase	U.S. FDA approved on 30 August 2017; E.U. EMA approved on 20 November 2018	Rempex Pharmaceuticals Inc. (wholly owned subsidiary of The Medicines Co.)	*E. coli*, *K. pneumoniae*, *E. cloacae* species complex, and CRE	cUTI including pyelonephritis	Anaphylactic and central nervous system reactions have been reported
Cefepime + zidebactam (WCK 5222)	β-Lactam (cephalosporin) + β-lactamase inhibitor (diazabicyclooctane)	PBP, β-lactamase	Phase I	Wockhardt Ltd.	ESKAPE pathogens, pneumococci, and streptococci	cUTI and HA and VA bacterial pneumonia	Highly broad-spectrum antimicrobial
ETX0282 + cefpodoxime + proxetil (ETX0282CPDP)	β-Lactam (cephalosporin) + β-lactamase inhibitor (diazabicyclooctane)	PBP, β-lactamase	Phase I	Entasis Therapeutics Inc.	MDR *A. baumannii* and CRAB	UTI	Designated a QIDP by U.S. FDA and awarded fast-track review
Meropenem + nacubactam OP0595/RG6080)	β-Lactam (carbapenem) + β-lactamase inhibitor (diazabicyclooctane)	PBP, β-lactamase, PBP2	Phase I	Meiji Seika Pharma Co. Ltd./Fedora Pharmaceuticals Inc. (Roche licensee)	CRE, CRPA	Bacterial infections	
Cefepime + AAI101	β-Lactam (cephalosporin) + β-lactamase inhibitor (β-lactam)	PBP, β-lactamase	Phase III	Allecra	CRE	cUTI including pyelonephritis, cIAI, and HA and VA bacterial pneumonia	Designated a QIDP by U.S. FDA and awarded fast-track review
Cefepime + taniborbactam (VNRX-5133)	β-Lactam (cephalosporin) + β-lactamase inhibitor (cyclic boronate)	PBP, β-lactamase	Phase III	VenatoRx Pharmaceuticals Inc.	MDR enteric organisms and ESBL-, KPC-, OXA-, and NDM-, VIM-producing *P. aeruginosa*	cIAI and cUTI	Designated a QIDP by U.S. FDA and awarded fast-track review
Sulbactam-durlobactam (ETX2514SUL)	β-Lactam (sulbactam) + β-lactamase inhibitor (diazabicyclooctane)	PBP, β-lactamase	Phase III	Entasis Therapeutics Inc.	CRAB	*A. baumannii* infections	
BOS-228 (LYS228)	β-Lactam (monobactam)	PBP	Phase II	Boston Pharmaceuticals (licensed from Novartis AG)	CRE	cUTI and cIAI	May be used in combination with other β-lactam antibiotics
Ceftobiprole (Zeftera)	β-Lactam (cephalosporin)	PBP	Phase III; E.U. EMA approved via decentralized procedure; Australian TGA approved for HA and CA pneumonia on 8 February 2016; Health Canada approved for HA and CA pneumonia on 12 October 2015; Health Canada approved for ABSSSI in June 2008	Basilea Pharmaceutica	*S. aureus*	ABSSSI and CA and HA bacterial pneumonia	
Tebipenem-pivoxil (SPR994/SPR859)	β-Lactam (carbapenem)	PBP	Phase III; Japanese PMDA approved on 22 April 2009	Spero Therapeutics Inc.	ESBL-producing *E. coli* and *K. pneumoniae*	CA bacterial pneumonia and complicated UTI	Oral administration for home-based care
Sulopenem/sulopenem-etzadroxil	β-Lactam (carbapenem)	PBP	Phase III	Iterum Therapeutics Ltd.	MDR Gram-negative pathogens	cUTI, uncomplicated UTI, and cIAI	Available as oral and intravenous preparations

(Continued on next page)

TABLE 3 (Continued)

Drug name	Drug class	Drug target	Development stage	Company	Pathogen target	Application[b]	Information of note[b]
Cefilavancin (TD-1792)	Glycopeptide–β-lactam (cephalosporin) hybrid	PG chain elongation, PBP	Phase III	R-Pharm/Theravance Biopharma Inc.		ABSSSI	
Delafloxacin (Baxdela/Quofenix)	Fluoroquinolone	Bacterial type II topoisomerase	U.S. FDA approved on 19 June 2017; E.U. EMA approved on 16 December 2019	Melinta Therapeutics Inc.	ESKAPE pathogens except *A. baumannii*	ABSSSI	Serious adverse reactions, including tendinitis, tendon rupture, and neuropathy
Lascufloxacin (Lasvic)	Fluoroquinolone	Bacterial type II topoisomerase	Japanese PMDA approved on 20 September 2019	Kyorin Pharmaceutical Co. Ltd.	*Klebsiella* spp, *Enterobacter* spp., MRSA, and *S. pneumoniae*	CA bacterial pneumonia	Activity against MRSA comparable to that of linezolid and vancomycin
Alalevonadifloxacin + levonadifloxacin (WCK 771/WCK 2349)	Fluoroquinolone	Bacterial type II topoisomerase	Phase III	Wockhardt Ltd.	MRSA, VRSA, and MDR pneumococci, *E. coli*, and *K. pneumoniae*	ABSSSI and HA bacterial pneumonia	Active against MSRA biofilm
OPS-2071	Quinolone	Bacterial type II topoisomerase	Phase II	Otsuka Pharmaceutical Co. Ltd.	*C. difficile*	*C. difficile* infection	
Nemonoxacin (Tiagexyn)	Quinolone	Bacterial type II topoisomerase	Phase II; approved in Taiwan, Russia, Turkey, China, and Latin America during 2016	TaiGen Biotechnology Co. Ltd.	*S. aureus*	CA bacterial pneumonia, diabetic foot infection, and ABSSSI	Designated a QIDP by U.S. FDA and awarded fast-track review
Zoliflodacin (ETX0914)	Spiropyrimidinetrione	Bacterial type II topoisomerase	Phase III	Entasis Therapeutics Inc.	*N. gonorrhoeae*	Uncomplicated *N. gonorrhoeae* infection	Designated a QIDP by U.S. FDA and awarded fast-track review
ACX-362E	DNA polymerase IIIC inhibitor	DNA polymerase IIIC	Phase 1	Acurx Pharmaceuticals LLC	*C. difficile*	*C. difficile* infections	Potential to be applied against all ESKAPE pathogens
MGB-BP-3	Distamycin	DNA minor groove binder	Phase II	MGB Biopharma Ltd.	*C. difficile*	*C. difficile*-associated diarrhea	Targets *C. difficile* in vegetative state before it sporulates
Sodium fusidate (ARV-1801)	Fusidane	Elongation factor G	Phase III; approved (for dosing regimens as an alternative to what is currently being tested in clinical trials) for ABSSSI in South Korea, Japan, Canada, the European Union, Australia, New Zealand, Thailand, India, and Taiwan	Arrevus Ltd.	MRSA	ABSSSI and prosthetic joint infections	Granted orphan drug designation by U.S. FDA
Omadacycline (Nuzyra)	Tetracycline	30S subunit of bacterial ribosome	U.S. FDA approved on 2 October 2018; E.U. EMA considered granting marketing authorization	Paratek Pharmaceuticals Inc.	ESKAPE pathogens	CA bacterial pneumonia and ABSSSI	Favorable oral and/or intravenous administration; Paratek Pharmaceuticals withdrew from E.U. EMA marketing authorization approval on 9 October 2019 due to commercial feasibility issues
Eravacycline (Xerava)	Tetracycline	30S subunit of bacterial ribosome	U.S. FDA approved on 27 August 2018; E.U. EMA approved on 9 September 2018	Tetraphase Pharmaceuticals Inc.	ESKAPE pathogens, including CRE and CRAB	cIAI	Not indicated for treatment of complicated UTI
KBP-7072	Tetracycline	30S subunit of bacterial ribosome	Phase I	KBP BioSciences Pharmaceutical Technical Co. Ltd.		CA bacterial pneumonia	Designated a QIDP by U.S. FDA and awarded fast-track review

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TABLE 3 (Continued)

Drug name	Drug class	Drug target	Development stage	Company	Pathogen target	Application[b]	Information of note[b]
TP-271	Tetracycline	30S subunit of bacterial ribosome	Phase I	Tetraphase Pharmaceuticals Inc.	Respiratory pathogens	CA bacterial pneumonia	Designated a QIDP by U.S. FDA and awarded fast-track review
TP-6076	Tetracycline	30S subunit of bacterial ribosome	Phase I	Tetraphase Pharmaceuticals Inc.	CRE and CRAB	Bacterial infections	CARB-X funded ($4 million)
Lefamulin (Xelenta)	Pleuromutilin	50S subunit of bacterial ribosome	U.S. FDA approved on 19 August 2019; E.U. EMA marketing authorization application submitted in May 2019 (now accepted); Chinese NMPA granted clinical trial application approval on 13 June 2019	Nabriva Therapeutics AG	MRSA	ABSSSI and CA and HA bacterial pneumonia	Low toxicity profile; available as both intravenous and oral treatments
Delpazolid (LCB01-0371)	Oxazolidinone	50S subunit of bacterial ribosome	Phase II	LegoChem Biosciences Inc.		Bacterial infections and tuberculosis	Granted orphan drug designation, a QIDP, and fast-track review by U.S. FDA
DNV3837 (MCB3837)	Oxazolidinone-quinolone hybrid	50S subunit of bacterial ribosome, bacterial type II topoisomerase	Phase I	Deinove SA (formerly Morphochem AG)	*C. difficile*	*C. difficile* infections	Narrow spectrum for *C. difficile*, which may reduce gut dysbiosis; designated a QIDP by U.S. FDA and awarded fast-track review
Contezolid (MRX-I/MRX-415)	Oxazolidinone	50S subunit of bacterial ribosome	Phase III	MicuRx Pharmaceuticals Inc.	MRSA and *S. pneumoniae*	ABSSSI	
Nafithromycin (WCK 4873)	Macrolide	50S subunit of bacterial ribosome	Phase II	Wockhardt Ltd.	MDR pneumococci	CA bacterial pneumonia	High level of lung and alveolar macrophage penetration; low hepatic toxicity
SPR206	Polymyxin	Cell membrane	Phase I	Spero Therapeutics Inc.	CRE, CRPA, CRAB, and XDR strains	cUTI and HA and VA bacterial pneumonia	Reduced nephrotoxicity
SPR741	Polymyxin	Cell membrane	Phase I	Spero Therapeutics Inc.	Gram-negative ESKAPE pathogens	Bacterial infections	Potentiator with reduced nephrotoxicity; antibiotic paring is yet to be announced
Afabicin (Debio 1450)	Benzofuran naphthyridine	FabI	Phase II	Debiopharm International SA	*Staphylococcus* sp.	ABSSI	Low propensity for resistance development
CG-549	Benzyl pyridinone	FabI	Phase II	Crystal Genomics Inc.	MRSA and VRSA	ABSSSI	
Iclaprim	2,4-Diaminopyrimidine	Dihydrofolate reductase	Complete response letter to Investigational New Drug application (U.S. FDA)	Motif Bio PLC	Gram-positive bacteria, including MRSA	ABSSSI and HA and VA bacterial pneumonia	Granted orphan status and designated a QIDP by U.S. FDA; low propensity for resistance development
CRS3123	Diaryldiamine	Methionyl-tRNA synthetase	Phase I	Crestone Inc.	*C. difficile*	*C. difficile* infections	Narrow spectrum for *C. difficile*, which may reduce gut dysbiosis
Brilacidin	Defensin mimetic	Cell membrane	Phase II	Innovation Pharmaceuticals Inc.		ABSSSI	New class of antibiotic; designated a QIDP by U.S. FDA and awarded fast-track review

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TABLE 3 (Continued)

Drug name	Drug class	Drug target	Development stage	Company	Pathogen target	Application[b]	Information of note[b]
Murepavadin (POL7080)	Antimicrobial peptide mimetic	LptD	Phase III	Polyphor Ltd.	CRPA	HA and VA bacterial pneumonia (caused by *P. aeruginosa*)	Designated a QIDP by U.S. FDA and awarded fast-track review
Ridinilazole (SMT 19969)	Bis-benzimidazole	Inhibition of cell division and reduction of toxin production	Phase III	Summit Therapeutics PLC	*C. difficile*	*C. difficile* infection	Narrow spectrum for *C. difficile*, which may reduce gut dysbiosis; designated a QIDP by U.S. FDA and awarded fast-track review

[a]The table includes data from reference 390. Abbreviations: CA, community acquired; HA, hospital acquired; VA, ventilator associated; UTI, urinary tract infection; cUTI, complicated UTI; cIAI, complicated intra-abdominal infection; ABSSSI, acute bacterial skin and skin structure infection; QIDP, qualified infectious disease product; U.S. FDA, U.S. Food and Drug Administration; E.U. EMA, European Union European Medicines Agency; Australian TGA, Australian Therapeutic Goods Administration; Chinese NMPA, Chinese National Medical Products Administration; Japanese PMDA, Japanese Pharmaceutical and Medical Devices Agency; BARDA, U.S. Biomedical Advanced Research and Development Authority; PBP, penicillin-binding protein; PG, peptidoglycan; MRSA, methicillin-resistant *S. aureus*; CRE, carbapenem-resistant *Enterobacterales*; CRAB, carbapenem-resistant *A. baumannii*; CRPA, carbapenem-resistant *P. aeruginosa*; XDR, extremely drug resistant.

[b]As defined by the company website.

to the commonly prescribed moxifloxacin for an early clinical response, as defined by survival, against CA bacterial pneumonia (397). Unlike the U.S. FDA, the E.U. EMA recommended granting marketing authorization for omadacycline solely for use in patients with ABSSSI and not in those with CA bacterial pneumonia. As a result, Paratek Pharmaceuticals Inc. withdrew omadacycline from the E.U. EMA marketing authorization application on 9 October 2019, stating that "it would not be commercially feasible to market Nuzyra just for the treatment of skin and skin structure infections" (398). The absence of omadacycline in Europe illustrates the current financial and practical problems facing antimicrobial R&D, i.e., balancing product profitability with appropriate stewardship practices. To combat these obstacles, DRIVE-AB has proposed a delinking initiative which provides a financial reward ($1 billion) per innovative antibiotic, allowing revenues for new antibiotics to be partially or fully delinked from the number of units sold, thus allowing for the revenues to be based upon the value to society (399).

In 2019, five new antimicrobial drug therapies were approved by either the U.S. FDA, the E.U. EMA, or the Japanese PMDA. Of these five therapies, four drugs, imipenem-cilastatin-relebactam (Recarbrio; Merck & Co., Inc.), lefamulin (Xelenta; Nabriva Therapeutics AG), lascufloxacin (Lasvic; Kyorin Pharmaceutical Co. Ltd.), and cefiderocol (Fetroja; Shionogi & Co. Ltd.) demonstrated efficacy against ESKAPE pathogens (note that pretomanid [TB Alliance] was approved for the treatment of MDR tuberculosis) (390) (Table 3). In July 2019, the three-drug combination imipenem, cilastatin, and relebactam was approved by the U.S. FDA for the treatment of complicated UTI and complicated intra-abdominal infection caused by *E. coli*, *E. cloacae*, *K. pneumoniae*, *K. aerogenes*, and *P. aeruginosa*) (400). Furthermore, the E.U. EMA adopted a positive opinion for imipenem-cilastatin-relebactam, recommending to grant a marketing authorization for the treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options (December 2019). Imipenem-cilastatin-relebactam was subsequently approved by the E.U. EMA in February 2020 (24). Imipenem-cilastatin-relebactam, comprised of the existing antibiotics imipenem and cilastatin, contains a novel β-lactamase inhibitor, relebactam, a third new β-lactamase inhibitor after avibactam and vaborbactam (401).

Lefamulin (Xelenta; Nabriva Therapeutics AG), developed for the treatment of CA bacterial pneumonia, was the second therapeutic to be approved by the U.S. FDA in 2019 (August) (402) (Table 3). In the LEAP 2 trial (a phase III, noninferiority trial that compared oral lefamulin to oral moxifloxacin), lefamulin demonstrated noninferiority to moxifloxacin in the management of CA bacterial pneumonia. Lefamulin presents a new oral and intravenous treatment against CA bacterial pneumonia, particularly for pneumonia caused by CA-MRSA (403). In May 2019, Nabriva Therapeutics AG submitted a marketing authorization application (now accepted) to the E.U. EMA for both intravenous and oral formulations of lefamulin for the treatment of CA bacterial pneumonia in adults 18 years of age and older (404, 405).

Lascufloxacin (Lasvic; Kyorin Pharmaceutical Co. Ltd.), a novel fluoroquinolone antimicrobial, was approved by the Japanese PMDA on 20 September 2019 for the treatment of CA bacterial pneumonia caused by a range of bacterial pathogens, including quinolone-resistant *Staphylococcus* and *Klebsiella* spp. (406–408). In a phase II clinical trial, oral administration of lascufloxacin (75 mg) demonstrated clinical cure rates of 90%, bacteriological eradication rates of 96%, and an overall incidence of adverse drug reaction of 11.1% (409). Furthermore, during a double-blind phase III clinical trial, lascufloxacin demonstrated noninferiority to orally administered quinolones in the management of CA bacterial pneumonia and sinusitis (410).

Cefiderocol (Fetroja; Shionogi & Co. Ltd.), approved by the U.S. FDA in November 2019, is a novel siderophore-cephalosporin conjugate approved for the treatment of patients 18 years of age or older with complicated UTI including kidney infections caused by susceptible Gram-negative pathogens (i.e., CRE, CRAB, and carbapenem-resistant *P. aeruginosa* [CRPA]) (21, 411) (Table 3). In a phase II, double-blind, randomized clinical trial, the safety and efficacy of cefiderocol were assessed. The trial found that 72.6% of the patients who were administered cefiderocol but only 54.6% who

those who received imipenem-cilastatin had resolution of symptoms and eradication of bacteria at 7 days posttreatment (412).

New Drug Classes in Clinical Trials

The portfolio of compounds currently in clinical trials more often than not consists of derivatives of chemical classes for which there is already an underlying mechanism of resistance. Over the past 24 months, all drugs approved by the U.S. FDA, E.U. EMA, and Japanese PMDA were drug analogs based on established antibiotic classes (390). Murepavadin is one of the few new class of antibiotics which entered into a phase III clinical trial (now temporarily suspended) (Table 3). Murepavadin is selective against the protein transporter LptD, which mediates the transport of LPS to the outer leaflet (413). As the first in class of the outer membrane protein-targeting peptidomimetic antibiotics, murepavadin displays potent activity against carbapenemase-producing and polymyxin-resistant *P. aeruginosa* strains (413). Murepavadin was under clinical development for the treatment of HA pneumonia and ventilator-associated (VA) pneumonia. Unfortunately, enrollment in phase III studies for the systemic treatment of nosocomial pneumonia has now been temporarily suspended due to higher-than-expected levels of acute kidney injury in participants. Aerosol formulations of murepavadin for the treatment of nosocomial and chronic *P. aeruginosa* respiratory infections are still being actively pursued (414).

Brilacidin (Innovation Pharmaceuticals Inc.), currently undergoing a phase II clinical trial, is a synthetic new class of defensin mimetic for the treatment of ABSSSI caused by *S. aureus* (Table 3). As a late-stage antibiotic drug candidate, brilacidin is being advanced to the clinic under the Qualified Infectious Disease Product designation by the U.S. FDA, enabling fast-track review (390).

New Drugs in Clinical Trials—Overcoming Antibiotic Toxicity

The innate toxicity of certain antibiotics, combined with the compromised state of the infected patient, often shapes clinical dosing regimens. The rates of drug-induced nephrotoxicity range from 14% to 26% in adults, and nephrotoxicity is the most common toxicity issue associated with antibiotic prescription (415). The nephrotoxic effects of last-resort polymyxin-class antibiotics and the widespread level of carbapenem resistance in ESKAPE pathogens have severely limited patient treatment options. In a bid to overcome these problems, two new polymyxin analogs, SPR206 and SPR741 (Spero Therapeutics Inc.), have been developed (390, 416) (Table 3). SPR206 is an investigational drug candidate in a phase I clinical trial with broad-spectrum antimicrobial activity against polymyxin-sensitive, Gram-negative pathogens (including CRE, CRPA, and CRAB) associated with complicated UTI, HA pneumonia, and VA pneumonia (416). SPR741, formerly NAB741, is a potentiator molecule that has been successfully evaluated in a phase I clinical trial, demonstrating potent synergy with azithromycin, clarithromycin, erythromycin, fusidic acid, mupirocin, retapamulin, rifampin, and telithromycin (417). SPR741 has the potential to treat a broad range of bacterial disease states, including those caused by CRE, CRPA, and CRAB strains. In contrast to polymyxin B, SPR206 yields an aromatic β-amino acid modification at the fatty acid-AA1 component of polymyxin B. SPR741 lacks two cationic diaminobutyryl residues in the linear portion of the peptide and lacks the 6-methyloctanoyl or 6-methylheptanoyl fatty acid tail found in polymyxin B (418). These respective structural modifications have significantly improved the safety and dose-limiting nephrotoxicity issues associated with polymyxin-class antibiotics.

Alternative Drug Trial Approaches

New drug trial strategies are emerging, focusing on both alleviating the increased demand for last-resort therapies and minimizing further infection complications by reducing patient hospital admission lengths. Such new trial strategies include testing new antibiotic-antibiotic potentiator combinations and reducing hospital-stay periods beyond the critical point of infection to improve treatment outcomes.

Carbapenems are still considered the most effective therapy for select ESKAPE pathogen infections, particularly those caused by ESBL-producing *Enterobacterales*. Unfortunately, the increased use of carbapenems in clinical settings has created a selection pressure for the emergence of carbapenem resistance. In an effort to define carbapenem-sparing alternatives, a recent drug trial (MERINO trial) examined whether piperacillin-tazobactam combinations could demonstrate efficacy comparable to that of carbapenems (419). Among patients with *E. coli* and *K. pneumoniae* bloodstream infections, 30-day survival did not improve upon piperacillin-tazobactam treatment compared to that achieved with meropenem therapy (420). Although results from the MERINO trial did not support the use of piperacillin-tazobactam as a carbapenem-sparing treatment, the trial highlighted the need for carbapenem-sparing strategies and for further study into β-lactam–β-lactamase inhibitor drug combinations.

Reducing the length of hospital stay following the initial stage of infection is associated with a decreased risk of further complications and better outcomes of the patient disease state (421, 422). In 2018, with the objective of reducing patient hospital admission times, the Partial Oral Treatment of Endocarditis (POET) trial evaluated the efficacy of intravenous antibiotics compared with that of oral antibiotics among stable patients with infective endocarditis (423). The premise of this study was to allow patient treatment to take place outside of hospitals, without the requirement for intravenous catheters. The primary outcome from the POET study showed that oral antibiotics were noninferior to intravenous antibiotics at preventing adverse events (i.e., all-cause death, unplanned cardiac surgery, embolic events, or relapse of bacteremia) (423). The impact of this landmark study may significantly minimize the challenges associated with parenteral treatment, including logistics, monitoring, and risks of complications associated with intravenous catheters (i.e., secondary local and systemic infections).

Combinational Drug Therapy

The protracted R&D of effective, novel antimicrobial drug candidates has contributed to the failure to combat the resurgence of AMR bacterial infections. Pairing existing antimicrobials with either other antimicrobials or nonantimicrobial compounds offers a valuable strategy to address the problem of AMR. This strategy is not new (424, 425), and it is well recognized that antibiotic monotherapy is not universally efficacious for all bacterial infections. Adjuvants are often administered in combination with antibiotic therapy, resulting in better patient outcomes. Antibiotic adjuvants can be divided into two classes: class I adjuvants, which act on the pathogen, and class II adjuvants, which act on host properties to potentiate antibiotic action (426).

Blocking resistance mechanisms against existing antibiotics. (i) Class I adjuvants. From the available repertoire of class I adjuvants, β-lactamase inhibitors have proven to be the most successful. Clavulanic acid, isolated from *Streptomyces clavuligerus* (427), inactivates Ser β-lactamases and has been paired with amoxicillin for over 30 years to create the drug Augmentin. Recently, several human clinical trials have examined the efficacy of class A and C β-lactamase inhibitors: avibactam, vaborbactam, and relebactam coformulated with ceftazidime and relebactam paired with imipenem against CRKP (428). In current clinical practice, β-lactamase inhibitors do not inhibit the class B, Zn-dependent MBLs found broadly in *Enterobacterales*, *Pseudomonas*, and *Acinetobacter* species (429). The fungus-derived aspergillomarasmine A has been shown to be efficacious against MBL-producing bacteria in *in vivo* models of infection (430). Aspergillomarasmine A functions to rescue the antibiotic activity of meropenem expressing NDM-1 and VIM MBLs by sequestering Zn^{2+} ions essential for catalytic activity. Other antibiotic class I adjuvants which have been investigated include 2-aminoimidazole-based compounds, which disrupt two-component signaling (431); anthracyclines, which potentiate rifampin and linezolid (432); SPR741, a polymyxin-derived molecule designed to minimize nephrotoxicity and potentiate rifampin activity (433); and hydroxyquinoline analogues, among others, which potentiate the activity of multiple classes of antibiotics against a range of Gram-positive AMR pathogens (389, 434).

(ii) Class II adjuvants. Enhancement of host defense mechanisms offers an alternative set of targets for antibiotic adjuvants. Over the past decade, several innate immune-enhancing peptides developed to treat sepsis (E-5564 [Eisai Pharmaceuticals] and TAK-242 [Takeda Pharmaceuticals]) have reached phase III clinical trials but failed to progress (435). Despite these shortcomings, new immune-stimulating therapies are continuing to be explored, with promising outcomes.

Recent studies have reported on the synthesis of novel immunotherapeutic compounds which successfully mediate the opsonization of *E. coli* and *P. aeruginosa* in human serum (436). This technology utilizes polymyxin B-hapten conjugates to facilitate a two-step process whereby the lipid A binding scaffold of polymyxin B decorates the surface of Gram-negative bacteria with antibody-recruiting haptens. Mortality arising from serious infection implies failure of the patient's innate immune response. To correct and enhance innate immune cell function, pharmacological strategies have been centered around hypoxia-inducible factor 1 (HIF), the central regulator of the cellular response to hypoxic stress (437). HIF has been proposed to be a master regulator of innate immunity (438). HIF functions to both control the recruitment of neutrophils to the site of infection and increase the functional neutrophil life span by inhibiting apoptotic pathways. A series of *in vivo* infection models has demonstrated that reduced HIF levels diminish neutrophil function and render mice more susceptible to serious group A *Streptococcus* and *P. aeruginosa* infections (439, 440). Conversely, elevated levels of HIF have demonstrated enhanced control of MRSA skin infection in mice (441). HIF modulation has the capacity to serve as a complementary therapy to classical anti-infective strategies, making it a significant target for immune-boosting therapy.

Alternative Nondrug Therapies

Preclinical and clinical R&D of new antimicrobials encompasses a wide range of drug discovery pathways: (i) bacteriophage therapy, (ii) drug repurposing, (iii) monoclonal antibody (MAb) therapy, (iv) vaccine development, and (v) fecal microbiota transplantation (FMT) are some of the many novel approaches currently being investigated to control the burden of AMR.

Bacteriophage therapy. Bacteriophage therapy was first applied in 1917 as an oral preparation to treat dysentery (387). As a result of antibiotic discovery, the use of bacteriophage treatment significantly reduced. Today, bacteriophage therapy again represents a potentially effective strategy for the control of AMR bacteria. Within the past 5 years, a number of phage preparations have undergone clinical trials. Examples include bacteriophage preparations for burn wound infections (ClinicalTrials.gov study identifier NCT02116010) and persistent postoperative respiratory infection (ClinicalTrials.gov study identifier NCT00945087) (387).

Through the utilization of the CRISPR technology, several companies have engineered bacteriophages which demonstrate *in vivo* efficacy against AMR bacterial infections. These distinct therapies, formulated by Locus and Eligo Bioscience, exploit the Cas3 and Cas9 enzyme systems, respectively, to degrade bacterial DNA, leading to cellular death. Therapies developed by both companies are expected to enter clinical trials within the next 12 months (442).

Although bacteriophages are not currently U.S. FDA approved for human use (due to the uncertainty surrounding the host immune response), the U.S. FDA has committed to facilitating the testing of phage therapy in clinical trials. In 2019, the U.S. FDA accepted an Investigational New Drug application by physician scientists at the University of California, San Diego (443, 444). In collaboration with AmpliPhi Biosciences Corporation, the proposed phase I/II trial will test AB-SA01, an experimental bacteriophage combination for the treatment of ventricular assisted devices infected with MDR *S. aureus*. The trial will evaluate the safety, tolerability, and efficacy of intravenously administered AB-SA01 bacteriophage therapy in combination with complementing antibiotic therapy (444).

Globally, the lack of an appropriate legal and regulatory framework has been a

significant obstacle to the advancement of phage therapy. In 2016, the Belgium government began implementing a magistral phage therapy framework that centers on the magistral preparation (compounded prescription drug product in the United States) of phage medicines tailor-made for the patient, providing for a broader and more structured application of phages in Belgium (445). For the proposed magistral phage strategy process, characterized and quality-tested phages are to be transferred to a hospital pharmacy for possible incorporation in patient-tailored magistral formulas. It is anticipated that other European Union members will adopt this phage therapy framework in the near future, hastening the clinical development of safe-for-human-use phage therapy.

Repurposing existing drugs used for noninfectious disease. Repurposing existing drugs represents a viable alternative to *de novo* drug discovery and favorably reduces the time, cost, and risk associated with drug innovation (446). Drug repurposing has already been shown to be efficacious against several Gram-positive and Gram-negative ESKAPE pathogens. Glatiramer acetate (Copaxone), a widely used treatment for multiple sclerosis, displays antibacterial activity against *E. coli*, *A. baumannii*, and, notably, *P. aeruginosa* clinical strains isolated from cystic fibrosis patients (447). Ebselen, a synthetic anti-inflammatory drug, and the oncology drugs adarotene and floxuridine have displayed bactericidal activity against MRSA and VRSA strains *in vivo* (448, 449). Efforts to repurpose existing drugs as antimicrobial agents or as antibiotic resistance breakers are continually being pursued both in the academic sector and in the industrial sector (371, 389, 450). Due to the marginal incentives of the current pharmaceutical R&D model for antibiotic development and discovery, drug repurposing may present an efficacious solution to the burden of AMR.

Monoclonal antibody therapy. Largely used as a therapeutic for oncology and rheumatic indications, MAb therapy presents a viable alternative for the treatment of AMR bacterial infections. The bacterial specificity of MAb therapy (i.e., it is not targeted to the host microflora), combined with a low propensity for resistance development, is a key feature which makes MAb therapy well positioned for the treatment of AMR bacterial infections (451). To date, only three MAbs have been approved for clinical use by the U.S. FDA, and none of them has been directed against ESKAPE pathogens. Both raxibacumab (Human Genome Sciences, Inc.; approved in December 2012) (452) and obiltoxaximab (Elusys Therapeutics, Inc.; approved in March 2016) are approved for the treatment of adult and pediatric patients with inhalational anthrax due to *Bacillus anthracis* (453), while bezlotoxumab (Merck Sharp & Dohme Corp.; approved in October 2016) is approved for the prevention of recurrent *Clostridioides difficile* infection in high-risk patients (454). Although no existing approved MAb therapy targets ESKAPE pathogens, several MAb therapies have been clinically evaluated for treatment of infections caused by MDR *P. aeruginosa*. Three MAbs, panobacumab (Adris Pharmaceuticals), KB001 (KaloBios), and MEDI3902 (AstraZeneca Pharmaceutical Company), have been evaluated in an early clinical trial targeting MDR *P. aeruginosa*. Panobacumab, currently in phase II clinical trials, is an antilipopolysaccharide IgM antibody directed against *O*-polysaccharide and is under investigation for the treatment of nosocomial pneumonia caused by *P. aeruginosa* O11 (455, 456). KB001 is a PEGylated MAb fragment directed against PcrV (a protein subunit of the *P. aeruginosa* type III secretion system) which was evaluated for use in mechanically ventilated CF patients suffering from chronic *P. aeruginosa* infection (457). KB001 was observed to be well tolerated in patients, reduced the levels of the sputum inflammatory marker interleukin-8, and significantly improved patient lung function (458). Able to facilitate opsonophagocytosis *in vitro*, MEDI3902 is a bivalent, bispecific MAb targeting PcrV and Psl (an exopolysaccharide involved in colonization and tissue adherence) (459). During a phase I dose-escalation study, subjects administered MEDI3902 demonstrated no serious treatment-related adverse effects, making it appropriate for use in ventilated intensive care unit (ICU) patients (460). In the ongoing EVADE phase II clinical trial, the safety and efficacy of MEDI3902 will be assessed for the prevention of VA pneumonia in adult ICU patients (461).

Vaccine development. Conceptually, bacterium-targeted vaccine therapies provide a means to decrease the public demand on existing antibiotics, while they also enable protection for those who are both vaccinated and unvaccinated (herd immunity). Unfortunately, vaccines are not currently available for infections caused by ESKAPE pathogens, with many vaccine candidates failing to elicit an immunogenic protective effect in clinical trials (462–464).

Of the limited ESKAPE pathogen-targeted vaccines which have recently undergone clinical trials, the *S. aureus* 4-antigen vaccine (SA4Ag; Pfizer; which has now ceased enrollment) was one of the few candidates which demonstrated efficacy in the prevention of invasive *S. aureus* infection in humans (465). SA4Ag consists of capsular polysaccharide serotypes 5 and 8 conjugated to the nontoxic mutant form of diphtheria toxin (CRM197), a recombinant mutant clumping factor A (ClfA), and a recombinant manganese transporter C (MntC) (465). In a phase I/II randomized trial, single-dose vaccination of healthy adults ranging from 65 to 80 years of age with SA4Ag was shown to be well tolerated and induced rapid high levels of bacterium-killing antibodies and sustained immune responses at 12 months postvaccination (465). Unfortunately, in December 2018, the respective clinical trials ceased enrollment due to meeting its prespecified futility criteria at an interim efficacy assessment. Despite this, a 36-month postvaccination serological extension study was still undertaken and recently completed. In this trial of 440 participants, persistent functional immune responses to *S. aureus* antigens were observed through a 36-month time period (466).

In the face of the limited number of vaccines in the clinical pipeline, encouraging preclinical studies have recently demonstrated the *in vivo* efficacy of vaccines against CRKP (467), *P. aeruginosa* (462), and *A. baumannii* (468). Vaccines have already been shown to be very effective at reducing the incidence of other AMR pathogens, such as *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (464). The prospect of new ESKAPE-targeted vaccines which complement existing AMR therapies will significantly aid in mitigating the spread and threat of ESKAPE pathogens.

FMT strategies. Antibiotic exposure, particularly in long-term acute care hospital patients, can alter the patient microbiota and significantly reduce colonization resistance (469). FMT-based approaches are currently being investigated for protection against AMR bacterial colonization. A recent study demonstrated that blood disorder patients treated with multiple FMT procedures exhibited gastrointestinal decolonization of VRE, ESBL-producing *Enterobacterales*, CRE, and CRPA in 60% of all cases (470). These data highlight the utility of FMT approaches in reversing the gut dysbiosis that predisposes patients to colonization with AMR ESKAPE pathogens.

OUTLOOK

AMR represents one of the few challenges that unites global interests and concerns for human and animal health and the food and agricultural sectors. Exacerbated by the acquisition of AMR genes, ESKAPE pathogens represent the paradigm for resistance, pathogenesis, and disease transmission in both the community and clinical settings. Although heterogeneous at the genetic level, the general mechanisms surrounding ESKAPE pathogen emergence and persistence are broadly shared. Mediated in part through HGT, resistance strategies encompassing drug inactivation, modification of the antibiotic target site, and a reduction of antibiotic accumulation in the bacterial cell are common strategies shared by all ESKAPE pathogens. Combined with the collective ability to form biofilm on innate and biological surfaces, ESKAPE pathogens remain highly prevalent in clinical settings.

To constrain the spread of ESKAPE pathogens, it is now well recognized that collaborative global and regional efforts are required by policy makers, funders, and those responsible for the treatment and management of ESKAPE pathogens (12, 35, 64). Aside from novel drug development, these collaborative endeavors will require sustainable stewardship practices to reduce the inappropriate use of antibiotics in both the human health and agricultural sectors. Despite efforts to coordinate international and national AMR surveillance, it would be well-advised for AMR policy, drug development,

and surveillance efforts to include both ESKAPE pathogens and other serious health threats, such as AMR *E. coli*, *Neisseria gonorrhoeae*, and *Campylobacter* spp. These will require equal attention to avoid selecting for a new group of AMR pathogen threats (12). Improvements in factors encompassing AMR surveillance, diagnostics, patient education, and patient treatment options will together help facilitate the control of AMR.

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