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REVIEW
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An Update of Mobile Colistin Resistance in Non-Fermentative Gram-Negative Bacilli

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Colistin, the last resort for multidrug and extensively drug-resistant bacterial infection treatment, was reintroduced after being avoided in clinical settings from the 1970s to the 1990s because of its high toxicity. Colistin is considered a crucial treatment option for *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, which are listed as critical priority pathogens for new antibiotics by the World Health Organization. The resistance mechanisms of colistin are considered to be chromosomally encoded, and no horizontal transfer has been reported. Nevertheless, in November 2015, a transmissible resistance mechanism of colistin, called mobile colistin resistance (MCR), was discovered. Up to ten families with MCR and more than 100 variants of Gram-negative bacteria have been reported worldwide. Even though few have been reported from *Acinetobacter* spp. and *Pseudomonas* spp., it is important to closely monitor the epidemiology of *mcr* genes in these pathogens. Therefore, this review focuses on the most recent update on colistin resistance and the epidemiology of *mcr* genes among non-fermentative Gram-negative bacilli, especially *Acinetobacter* spp. and *P. aeruginosa*.

Keywords: colistin resistance, *mcr* genes, *Acinetobacter*, *Pseudomonas*, polymyxin

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1 INTRODUCTION

Presently, beta-lactams, cephalosporins, carbapenems, fluoroquinolones, aminoglycosides, and macrolides are frequently used to treat bacterial infections. However, the emergence of drug-resistant microorganisms, particularly Gram-negative pathogens, has become a public health threat. In 2017, the World Health Organization classified carbapenem-resistant (CR) *Acinetobacter baumannii* and *Pseudomonas aeruginosa* as priority pathogens in critical need of alternative treatment options (World Health Organization, 2017). *P. aeruginosa*, *A. baumannii*, *Stenotrophomonas maltophilia*, and *Burkholderia cepacia* complex are non-fermentative Gram-negative bacteria that cause significant problems in healthcare settings. Because these bacteria are highly adaptable and have various intrinsic and acquired resistance mechanisms, they are typically resistant to major classes of antimicrobial agents, leaving only a few therapeutic options (Enoch et al., 2007). Among these, *P. aeruginosa* and *A. baumannii* are the most common causes of nosocomial infections (Mancuso et al., 2021). *P. aeruginosa* is the most common pathogen in the *Pseudomonas* genus. This bacterium is an opportunistic pathogen that causes skin, wound, and lung infections. Respiratory infections caused by *P. aeruginosa* are often associated with defective

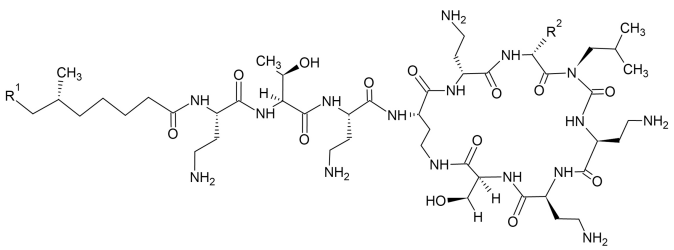
respiratory systems or ventilation, such as in cystic fibrosis (Bassetti et al., 2018). In contrast, *A. baumannii* is one of the most common causes of nosocomial infections, such as bloodstream infections and pneumonia (Garnacho-Montero and Timsit, 2019). This organism is part of what is known as the *Acinetobacter calcoaceticus–baumannii* complex, which also includes *Acinetobacter pittii*, *Acinetobacter nosocomialis*, and *Acinetobacter calcoaceticus* (Ramirez et al., 2020).

With the limitations of new drug development, many outdated antibiotics have been reintroduced into the clinical setting despite their high toxicity, including the polymyxin drug group (Hermsen et al., 2003). As there are no other options available, this drug group has become crucial to combat antibiotic resistance (Bialvaei and Samadi Kafil, 2015). Modern therapeutic drug monitoring of colistin is prone to have a lower incidence rate of toxicity when compared to the past.

The polymyxin group contains many drugs, but polymyxin E, also known as colistin, is recognized as the main agent (Rhouma et al., 2016b). Colistin is one of the remaining treatment options for life-threatening infections caused by multidrug and extensively drug-resistant *A. baumannii* and *P. aeruginosa* (Bialvaei and Samadi Kafil, 2015). Moreover, colistin resistance mechanisms are quite rare and chromosomally encoded, which makes transfer difficult (Olaitan et al., 2014). Therefore, the resistance rate against colistin in Gram-negative pathogens appears to be lower than that of other antibiotic classes. However, the increasing trend of colistin resistance in Enterobacteriaceae led to the discovery of the transmissible resistance mechanism of colistin in 2015 (Liu et al., 2016). Since then, the resistance rate of last-resort drugs has been closely monitored; the more the antibiotic resistance rate increases, the fewer treatment options are available. Transferable polymyxin resistance has been extensively reported worldwide. To date, at least ten variations in *mcr* genes have been described and are currently ongoing. This problem is critical, especially for pathogens with limited treatment options, such as *A. baumannii* and *P. aeruginosa*. Therefore, this review focuses on colistin drug resistance and its epidemiology among the non-fermentative Gram-negative bacilli, *Acinetobacter* spp., and *P. aeruginosa*.

2 THE POLYMYXINS

Colistin (polymyxin E) belongs to the polymyxin drug group and appears commercially in two forms as inactive prodrugs: colistin methanesulfonate for parenteral use and colistin sulfate for topical use and use in animal production in some countries (Rhouma et al., 2016b). Another type of polymyxin used in clinical practice is polymyxin B, which is administered in its active form (Tsuji et al., 2019). These antibiotics have been described as old-generation antibiotics, but because of the limitations of antibiotic options, colistin was reintroduced as a last resort for multidrug-resistant (MDR) and extensively drug-resistant (XDR) bacterial infection treatment. Polymyxins were discovered in the 1940s from *Bacillus polymyxa*, later known as *Paenibacillus polymyxa*, and were approved by the United States Food and Drug Administration before being used in hospitals in the 1950s (Lim et al., 2010). Polymyxins are polypeptide antibiotic groups that include five different chemical compounds: polymyxins A, B, C, D, and E; however, only polymyxin B and polymyxin E are used in clinical settings (Bialvaei and Samadi Kafil, 2015). Polymyxin B consists of two compounds, polymyxins B1 and B2, whereas colistin contains polymyxins E1 and E2. Colistin differs from polymyxin B in its amino acid composition (**Figure 1**) (Hermsen et al., 2003; Nation and Li, 2009; Bialvaei and Samadi Kafil, 2015). It has a molecular weight of 1,750 Da and consists of a polycationic cyclic heptapeptide attached to a lipophilic fatty acid side chain (Bialvaei and Samadi Kafil, 2015). The structure of colistin is amphipathic, containing both aqueous and non-aqueous soluble parts (Hermsen et al., 2003).



R^1	CH_3	H	CH_3	H
R^2				
	Polymyxin B (1)	Polymyxin B (2)	Polymyxin E (1)	Polymyxin E (2)

FIGURE 1 | Chemical structures of polymyxin B and E.

Colistin has been demonstrated to have a concentration-dependent bactericidal effect, but its mechanism of action is unclear (Nation and Li, 2009; Bialvaei and Samadi Kafil, 2015). The proposed mechanism of action is based on the chemical structure of colistin, which destabilizes lipopolysaccharide (LPS), increases membrane permeability, and leads to bacterial cell leakage (Hermsen et al., 2003; Nation and Li, 2009). The antibiotic spectrum of colistin is narrow, but it is active against many important MDR Gram-negative bacteria, including *P. aeruginosa*, *A. baumannii*, *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter* spp., and some other bacteria in Enterobacterales (Hermsen et al., 2003; Nation and Li, 2009; Bialvaei and Samadi Kafil, 2015). Colistin is generally not recommended for Gram-positive pathogens because they lack an outer membrane structure.

Its prominent toxicity, including nephrotoxicity and neurotoxicity, is a drawback of colistin use (Nation and Li, 2009). However, toxicity is usually reversible upon discontinuing the medication and is believed to be dose dependent (Li et al., 2006). In the early 2000s, when a resurgence of colistin use occurred, the lack of information on appropriate colistin dosage was the main problem. The International Consensus Guidelines for the Optimal Use of Polymyxins were published in 2020, making colistin safer for use. The recommended PK/PD therapeutic target for efficacy maximization of colistin is a target plasma colistin $C_{ss,avg}$ of 2 mg/L, which can provide an area under the plasma concentration–time curve across 24 h at a steady state ($AUC_{ss,24\ h}$) of approximately 50 mg h/L (Tsuji et al., 2019). This concentration is considered the maximum tolerable exposure. Higher concentrations can increase the nephrotoxicity incidence and severity (Tsuji et al., 2019). Patients with renal impairment should have their colistin dosage adjusted based on creatinine clearance (Tsuji et al., 2019).

3 THE LABORATORY DETECTION OF COLISTIN RESISTANCE

The phenotypic detection of colistin resistance is usually based on antimicrobial susceptibility testing. Clinical and Laboratory Standards Institute (CLSI) guidelines recommend that the broth dilution method be used for colistin because the disc diffusion method is unreliable (Falagas et al., 2010). As a result, the CLSI-EUCAST Working Group recommended a reference method for polymyxin susceptibility testing using broth microdilution without additives (Dafopoulou et al., 2019). The microbe is considered colistin or polymyxin B resistant when the minimum inhibitory concentration (MIC) is equal to or greater than 4 mg/ml in tested organisms, including in Enterobacterales, *P. aeruginosa*, and *Acinetobacter* spp. (Clinical and Laboratory Standards Institute, 2022). Colistin resistance in Enterobacterales and *Acinetobacter* spp. is when the MIC is greater than 2 mg/ml, but resistance in *P. aeruginosa* is when the MIC is greater than 4 mg/ml, according to the EUCAST breakpoints table (The European Committee on Antimicrobial Susceptibility Testing, 2022). Additionally, sulfate salts of polymyxins must be used instead of colistin methanesulfonate because of their slow breakdown from the inactive prodrug form (Tsuji et al., 2019). Agar dilution is another antimicrobial susceptibility method based on dilution techniques. However, the reliability of the MICs obtained using this method remains inconclusive. Therefore, the CLSI-EUCAST Working Group advised to avoid using the agar dilution method until more data are available (Dafopoulou et al., 2019). Notably, the phenotypic detection method cannot distinguish between colistin resistance mechanisms. To identify the resistance mechanisms, analyses at the genotypic level should be applied subsequent to the antimicrobial susceptibility test. Genotypic detection is based on polymerase chain reaction (PCR) and whole-genome sequencing (WGS) methods. WGS seems to be the most effective strategy for collecting these data because it can identify all targeted antimicrobial resistance genes, including acquired colistin resistance genes (World Health Organization, 2020). The PCR detection method has limitations owing to its selective amplification of only the known sequence. If suspected organisms carry novel *mcr* genes or mutations, the PCR method alone may not detect that information (World Health Organization, 2021).

Since the presence of *mcr* genes on transmissible plasmids was reported, the colistin resistance rate has increased significantly, especially in Asia, Africa, and Europe. Therefore, rapid screening methods for *mcr*-harboring microorganisms are necessary. The only recommended phenotypic detection method is broth dilution, which is laborious compared to the disc diffusion or gradient diffusion methods. Although genetic-based detection methods are the gold standard, they require sophisticated instruments and experienced users. It is also difficult to detect all the responsible colistin resistance genes, especially the acquired genes. Therefore, a more practical method for routine laboratory screening is required (World Health Organization, 2021). Phenotypic detection methods that are still under development have been proposed, such as agar-based screening media (CHROMID® Colistin R agar, Superpolymyxin™, CHROMagar™ COL-APSE), the Rapid Polymyxin NP test, Colispot, and disc prediffusion (Boyen et al., 2010; Nordmann et al., 2016a; Nordmann et al., 2016b; Abdul Momin et al., 2017; Jouy et al., 2017; Garcia-Fernandez et al., 2019).

4 COLISTIN RESISTANCE SURVEILLANCE

Public health awareness of the increasing prevalence of antimicrobial-resistant microorganisms has led to the implementation of antimicrobial stewardship programs worldwide. One strategy is to monitor the resistance of bacteria to slow the spread of resistant microorganisms. Therefore, many surveillance programs have been initiated to monitor antimicrobial resistance in all countries, including the Global Antimicrobial Resistance and Use Surveillance System (GLASS), Central Asian and European Surveillance of Antimicrobial Resistance (CAESAR), Latin American and

Caribbean Network for Antimicrobial Resistance Surveillance (ReLAVRA), and the European Antimicrobial Resistance Surveillance Network (EARS-Net). A report of colistin resistance in bloodstream infections from the SENTRY program from 2009 to 2016 showed a resistance rate of less than 1% in *P. aeruginosa*, 3.1% in *A. baumannii*, and more than 10% in Enterobacteriaceae (Diekema et al., 2019). In Canada, the CANWARD surveillance study showed that between 2007 and 2016, *Enterobacter cloacae*, *P. aeruginosa*, and *A. baumannii* were the top three microorganisms with the highest colistin resistance rates of approximately 18.1%, 5.0%, and 2.5%, respectively (Zhanel et al., 2019). Similar results were obtained by Bialvaei and Kafil, who also detected a high resistance rate of colistin among Enterobacteriaceae, especially from *Enterobacter* spp. and *K. pneumoniae*, in the Asia-Pacific and Latin American regions (Bialvaei and Samadi Kafil, 2015). The abrupt increase in colistin resistance in Asian countries has led to the discovery of mobile colistin resistance (MCR). In Thailand, the National Antimicrobial Resistance Surveillance Center, Thailand (NARST) also monitors colistin resistance in clinically important microorganisms. Fortunately, the resistance rates to colistin in *E. coli*, *K. pneumoniae*, *P. aeruginosa*, and *A. baumannii* in Thailand in 2019 were less than 5% (National Antimicrobial Resistant Surveillance Center, 2020).

5 THE IMPORTANCE OF THE POLYMYXINS IN NON-FERMENTATIVE BACTERIA TREATMENT

Polymyxins and carbapenems are considered last-resort antibiotics for the treatment of Gram-negative bacteria; however, owing to their misuse, the problem of antibiotic resistance is worsening, particularly in low- to middle-income countries (de Carvalho et al., 2022). A multicenter surveillance study in Taiwan found that the incidence of MDR, XDR, and CR *P. aeruginosa* infections in hospitalized patients increased from 25.1% to 27.5%, 7.7 to 8.4%, and 19.7% to 27.5%, respectively, between 2016 and 2018 (Jean et al., 2022). In the past decade, hospital-associated *P. aeruginosa* has showed high MDR/CR numbers in Europe, with prevalence rates of more than 30% (Micek et al., 2015). In 2020, more than half of the countries in Europe showed carbapenem resistance of more than 25% among invasive isolates (European Centre for Disease Prevention and Control, 2022). A meta-analysis found that colistin is the most effective antibiotic for the treatment of *Pseudomonas* spp. Throughout the study period, colistin was the only antibiotic with a resistance rate of less than 10% (Bonyadi et al., 2022).

In China, *Acinetobacter* spp. showed a high level of resistance to all carbapenems caused by plasmids carrying various carbapenemase genes (Jean et al., 2022). In a 2022 report from Europe, healthcare-associated isolates of CR-*Acinetobacter* spp. were >50% in at least 20 countries, especially in southern and eastern Europe (European Centre for Disease Prevention and Control, 2022). Data from many surveillance studies have indicated that carbapenem resistance has been increasing over the last decade, suggesting that carbapenems may not be a suitable standard treatment for MDR, XDR, and CR non-fermentative Gram-negative bacteria. Therefore, polymyxin-based therapy has become the recommended treatment option for CR *A. baumannii* (CRAB) and XDR *P. aeruginosa* infections (de Carvalho et al., 2022). In clinical practice, colistin or polymyxin has always been used in combination therapy with at least one additional antibiotic from a different class against CR microorganisms or in patients with risk factors (Bassetti et al., 2018; Doi 2019).

The "Guidelines Recommendations for Evidenced-based Antimicrobial use in Taiwan" (GREAT) working group has launched recommendations and guidelines for the treatment of infections caused by MDR organisms (Sy et al., 2022). In bloodstream infections caused by CRAB, the recommended treatment is colistin 5 mg/kg IV loading dose, followed by IV every 12 h of 2.5 mg × (1.5 × creatine clearance + 30) and/or imipenem/cilastatin 500 mg IV every 6 h or meropenem 2 g IV every 8 h. In pneumonia caused by CRAB, the recommended treatment is colistin 5 mg/kg IV loading dose, then IV every 12 h of 2.5 mg × (1.5 × creatine clearance + 30) and/or imipenem/cilastatin 500 mg IV every 6 h or meropenem 2 g IV every 8 h and adjunctive colistin inhalation 1.25–15 MIU/day in 2–3 divided doses. For any clinical symptoms caused by difficult-to-treat *P. aeruginosa*, one of the recommended regimens is colistin 5 mg/kg IV loading dose, followed by IV every 12 h at 2.5 mg × (1.5 × creatine clearance + 30) or combination therapy for 5–14 days. Colistin plays a crucial role in MDR microorganism treatment. Therefore, if colistin resistance mechanisms can be transmitted more easily like MCR, it would significantly impact non-fermentative Gram-negative bacterial treatment.

6 CHROMOSOMAL RESISTANCE OF COLISTIN

Before the 2000s, reports of resistance to colistin were quite rare, which might have been caused by its low usage over the last 30 years (Nation and Li, 2009). The main mechanism of polymyxin resistance in Gram-negative bacteria is the modification of lipid A, which reduces electrostatic interactions with polymyxins (Cai et al., 2012). Some Gram-negative bacteria, such as *Proteus* spp. and *Burkholderia* spp., demonstrated resistance to polymyxins naturally by modifying LPS with 4-amino-4-deoxy-L-arabinose (L-Ara4N) (Olaitan et al., 2014). Chromosomal encoding enzymes (EptA, EptB, and EptC) have been identified in some Gram-negative bacteria, such as Salmonella. EptA, also known as PmrC, is a complex operon. These enzymes, encoded by phosphoethanolamine (pEtN) transferases, can add pEtN to LPS (Zhang et al., 2019; Hamel et al., 2021).

The acquired resistance mechanisms of chromosomally encoded polymyxins are mainly caused by modification of the LPS charge (Olaitan et al., 2014). These resistance mechanisms have been reported in many Gram-negative microorganisms, such as *Salmonella enterica*, *K. pneumoniae*, *A. baumannii*, *P. aeruginosa*, and *E. coli*. They are involved in the two-component system genes *phoP*/*phoQ* and *pmrA*/*pmrB* (Needham and Trent, 2013; Olaitan

et al., 2014). PhoQ and PmrB proteins possess tyrosine kinase activity, which phosphorylates the regulator protein (PhoP or PmrA), activates the *pmrHFIJKLM* operon, and finally modifies the surface of bacteria by adding L-Ara4N or pEtN to lipid A (Ayoub Moubareck, 2020). PhoP/PhoQ is also regulated by the ColR/ColS and CprR/CprS systems. Mutations in these regulatory systems can lead to overexpression of PhoP/PhoQ in *P. aeruginosa* (Gutu et al., 2013). ParR/ParS is also involved in colistin resistance in *P. aeruginosa*, with upregulation of the LPS modification operon at sub-inhibitory concentrations of polymyxins (Fernandez et al., 2010). The two-component systems found in *P. aeruginosa* are PhoP/PhoQ and PmrA/PmrB, but only PmrA/PmrB has been reported in *A. baumannii* (McPhee et al., 2003; Adams et al., 2009; Beceiro et al., 2011). In addition, in *A. baumannii*, the insertion of ISAba11 into the biosynthesis genes *lpxA*, *lpxC*, and *lpxD* leads to the complete loss of LPS and colistin resistance (Moffatt et al., 2010; Moffatt et al., 2011).

Additional resistance mechanisms, such as overexpression of efflux pumps, outer membrane remodeling, and lack of LPS formation, have also been reported to be involved in colistin resistance (Olaitan et al., 2014; Ayoub Moubareck, 2020). However, these resistance mechanisms appear to be located on the chromosome. Therefore, the transmission of these mechanisms is difficult, and the horizontal gene transfer of these mechanisms has never been reported (Liu et al., 2016).

7 TRANSMISSIBLE RESISTANCE OF COLISTIN

Although the use of colistin in human clinical settings was reduced in the 1970s and was reintroduced in the late 1990s, colistin is commonly consumed in animal farming to prevent *E. coli* and *Salmonella* spp. infections (Kempf et al., 2013; Rhouma et al., 2016a). Prior to the discovery of MCR-1, surveillance of antimicrobial resistance revealed a significant increase in colistin resistance. In 2015, the first mobilized colistin resistance gene, *mcr*-1, was discovered in *E. coli* in a Chinese pig farm using a routine antimicrobial resistance surveillance program (Liu et al., 2016). MCR-1 encodes pEtN-lipid A transferase, which can modify the lipid A portion of LPS by the addition of pEtN. MCR-1 also demonstrates transmission and maintenance properties in *K. pneumoniae* and *P. aeruginosa* (Liu et al., 2016). Moreover, the microorganisms that harbored MCR-1 showed an increase in the MIC values of colistin. Furthermore, researchers have identified the *mcr-1* gene in clinical isolates from inpatients in the same area of a pig farm (Liu et al., 2016). Therefore, awareness of this gene's transferable properties is of great concern because colistin is currently considered one of the last-resort treatments for XDR microorganisms.

7.1 The Variation of MCR

After the MCR-1 discovery, many surveillance programs discovered MCR variation. The nomenclature of *mcr* genes was proposed in 2018 (Partridge et al., 2018). As of January 2022, ten *mcr*-gene families with more than 100 variants have been reported in GenBank. The highest number of MCR variants was found in MCR-3 followed by MCR-1, with 42 and 32 variants, respectively (Medicine, 2022). Only MCR-6 and MCR-7 showed one variant each. MCR-5, MCR-8, and MCR-10 all had four variants. The rest of the MCR families, i.e., MCR-2, MCR-4, and MCR-9, have 8, 6, and 3 variants, respectively. The phylogenetic tree of the MCR families is shown in **Figure 2**.

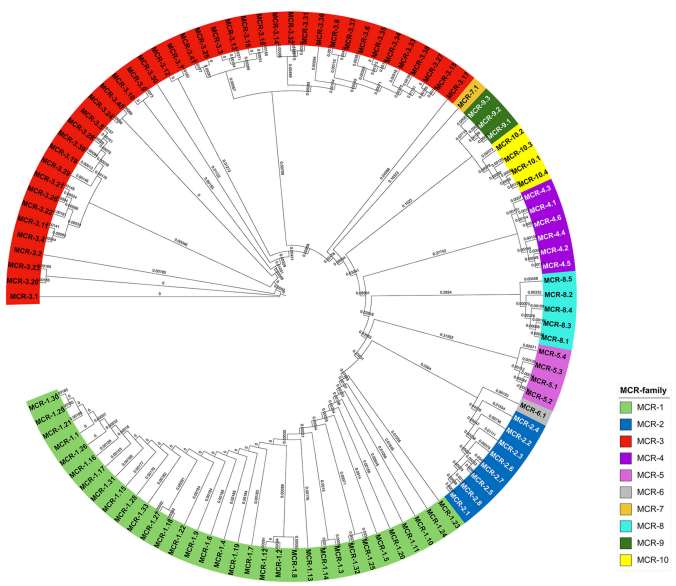


FIGURE 2 | The phylogenetic tree of MCR-gene variants using the Neighbor-Joining method alignment. Multiple sequence alignment was calculated by the clustal omega (Madeira et al., 2019), and the results were illustrated by the Interactive Tree of Life (Letunic and Bork, 2021).

7.2 The Epidemiology of the *mcr* Gene

The discovery of the *mcr* gene occurred from a surveillance study in China before it spread around the world (Liu et al., 2016). In 2016, many countries across all continents except Australia reported the discovery of MCR-1 (**Table 1**). Most MCR-harboring microorganisms belong to the Enterobacterales order, such as *E. coli*, *Salmonella* spp., and *K. pneumoniae*. Apart from Enterobacterales, colistin was also considered a last-resort antibiotic option for non-fermentative Gram-negative bacteria, *Acinetobacter* spp., and *P. aeruginosa*. *Pseudomonas* spp. and *Acinetobacter* spp. are the most common microorganisms that cause nosocomial infections. They have many intrinsic resistance mechanisms and readily acquire transmissible antibiotic resistance genes, which limit antibiotic treatment options. These organisms belong to ESKAPE (*Enterococcus faecium*, *Staphylococcus aureus*, *K. pneumoniae*, *A. baumannii*, *P. aeruginosa*, and Enterobacteriaceae), a group of bacteria that are considered an emerging threat in this century (Boucher et al., 2009). Transferable colistin resistance

TABLE 1 | List of countries that reported the *mcr-1* gene in 2016.

Continent	Country	List of organisms	Source of specimens	Reference
Africa	Algeria	*E. coli*	A, C	(Berrazeg et al., 2016; Olaitan et al., 2016)
	Egypt	*E. coli*	A, C	(Elnahriry et al., 2016; Khalifa et al., 2016)
	South Africa	*E. coli*	A, C	(Perreten et al., 2016; Poirel et al., 2016)
	Tunisia	*E. coli*	A	(Grami et al., 2016)
Asia	Bahrain	*E. coli*	C	(Sonnevend et al., 2016)
	Cambodia	*E. coli*	C	(Stoesser et al., 2016)
	China	*E. coli*	A, C	(Li et al., 2016; Liu et al., 2016; Zeng et al., 2016; Zhao and Zong, 2016)
		K. pneumoniae	A,C	
		E. aerogenes	C	
		E. cloacae	C	
		Kluyvera ascorbata	E	
		S. entirica	A	
	Japan	*E. coli*	A	(Kusumoto et al., 2016; Suzuki et al., 2016)
		S. enterica	A	
	Laos	*E. coli*	A, C	(Olaitan et al., 2016)
		K. pneumoniae	C	(Rolain et al., 2016)
	Malaysia	*E. coli*	A, E, C	(Yu et al., 2016)
	Pakistan	*E. coli*	C	(Mohsin et al., 2017)
	Singapore	*E. coli*	C	(Teo et al., 2016a; Teo et al., 2016b)
		E. aerogenes	C	
		K. pneumoniae	C	
	Saudi Arabia	*E. coli*	C	(Sonnevend et al., 2016)
	South Korea	*E. coli*	A	(Lim et al., 2016)
	Thailand	*E. coli*	C	(Olaitan et al., 2016)
	United Arab Emirates	*E. coli*	C	(Sonnevend et al., 2016)
	Vietnam	*E. coli*	A	(Malhotra-Kumar et al., 2016b)
		Shigella sonnei	C	(Pham Thanh et al., 2016)
Australia	–			
Europe	Denmark	*E. coli*	A, C	(Hasman et al., 2015)
	Estonia	*E. coli*	A	(Brauer et al., 2016)
	Germany	*E. coli*	A, C	(Falgenhauer et al., 2016)
	France	*Salmonella* spp.	A	(Webb et al., 2016)
		E. coli	A	(Haenni et al., 2016)
		K. pneumoniae	C	(Rolain et al., 2016)
	Belgium	*E. coli#*	A	(Malhotra-Kumar et al., 2016a; Xavier et al., 2016)
	Italy	*E. coli*	A, C	(Cannatelli et al., 2016; Carnevali et al., 2016; Di Pilato et al., 2016; Zogg et al., 2016)
		*K. pneumoniae**	C	
		Salmonella spp.	A, C	
	Lithuania	*E. coli*	A	(Ruzauskas and Vaskeviciute, 2016)
	Netherlands	*E. coli*,	A, C	(Arcilla et al., 2016; Kluytmans-van den Bergh et al., 2016; Veldman et al., 2016)
		Salmonella spp.	A	
	Norway	*E. coli*	C	(Solheim et al., 2016)
	Poland	*E. coli*	C	(Izdebski et al., 2016)
	Portugal	*E. coli*	E	(Campos et al., 2016; Figueiredo et al., 2016; Jones-Dias et al., 2016)
		Salmonella spp.	A, C	
	Russia	*E. coli*	C	(Castanheira et al., 2016)
	Spain	*E. coli*	A, C	(Prim et al., 2016; Quesada et al., 2016)
		Salmonella spp.	A	
	Sweden	*E. coli*	C	(Vading et al., 2016)

(Continued)

TABLE 1 | Continued

Continent	Country	List of organisms	Source of specimens	Reference
	Switzerland	*E. coli*	E, C	(Zurfuh et al., 2016) (Nordmann et al., 2016c)
	United Kingdom	*E. coli*	C	(Doumith et al., 2016)
		S. enterica	A, C	
North America	Canada	*E. coli*	A, C	(Mulvey et al., 2016)
	United States of America	*E. coli*	A, C	(McGann et al., 2016; Meinersmann et al., 2016)
South America	Argentina	*E. coli*	A, C	(Liakopoulos et al., 2016; Rapoport et al., 2016)
	Brazil	*E. coli*	A	(Fernandes et al., 2016)
	Ecuador	*E. coli*	C	(Ortega-Paredes et al., 2016)
	Venezuela	*E. coli*	A, C	(Delgado-Blas et al., 2016)

*A, animal sources; C, clinical sources; E, environmental sources; *mcr1.2 gene reported; #mcr-1 and mcr-2 gene reported.*

mechanisms in these organisms are a serious problem in the healthcare setting. Therefore, monitoring the *mcr* gene in non-fermentative Gram-negative bacteria is necessary to combat multidrug resistance.

7.2.1 The Epidemiology of the *mcr* Gene in *Pseudomonas* spp.

MCR-1 is the major MCR family member found in *Pseudomonas* spp. (**Table 2**). *Pseudomonas* spp. harboring the *mcr*-gene have been reported by at least one country in all continents, except Australia (**Figure 3**). *P. aeruginosa* is a major species of *Pseudomonas* that harbors the *mcr* gene. There are also some reports of *mcr* genes in *Pseudomonas putida* (Caselli et al., 2018; Ara et al., 2021). PCR is used as the primary detection method for *mcr* genes in *Pseudomonas* spp. However, the first report of *Pseudomonas* spp. carrying the *mcr* gene by Snesrud et al. used the WGS method combining short-read and long-read sequences (Snesrud et al., 2018). Moreover, they also

TABLE 2 | Summary of the *mcr* gene identified in *Pseudomonas* spp., specimen description, MCR family, and susceptibility profile.

Country	Sources of samples [details (if any)]	Detection method	Year of sample collection	Genus species	MCR family	Number of detected samples	Susceptibility profile (μg/ml) (determination method)	Reference
Bangladesh	Clinical samples (urine)	PCR	2017–2018	*P. putida*	MCR-1	3	32–128 (Agar dilution)	(Ara et al., 2021)
Brazil	Clinical sample (urine)	PCR	2015–2016	*P. aeruginosa*	MCR-1	1	≥8 (Vitek R 2 Compact)	(Nitz et al., 2021)
Brazil	Animal samples (ear swabs from cat and dog)	PCR	2018–2020	*Pseudomonas* spp.	MCR-1	11	n/a (Disk diffusion)	(Martins et al., 2022)
Egypt	Clinical samples	PCR	No data	*P. aeruginosa*	MCR-1	8	8–256 (Agar dilution)	(Abd El-Baky et al., 2020)
Egypt	Animal samples (bird feces)	PCR	2017–2018	*P. aeruginosa*	MCR-1	6	n/d	(Ahmed et al., 2019)
					MCR-2	1	n/d	
Egypt	Animal samples (milk from dairy cows)	PCR	2018–2020	*P. aeruginosa*	MCR-1	3	32–>128 (Broth microdilution)	(Tartor et al., 2021)
					MCR-2	1	128 (Broth microdilution)	
					MCR-3	3	16–64 (Broth microdilution)	
					MCR-7	1	128 (Broth microdilution)	
Egypt	Clinical sample	PCR	2019	*P. aeruginosa*	MCR-1	1	≥4 (E-test®)	(Shabban et al., 2020)
Iran	Clinical samples (burn and wound)	PCR	2017–2018	*P. aeruginosa*	MCR-1	3	>4 (Broth microdilution)	(Tahmasebi et al., 2020b)
Iran	Clinical samples (blood)	PCR	2018–2019	*P. aeruginosa*	MCR-1	10	≥4 (E-test®)	(Tahmasebi et al., 2020a)

(Continued)

TABLE 2 | Continued

Country	Sources of samples [details (if any)]	Detection method	Year of sample collection	Genus species	MCR family	Number of detected samples	Susceptibility profile (μg/ml) (determination method)	Reference
Italy	Environment sample (hospital surfaces)	PCR	2016–2017	*P. aeruginosa*	MCR-1	1	4 (Broth microdilution)	(Caselli et al., 2018)
				P. putida	MCR-1	1	8 (Broth microdilution)	
Japan	Environment sample (soil)	WGS	1983	*P. aeruginosa*	MCR-5[a]	1	n/a	(Fujihara et al., 2015)
Pakistan	Clinical sample (urine)	PCR	2017–2018	*P. aeruginosa*	MCR-1	1	16 (Broth microdilution)	(Hameed et al., 2019)
Pakistan	Animal sample	PCR	No data (18 months)	*P. aeruginosa*	MCR-1	1	≥8 (SensiTest™ Colistin)	(Javed et al., 2020)
Pakistan	Clinical samples (urine, wound)	PCR	No data (6 months)	*P. aeruginosa*	MCR-1	2	≥4 (SensiTest™ Colistin)	(Ejaz et al., 2021)
United States of America	Clinical sample (wound)	WGS (short read and long read)	2012	*P. aeruginosa*	MCR-5	1	4 (Broth microdilution)	(Snesrud et al., 2018)

[a]*Antimicrobial resistance gene database (NCBI). n/d, not determined; n/a, no data available.*

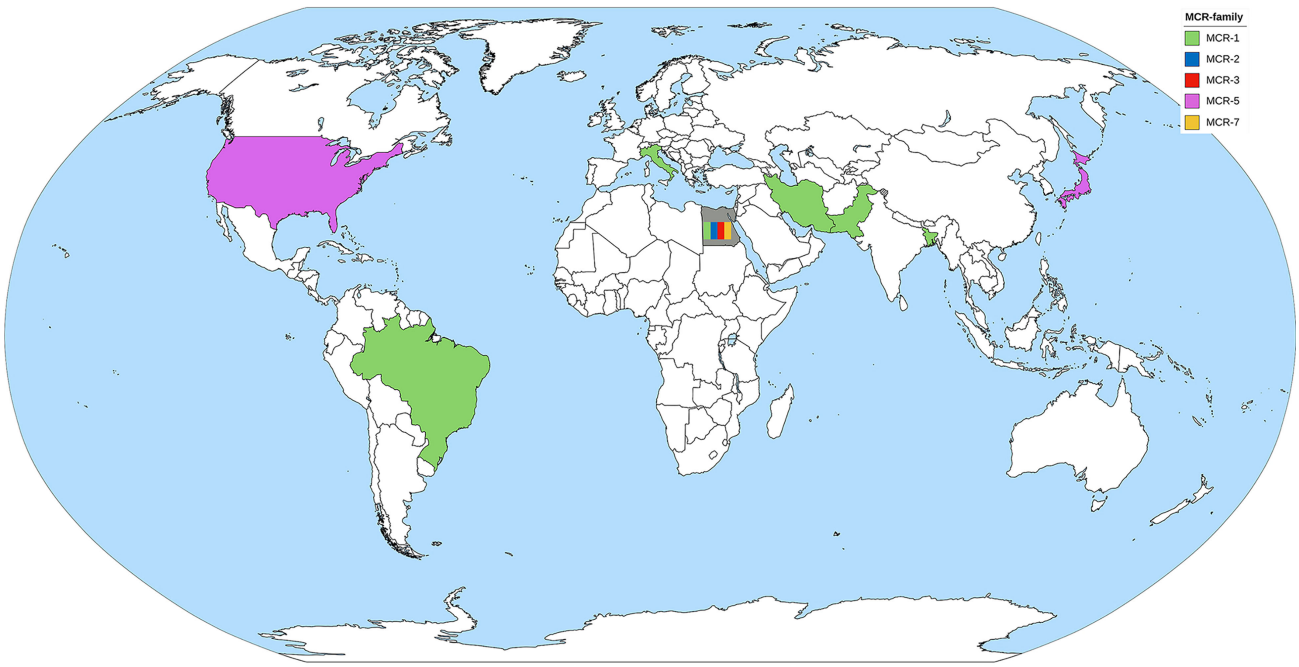


FIGURE 3 | The worldwide dissemination of the *mcr* gene in *Pseudomonas* spp. Countries that reported only one type of *mcr* gene were colored to represent the *mcr* gene. The country that reported more than one type of *mcr* gene was filled with gray background containing color bands of the reported *mcr* gene.

found that the *mcr*-5 gene was located within a Tn3-like transposon structure on the chromosome (Snesrud et al., 2018). Considering a health approach, animal and environmental sources may also be reservoirs of *mcr* genes. Ahmed et al. collected fecal samples from migratory birds in Egypt during the winter season and detected MCR-1 in *P. aeruginosa* (Ahmed et al., 2019). Some studies have detected *mcr* genes in cow's milk, animal meat, and soil (Fujihara et al., 2015; Javed et al., 2020; Tartor et al., 2021). It is noteworthy that the oldest specimen was retrieved from the environment in 1983 but was never recognized until the WGS era (Fujihara et al., 2015). Therefore, dissemination of the *mcr* gene in the environment *via* animal hosts is another issue that needs to be considered.

Because of the low incidence of the *mcr* gene in *Pseudomonas* compared to other microorganisms in ESKAPE pathogens, this raises the question of the fitness barrier or transferability properties of the *mcr* gene among *Pseudomonas*. The transmissibility of *mcr* genes in *P. aeruginosa* was demonstrated by Tartor et al. *via* conjugation with *E. coli* J53 (Tartor et al., 2021). Four *mcr* genes, *mcr*-1, *mcr*-2, *mcr*-3, and *mcr*-7, were able to transfer into the recipient bacteria and increased the MIC of the recipient cells up to 64 μg/ml (Tartor et al., 2021). Cervoni et al. also demonstrated that MCR-1 increases colistin resistance in recipient cells. Moreover, the expression of MCR-1 in *Pseudomonas* does not affect bacterial growth or cell envelope homeostasis (Cervoni et al., 2021).

7.2.2 The Epidemiology of the *mcr* Gene in *Acinetobacter* spp.

MCR-1 and MCR-4 are the major MCR families reported in *Acinetobacter* spp. (**Table 3**). Other *mcr* genes found in *A. baumannii* include *mcr*-2 and *mcr*-3 (Al-Kadmy et al., 2020). Reports of MCR harboring *Acinetobacter* spp. have been obtained from all continents, except North America and Australia (**Figure 4**). The oldest *Acinetobacter* specimen in which *mcr* genes were identified was from a stored clinical sample retained from a patient in Brazil in 2008, indicating that the *mcr* gene circulated for quite a period prior to its discovery by Liu et al. in 2015 (Martins-Sorenson et al., 2020). PCR has been used in *Acinetobacter* spp. for *mcr* gene detection, but short- and long-read WGS has been

TABLE 3 | Summary of the *mcr* gene identified in *Acinetobacter* spp., specimen description, MCR family, and susceptibility profile.

Country	Sources of samples [details if any]	Detection method	Year of sample collection	Genus species	MCR family	Number of detected samples	Susceptibility profile (μg/ml) (determination method)	Reference
Brazil	Clinical sample (cerebrospinal fluid)	WGS	2008	*A. baumannii*	MCR-4.3	1	64 (Broth dilution)	(Martins-Sorenson et al., 2020)
China	Clinical sample	PCR	2018	*A. baumannii*	MCR-1.1	1	8 (Broth microdilution)	(Fan et al., 2020)
China	Animal sample (pig feces)	WGS	2018	*A. baumannii*	MCR-4.3	1	8 (Broth dilution)	(Hameed et al., 2019)
China	Animal sample (pig lung)	WGS	2018[a]	*A. pittii*	MCR-1[b]	1	n/a	(Yang and Zhang, 2018)
Czech Republic	Animals sample (imported aquaculture products)	WGS	2019	*A. baumannii*	MCR-4.3	1	>16 (Broth microdilution)	(Kalova et al., 2021)
				A. nosocomialis	MCR-4.3	1	>16 (Broth microdilution)	
Czech Republic	Animal sample (imported raw turkey liver)	WGS	2017	*A. baumannii*	MCR-4.3	1	16 (Broth microdilution)	(Bitar et al., 2019)
	Clinical sample (tracheal)	WGS	2017	*A. baumannii*	MCR-4.3	1	16 (Broth microdilution)	
Egypt	Clinical samples	PCR	2019	*A. baumannii*	MCR-1	2	≥4 (E-test®)	(Shabban et al., 2020)
Finland	Environment sample (paper pulp mill)	WGS	2020[a]	*A. baumannii*	MCR-4[b]	1	n/a	(Hamidian et al., 2020)
Iraq	Clinical samples	PCR	2014–2018	*A. baumannii*	MCR-1	22	≥4 (Broth microdilution)	(Kareem, 2020)
Iraq	Clinical and environmental samples	PCR	2016–2018	*A. baumannii*	MCR-1 MCR-2 MCR-3	89 78 82	>2 (Broth microdilution)	(Al-Kadmy et al., 2020)
Italy	Environment samples (hospital surfaces)	PCR	2016–2017	*A. lwoffii*	MCR-1	4	4-8 (Broth microdilution)	(Caselli et al., 2018)
Pakistan	Clinical sample (blood)	PCR	2017–2018	*A. baumannii*	MCR-1	1	16 (Agar dilution and broth microdilution)	(Hameed et al., 2019)
Pakistan	Clinical samples (pus, wound, tracheal)	PCR	No data (6 months)	*A. baumannii*	MCR-1	3	≥4 (SensiTest™ colistin)	(Ejaz et al., 2021)
Republic of Korea	Animal sample (imported pork)	WGS	2019	*A. nosocomialis*	MCR-4.3	1	16 (Broth microdilution)	(Cha et al., 2021)
South Africa	Clinical sample	PCR, WGS	2017	*A. nosocomialis*	MCR-4.3	1	16 (Broth microdilution and SensiTest™ Colistin)	(Snyman et al., 2021)
Thailand	Clinical sample	WGS	2010	*A. nosocomialis*	MCR-4.3[b]	1	n/a	(Kamolvit et al., 2014)

[a]*Year of genome assembly.*

[b]*Antimicrobial resistance gene database (NCBI); n/a, no data available.*

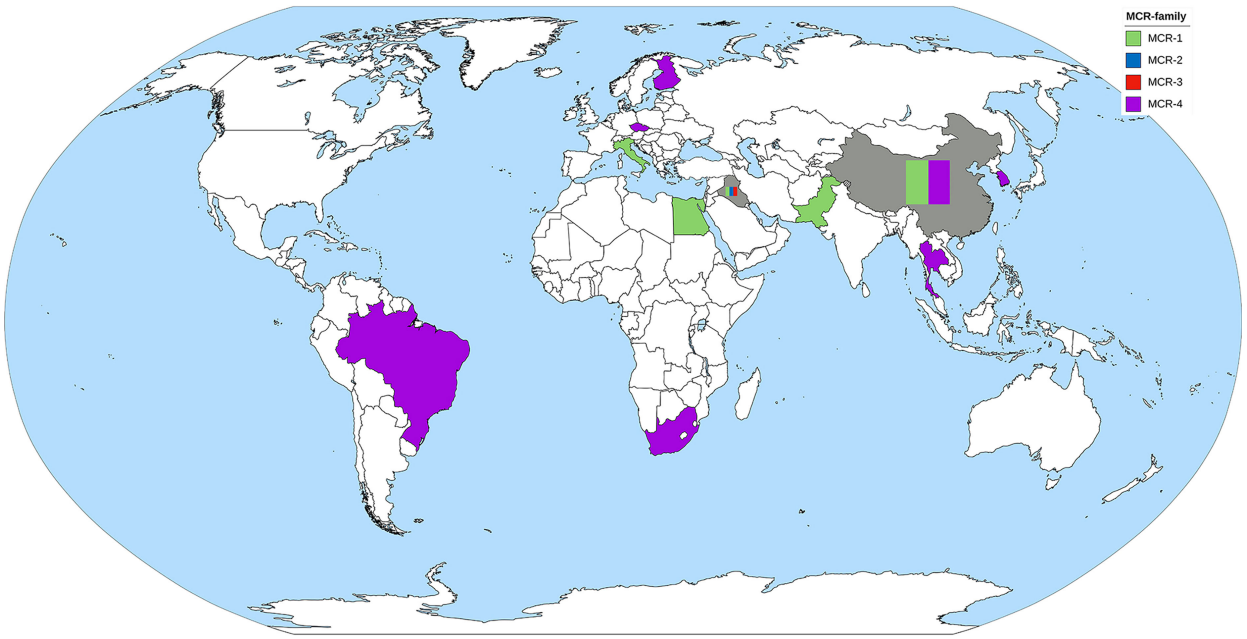


FIGURE 4 | The worldwide dissemination of the *mcr* gene in *Acinetobacter* spp. Countries that reported only one type of *mcr* gene were colored to represent the *mcr* gene. Countries that reported more than one type of *mcr* gene were filled with gray background containing color bands of the reported *mcr* gene.

TABLE 4 | Location of the *mcr* gene in *Acinetobacter* spp. and surrounding mobile genetic elements.

Bacteria strain	MCR family	Type of WGS	Gene location	Mobile genetic elements surrounding MCR gene	Year of sample collection	Reference
A. baumannii 597A	MCR-4.3	Short and long read	pAb-MCR4.3	-Tn3-family transposon -Insertion sequence IS*Aba19*	2008	(Martins-Sorenson et al., 2020)
A. baumannii LEV1449/17Ec	MCR-4.3	Short and long read	pEC_mcr4.3 (nonconjugative and nontransformable plasmid)	Insertion sequence IS*Aba19*	2017	(Bitar et al., 2019)
A. baumannii 39741	MCR-4.3	Short and long read	pEH _mcr4.3 (nonconjugative and nontransformable plasmid)	Insertion sequence IS*Aba19*	2017	(Bitar et al., 2019)
A. nosocomialis CAC13	MCR-4.3	Short and long read	Plasmid pCAC13a	-IS3 family transposase (IS*Aba19*) -Tn3 family transposase (IS*Psy42*)	2017	(Snyman et al., 2021)
A. baumannii AB18PR065	MCR-4.3	Short read	pAB18PR065 (nonconjugative plasmid)	Tn3 element	2018	(Hameed et al., 2019)
A. baumannii CT263	MCR-4.3	Short and long read	Untypeable plasmid	Tn3 family transpose IS*Psy42*	2019	(Kalova et al., 2021)
A. nosocomialis KUFSE-ACN036	MCR-4.3	Short read	Unidentified location due to the limitation of the short-read WGS technique	-Insertion sequence IS*Aba19* -Transposase	2019	(Kalova et al., 2021)
A. nosocomialis CT237	MCR-4.3	Short and long read	Untypeable plasmid	Tn3 family transpose IS*Psy42*	2019	(Cha et al., 2021)

applied in *Acinetobacter* spp. genome studies and many mobile genetic elements involved in gene transfer have been identified (**Table 4**). While *A. baumannii* has been shown to harbor a plasmid carrying the *mcr* gene, plasmids in *A. nosocomialis* have also been reported (Cha et al., 2021; Kalova et al., 2021; Snyman et al., 2021). The *mcr*-4.3 gene in *Acinetobacter* spp. was found on a plasmid surrounding the transposon Tn3-family and/or insertion sequence. These mobile genetic elements are important for the transfer of many antibiotic resistance genes. Interestingly, some of these plasmids were unable to conjugate and/or were transferable between bacterial species.

8 CONCLUDING REMARKS

Colistin is recognized as a highly toxic old-generation antimicrobial agent. Owing to the shortage of antibiotic options in fighting against MDR Gram-negative bacteria, this

drug was reintroduced into the clinical setting and has been recognized as one of the last-resort drugs. Non-fermentative Gram-negative bacteria such as *A. baumannii* and *P. aeruginosa* are already recognized as major threats in this century; when combined with resistance to last-resort antibiotics, the severity of the situation is critical. The resistance mechanism against colistin is considered to be chromosomally encoded and difficult to transfer. MCR was discovered in 2015, and several investigations have been subsequently published. To date, ten families of the *mcr* gene with more than 100 variants have been registered. More efforts are now being made to address this issue, and rapid detection with a high-sensitivity method is essential to track the resistance pattern. A sophisticated approach, such as WGS, is also needed to enhance the knowledge of resistance mechanisms. While waiting for the discovery of a rapid detection technique and more information, a strategy to control the resistant pathogens should be implemented along with the antibiotic stewardship program, which is recognized as a good practice in hospital settings.

AUTHOR CONTRIBUTIONS

PK wrote the manuscript and conceived the figures. MC and KT reviewed the manuscript draft. All authors contributed to the article and approved the submitted version.

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