

Global Epidemiology on Colistin Resistant *Acinetobacter baumannii*

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Abstract

While colistin remains a last resort agent to treat multi-drug resistant *Acinetobacter baumannii*, resistance to colistin has been reported throughout the world. The resistance has been attributed to mutations in lipid A biosynthesis genes and point mutation in PmrAB-two component response regulator and sensor kinase system. The emergence of plasmid mediated colistin resistance (*mcr-1*), in multidrug-resistant enterobacteriaceae raised concerns, though *mcr-1* has not yet been reported in *A. baumannii*. Lately, colistin resistance has been attributed to efflux pumps belonging to RND family. While various reports of emergence of colistin resistance are associated with previous treatment with colistin, other reports concern patients without any prior therapy.

Keywords: Colistin resistance; *A. baumannii*; Global reports; Nosocomial pathogen

Introduction

Acinetobacter baumannii is a Gram negative, non-fermenting, opportunistic isolate, that is recognized as a major nosocomial pathogen. It can cause infections at various anatomical sites; bacteremia, pneumonia, meningitis and urinary tract infection, most commonly in immunocompromised and critical care patients. The capacity to endure on dry surfaces and its relative resistance to disinfectants allows this non-fermenter to survive well in the hospital environment [1]. *A. baumannii* isolates are resistant to almost all available antibiotics including β -lactams, fluoroquinolones, tetracyclines, aminoglycosides and carbapenems [2]. More importantly, pandrug-resistant and extremely drug-resistant isolates have emerged [3] and are on the rise worldwide. Colistin (polymyxin E) and tigecycline are frequently the only antibiotics remaining to treat multidrug resistant (MDR) *A. baumannii* infections [4]. However, hetero-resistance and resistance against colistin have been reported in clinical settings throughout the world [5]. Here we review the reports all over the world and epidemiology of colistin resistance in *A. baumannii*.

Resistance against Colistin

Colistin, a natural substance produced by *Bacillus polymyxa* and a cationic lipopeptide (cyclic decapeptide) discovered in 1949. It has not typically been included in regimens to treat *Acinetobacter* infections because (Albeit debatable) of its neurotoxicity and nephrotoxicity. However, it has been as a therapeutic option for the treatment of ventilator associated pneumonia caused by drug resistant gram-negative organism [6]. Colistimethate sodium and Colistin sulfate are two commercially available forms and recently colistin has progressively been used as rescue therapy for severe infections in critically ill patients [7]. It is bactericidal against Gram negative bacteria; its amphiphilic nature allows it to interact with lipid A moiety of lipopolysaccharide (LPS) causing disarray in the bacterial

outermembrane. Colistin consists of cyclic heptapeptide covalently attached to a fatty acyl chain [8]. Typically colistin resistance is by chromosomally mediated modulations. There is relatively little research has been done on colistin resistance in *A. baumannii* and there are two main hypotheses of colistin resistance.

The first hypothesis of colistin resistance is mediated by loss of LPS production, caused by mutations in any of lipid A biosynthesis genes (*lpxA*, *lpxC* and *lpxD*) terminating complete production of LPS. Furthermore, presence of insertion sequence *ISAbal1* in either *lpxC* or *lpxA* not only causes loss of LPS production but also causes high level colistin resistance [9]. In countering to total LPS loss, *A. baumannii* modify the expression of critical transport and biosynthesis systems associated with modulating the composition and structure of the bacterial surface. Eventually, LPS deficiency causes less negative charge and thus might be the reason for the loss of affinity towards colistin [10].

Secondly, colistin resistance has been hypothesized to PmrAB-two component response regulator and sensor kinase system. This system allows bacteria to sense and respond to various environmental conditions such as pH or Fe³⁺ and Mg²⁺ levels, also affecting expression of genes implicated in lipid A modification and thus causing colistin resistance [11]. Point mutations in *pmrA* and *pmrB* genes of PmrAB two-component regulatory system showed upregulated expression of *pmrAB*. The increase expression results in remodeling of bacterial membrane causing decreased membrane permeability [12].

Recently, colistin resistance has shown to be singularly due to plasmid mediated *mcr-1* gene. Although there is no report of *mcr-1* being detected in *A. baumannii*, the prevalence has been investigated in *E. coli* and *K. pneumoniae* [13,14]. If *mcr-1* gene is similar to *NDM-1* colistin resistance could become endemic in the world. The rapid dissemination of previous antibiotic resistance indicates that, with the advent of transmissible colistin resistance, progression of *A. baumannii* from multidrug to pandrug resistance is unavoidable. Although the levels of maximum inhibitory concentration of colistin are not high (4–8 mg/L), acquaintance of *mcr-1* by carbapenem

resistance *A. baumannii* isolates will make them resistance to all antibiotics [14]. The potential of *mcr-1* to become global depend upon several factors: use of irrational doses of colistin, the stability of *mcr-1* mediated plasmid and their ability to transfer in humans. Effective strategies that limit selection and further dissemination of plasmid-associated *mcr-1* are clearly needed. It is important to prevent the dissemination of colistin by developing agents which provide effective reverse resistance strategies.

Lately, colistin resistance has been found due to efflux pumps [15] in which efflux pump inhibitors (EPIs) were used to suppressed colistin resistance. Colistin resistance has been attributed to efflux pumps belonging to RND (resistance-nodulation-cell division) family [16]. The efflux pump consists of two component regulatory system mediating adaptive response of bacterial cells to a range of environmental stimuli. Genes are organized as operon *adeA*, *adeB*, and *adeC* and regulated by *adeR* gene. *adeA* is a membrane fusion protein and *adeC* is an outer membrane protein channel, in which *adeB* acquire its substrate and transports from cytoplasm or within phospholipid bilayer to extracellular medium [17].

Global Epidemiology of Colistin Resistance

Colistin resistance has been reported all over the world. The highest resistance was reported from Asia followed by Europe and others parts of the globe. Colistin resistance have been uncommon during 90s, however, the first case was reported from Czech Republic in 1999 [18]. The Clinical and Laboratory Standards Institute (CLSI) has selected an MIC of ≤ 2 $\mu\text{g/ml}$ as susceptible and an MIC of ≥ 4 $\mu\text{g/ml}$ as resistant for colistin [19]. Furthermore, SENTRY antimicrobial surveillance reported from 2006 to 2009 showed *Acinetobacter* isolates with polymyxin B MIC ≥ 4 $\mu\text{g/ml}$ were detected in all regions with highest occurrence in the USA (1.1%), followed by Latin America (0.9%), the APAC region (0.7%) and Europe (0.4%) [18]. Indeed, a surveillance study of USA hospitals revealed that all 5.3% of all *Acinetobacter* isolates are resistant to colistin [20]. Since then, there are numerous reports across the world increasing every year. Emergence of colistin resistant *A. baumannii* has been observed in several countries;

moreover, since 2011 many reports were recorded. In most of the cases, colistin resistance was attributed to mutations in lipid A biosynthesis genes and PmrAB two-component regulatory system. The bacteria were isolates from sputum, nasal aspirate, wound, urine; however, blood remained predominant source of isolation.

Most of the reports observed colistin resistance at ≥ 4 $\mu\text{g/ml}$; however, some reported higher folds of resistance. A study from Australia [19] reporting colistin heteroresistant isolates 15 *A. baumannii* by population analysis profiling (PAP). The clinical isolate contained resistant subpopulations that grew in the presence of up to 10 μg of colistin (sulfate)/ml, even though both had an MIC of 1.0 $\mu\text{g/ml}$ and one isolate was able to grow in MIC >128 and 32 $\mu\text{g/ml}$, respectively. Case histories of the patients showed from whom the isolates in the study were obtained had not been exposed previously to colistin, since it was only recently introduced in this hospital due to infections caused by multidrug-resistant *A. baumannii*; it is never used by inhalation or for prophylaxis. Thus, the heteroresistance observed in the present study is unlikely to be related to previous exposure to colistin. As a result of the substantially decreased proportion of the colistin-resistant subpopulations after passage in drug-free broth it is very likely that they were not stable mutators. Heteroresistance has been noticed in many countries including Italy [21], in which no colistin resistant isolate was found in ICU survey took place in October 2008-march 2009; however, restricted outbreak of colistin resistance were recorded in different time periods. In the first case colistin resistant isolate was recovered on the day 20th of hospitalization in January 2010. Approximately a year later 3 cases of colistin resistance were identified from two patients hospitalized three months apart. Another study from USA [20] reported high mortality rates among almost all patients suffering from ventilator-associated pneumoniae treated with colistin combination therapy in the presence of colistin resistance. The clinical importance of colistin-resistant strains may be seen in the context of heteroresistance in *A. baumannii* strains and the emergence of colistin-resistant pathogens following treatment of MDR isolates with colistin [21,22]. In Argentina [23] heteroresistance was determined by plaque efficiency in 14 isolates of them with a greater than 8 fold increase in MIC in some cases summarized in Table 1.

Country	Colistin MIC ($\mu\text{g/ml}$) and resistance	Number of isolates	Source	Year	Antibiotic therapy	Mortality	Ref.
Australia	3-10 (heteroresistance)	15(93.7%)	sputum, nasal aspirate, wound, blood, urine, bronchoalveolar lavage samples	2006	no data	no data	[19]
Taiwan	4	14(10.4%)	blood	2012	no data	no data	[31]
South Korea	4	11(100%)	blood	2014	no data	no	[32]
Japan	4 (colistin resistance noticed after therapy)	1(100%)	sputum	2015	yes (piperacillin, tazobactam, colistin, minocycline)	no	[30]
USA	4-256 (colistin resistance noticed before therapy)	20(100%)	sputum, nasal aspirate, wound, blood, urine, bronchoalveolar lavage samples	2015	yes (colistin, doripenem, ampicillin-sulbactam)	30 day mortality 6 out of 20 patients	[20]
Argentina	2-16 (colistin heteroresistance)	14(18.7%)	blood	2011	no data	no	[23]

Iran	4	8(13%)	blood, bronchial secretions	2015	yes (colistin, rifampicin, tigecycline)	no	[16]
Jordan	4	2 (1.7%)	blood, sputum, urine, pus swab	2015	no data	no	[33]
India	0.016-256 (colistin resistance noticed after therapy)	8(16%)	urine	2011	yes (colistin, tigecycline, carbapenems)	no	[34]
Saudi Arabia	4	61(4.7%)	blood	2013	no data	no data	[28]
Kuwait	0.016-256	30 (12%)	respiratory tract, postoperative wound, urine, blood, cerebrospinal fluid (CSF)	2011	no data	no	[29]
Tunisia	2 (colistin resistance noticed after therapy)	1 (Case report)	blood	2015	yes (rifampicin, amikacin and colistin)	no	[35]
Algeria	16	1 (Case report)	blood	2015	no data	no data	[36]
Egypt	4-8	2(5%)	drain, urine	2014	no data	no data	[37]
Romania	4	2(1%)	blood, urine	2014	no data	no data	[38]
Greece	16-64	86(7.7%)	blood, bronchial secretions	2015	no data	no data	[5]
Portugal	4	9(4%)	blood, bronchial secretions	2007	no data	no data	[39]
Turkey	4	1(2.5%)	bronchial secretions	2015	no data	no data	[40]
Italy	32-256 (colistin resistance noticed before therapy)	9(34.6%)	blood, sputum, urine, pus swab, bronchial secretions	2014	yes (colistin, meropenem, tigecycline, teicoplanin, rifampicin)	no data	[21]
Spain	4 (colistin resistance noticed after therapy)	1 (Case report)	blood	2011	yes (vancomycin, meropenem, sulbactam, cefepime)	no	[26]
France	4 (colistin resistance noticed after therapy)	1 (Case report)	blood and urine	2011	yes (imipenem, amikacin, colistin)	no	[22]
Germany	128 (colistin resistance noticed before therapy)	1 (Case report)	skin and rectal swabs	2014	yes (colistin, meropenem, linezolid, fosfomycin, caspofungin)	no	[27]
Brazil	8-64	7(35%)	blood	2016	Vancomycin plus specific therapy	Yes (Non-specific colistin resistance)	[25]

Table 1: Global reports of emergence of colistin resistant *A. baumannii*.

In Iran 13% of isolates from ICU were found to be resistant to colistin, interestingly majority of isolates were also resistant to imipenem [16]. In a recent study [24] from Romania colistin resistant *A. baumannii* was isolated from bronchial suction from ICU. Another study from Brazil [25] reported 7 out of 20 isolates were colistin resistant in which 14 patients received therapy and 8 died during therapy and vancomycin plus colistin therapy showed highest synergy against colistin resistant isolates. There are various case reports from

Spain [26], France [22], Germany [27], Tunisia [28], Algeria [29] and Japan [30] reporting colistin resistance, however, reports from Germany and Japan showed colistin resistant *A. baumannii* were isolated from international travelers. All above colistin resistance reports have been summarized in Table 1.

Conclusion

Colistin, a last resort antibiotic available to treat infections caused by MDR *Acinetobacter baumannii* has received a lot of attention in last decade. Notwithstanding, increased prevalence of colistin resistance in *Acinetobacter* isolates has been reported throughout the world, albeit with a great variability in the occurrence in different geographic areas. The highest resistance rate was reported from Asia-Pacific followed by Europe, Americas and Africa. Furthermore, resistance in Northern Europe and Northern Asian countries has not been reported yet. There are reports from almost all Mediterranean countries like Turkey, Greece, Italy, Spain, Portugal, Egypt, Algeria and Tunisia. We could also speculate due to immigration from developing countries to Europe, there could have been transfer of colistin resistance. The intrinsic mechanisms of resistance are related to a loss of LPS or/and the PmrAB two-component system, additionally extrinsic colistin resistance has been attributed to cause by *mcr-1* genes carried on plasmids. With the ever increasing rate of infections that *A. baumannii* isolates can cause, the emergence of pan drug resistance signifies the need to introduce strict preventive measures in hospitals and to use novel agents or combination therapy. Although colistin resistance is increasing continuously, clinicians should carefully detect risk factors for its cause. Colistin resistance can be suppressed through reversing efflux pump activity by using EPIs such as cyanide 3-cholophenylhydrazone (CCCPC), phenyl-arginine- β -naphthylamide (PA β N), and 1-(1-naphthylmethyl)-piperazine (NMP) could be used. Earlier, *in vitro* study has shown CCCPC to significantly decrease MICs of colistin resistance strains [41]; PA β N and NMP can partially decrease MICs of colistin resistant *A. baumannii*. CCCPC restore negative charge of membrane through the disruption of proton motive force. However, CCCPC cannot be used clinically due to its intrinsic cytotoxicity and needs further investigation to nullify its cytotoxicity or develop new agents to protect the activity of colistin.

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