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Prevalence of Colistin Resistance among *Enterobacteriaceae*, A 10-year glance

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Abstract

Multidrug resistance is a global healthcare problem. Gram-negative organisms, particularly *Enterobacteriaceae* strains are responsible for almost 60% of nosocomial infections. Colistin acts as the last treatment resort in complicated, critical, and MDR cases; also become resistant in the last few years in an escalating manner. Its resistance has been reported almost all over the world. Since there is no alternative antibiotic of colistin-resistant isolates is available [1, 2]. The last year of 2020 was completely engaged with the Covid-19 pandemic for global healthcare systems. This issue is still persisting with no solution. Strict infection control policies and a noval antibiotic with lesser side effects are great in demand to resolve this issue [3].

We gathered 28 studies from 2010 that reported colistin resistance among *Enterobacteriaceae* throughout the world. Colistin resistance still reported and escalated globally with no available solution. Asia was the leading region with 50% of selected studies followed by Europe and *Klebsiella pneumonia* and *Klebsiella species* were the leading organisms of colistin resistance among *Enterobacteriaceae*.

This mini-review was designed to highlight the global importance of colistin-resistant isolates among Enterobacteriaceae, which still an unanswered question.

Keywords: Colistin; Colistin Resistance; *Enterobacteriaceae*; *Escherichia Coli*; *Klebsiella pneumoniae*

1. Introduction

Enterobacteriaceae is responsible for the major burden of gram-negative infections in both the hospital settings and community. The most common clinical pathogens reported globally among *Enterobacteriaceae* were *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus*, and *Enterobacter species*. Pathogens of hospital settings are always at greater risk of antibiotic resistance and new resistance mechanisms reported throughout the world [1]. Carbapenems were the absolute drug of choice and life saving for crucial *Enterobacteriaceae* infections. In the last 15 years, the resistance of carbapenem-resistant *Enterobacteriaceae* (CRE) was escalated globally leads to the only treatment choice was Colistin [2].

Colistin is a polymyxin, bactericidal polypeptide antibiotic that causes Gram negative's cell death by binding the lipopolysaccharides and phospholipids of the Cell membrane and cause intracellular leakage. It was first used in 1952, although, FDA-US has approved this antibiotic in 1959 for treating infections of Gram-negative organisms [3]. Commercially, two formations of colistin are available, colistin sulfate and colistimethate sodium (CMS). Colistin sulfate is easily accessible and widely used for oral and topical applications in many countries, and colistimethate sodium (CMS) is recommended for parenteral and aerosol treatment [3]. However, colistin was abandoned in the 1980s due to its potential side effects, toxicity, and availability of other antibiotic options. Prevalence of multidrug-resistant (MDR) isolates in the mid of 1990s increased both morbidity and mortality in critical hospitalized

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patients with nonavailability of new antibiotics [4]. Colistin was re-emerged as a last resort option with the defined guidelines of its use to minimize its adverse effects and potential toxicity and make it a safe option for MDR patients [5]. The global trouble was begun when reports of extensively drug-resistant (XDR), and pandrug-resistant (PDR) isolates were published from all over the world with no treatment choice left [6]. CRE and col-RE strains were reported from all over the world. Risk factor identification is also crucial to overcome the global spread and must need to implement the infection control strategies, healthcare surveillance, community control, and strict caution to prescribe broad-spectrum antibiotics especially Carbapenem and Colistin [1].

1.1. Mechanism of Colistin resistance

Colistin is a wide spectrum antibiotic against Gram-negative organisms and its resistance is a global threat. The earlier studies reported the resistance mechanism of Colistin in two ways, plasmid-mediated and chromosomal mutations. Additionally, a distinctive resistance mechanism of MCR-1 genes was reported in *Enterobacteriaceae* species. However, some strains of *Enterobacteriaceae* are intrinsically resistant to colistin including Proteus, Providencia, Morganella, Serratia, and Burkholderia. Most of the Carbapenem resistant isolates are susceptible to colistin, but not always in all cases. The alarming situation is rising because when CRE isolates are also resistant to colistin, there is no treatment choice is available [1, 7].

Colistin resistant isolates *Enterobacteriaceae* (col-RE) were reported throughout the world for the last 10 years, are great worrisome globally due to no development in any new antibiotic. This mini-review aimed to evaluate the prevalence of colistin resistance among *Enterobacteriaceae* globally.

2. Methods

2.1. Search strategy and inclusion criteria

Studies were searched through Pubmed, google scholar, Scopus, and all open online sources from 2010-2020 by using a combination of different keywords. All studies were based on clinical isolate testing, reported colistin-resistant isolate among *Enterobacteriaceae* were included in this review. We included the studies from the publication year of 2010, although, some studies even analyze the data from the year 1990 [16]. All included studies were published in English; this might miss data published in other languages.

3. Results

Twenty-eight studies from 2010-2020 were included in this review. The reported numbers of resistant isolates included in our study were 186 *Enterobacteriaceae,* 1408 *Klebsiella pneumonia,* and *Klebsiella specie,* 159 *Enterobacter aerogenes*, *Enterobacter cloacae, Enterobacter asburie, and Enterobacter specie,* 127 *Escherichia coli,* 08 *Citrobacter freundii*, 06 *Hafnia alvei*, 06 *Salmonella specie*, 04 *Pantoea species*. Our results confirm the colistin resistance prevalence globally. Studies reported from all over the world see Table 1. The last included study was published in 2020, although, colistin resistance data was included till 2018 [8]. Some studies did not report colistin resistance among strain distribution of *Enterobacteriaceae*, and reported collective resistance data, while some studies reported all strains like *Escherichia coli*, *Klebsiella pneumonia, Enterobacter, etc.* In included studies also reported *Klebsiella pneumonia* and *Klebsiella species* as a dominant strain in colistin resistance among *Enterobacteriaceae* [1]. Many *Enterobacteriaceae* strains are inheritally resistant to colistin and exclude from the study; including *Proteus mirabilis*, *Proteus Vulgaris*, *Morganella morganii*, *Providencia*, *Serratia marcescens*, and *Burkholderia* [7].

Table 1 Selected Studies of Colistin Resistance among Enterobacteriaceae spp. from 2010- 2020

S. No	First author, and reference number	Year of Study	City, Country	Continent	Strain	Number of strains	Total number of resistant strains
1	Toth et al, [9]	2010	Hungary	Europe	*Klebsiella pneumonia*	9	8
2	Lee et al, [10]	2011	Korea	Asia	*Enterobacteriaceae*	344	31
3	Morfin-otero et al, [11]	2005-2010	Mexico	North America	*Klebsiella spp.*	329	1
4	Morfin-otero et al, [11]	2005-2010	Mexico	North America	*Escherichia coli*	563	1
5	Zakeri et al, [12]	2012	Tabriz, Iran	Asia	*Escherichia coli*	200	12
6	Lübbert et al, [13]	2010-2012	Germany	Europe	*Klebsiella pneumonia*	90	17
7	Halaby et al, [4]	2001 and January 2008	The Netherlands	Europe	*Klebsiella pneumonia*	134	74
8	Marchaim et al, [14]	2008-2009	Michigan	North America	*Enterobacteriaceae*	92	15
9	Marzi et al, [15]	2012-2013	Turkey	Western Asia	*Enterobacteriaceae*	168	9
10	Yezli et al, [16]	1990 to 2013	Riyadh, Saudi Arabia	Asia	*Klebsiella pneumonia*	95	5
11	Qamar et al, [17]	2015 - 2016	Karachi, Pakistan	Asia	*Enterobacteriaceae*	251	40
12	Pourali et al [18]	2015	Shiraz, Iran	Asia	*Klebsiella pneumonia*	111	4
13	Bashir et al, [5]	2014	Karachi, Pakistan	Asia	*Escherichia coli*	476	2
14	Liassine et al, [19]	2016	Switzerland	Europe	*Klebsiella pneumonia*	2049	2

					Escherichia coli		2
					Hafnia alvei		1
					Salmonella specie		1
15	Bathoorn et al, [20]	2010 & 2013–14	Greece	Europe	*Klebsiella pneumonia*	34	21
16	Teo et al, [21]	2016	Singapore	Asia	*Escherichia coli*	166	2
					Klebsiella pneumonia	87	1
17	Prim et al, [22]	2012-2015	Spain	Europe	*Enterobacteriaceae*	13579	91
18	Ellem et al, [23]	2007-2016	Australia	Australia	*Klebsiella pneumonia*	4555	44
					Klebsiella oxytoca		8
					Escherichia coli		18
					Enterobacter specie		19
					Hafnia alvei		5
					Citrobacter freundii		2
19	Rossi et al, [24]	2010-2014	Brazil	South America	*Klebsiella pneumonia*	16533	975
					Enterobacter cloacae		86
					Enterobacter aerogenes		42
					Escherichia coli		36
					Citrobacter freundii		6
					Salmonella specie		5
					Pantoea specie		4
					Klebsiella ornithinolytica		3

					Enterobacter asburie		3
20	Aykac et al, [6]	2012-2016	Turkey	Western Asia	*Klebsiella spp.*	119	6
					Escherichia coli	67	2
21	Arjun et al, [25]	January 2014-June 2015	India	Asia	*Klebsiella pneumonia*	NR	21
					Escherichia coli		1
					Enterobacter spp.		1
22	Principe et al, [26]	2016	Italy	South-central Europe	*Escherichia coli*	3902	18
23	Moubareck et al, [27]	2015-2016	Dubai, United Arab Emirates	Asia	*Klebsiella pneumonia*	70	22
24	Akin et al, [28]	2014-2015	Turkey	Western Asia	*Klebsiella spp.*	135	15
25	Richter et al, [29]	January 2006 through November 2016	Los Angeles, California, USA	North America	*K. pneumoniae isolates*	4,557	128
					Enterobacter spp.	2423	8
					Escherichia spp.	10720	5
26	Lu et al, [30]	December 2015 and July 2016	Sichuan, China	Asia	*Klebsiella pneumonia*	112	5
27	Zafer et al, [31]	January 2016 and June 2017	Cairo, Egypt	Africa	*Klebsiella pneumonia*	234	22
					Escherichia coli	200	18
28	Santimaleeworagun et al, [8]	May 2017–April 2018	Thailand	Asia	*Klebsiella pneumonia*	124	26
					Escherichia coli	339	10

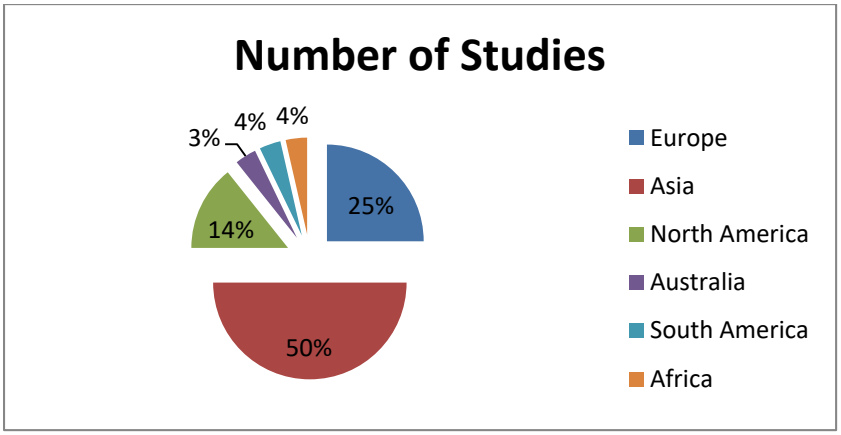

Figure 1 Continent wise distribution of included studie

4. Discussion

We designed this study to see the colistin resistance among clinical isolates of the *Enterobacteriaceae* family. *Enterobacteriaceae* is responsible for almost 60% of hospital-acquired infections with the most frequent clinically isolated strains were *Escherichia coli*, *Klebsiella pneumoniae*, and Enterobacter species [6, 16]. Multi-drug resistance among gram-negative bacteria is a global threat due to lesser treatment options available, difficulty to treatment, and resistance transfer potential. Studies reported South East Asia and the Mediterranean is the most prevalent zone of colistin resistance followed by Europe, rising in an escalating manner. However, the global prevalence is varied among continents and countries [3, 6]. Our study also confirms the colistin-resistance reporting from almost all over the world, including both developed countries like the USA, Europe, Australia, China, Switzerland, Singapore, The Netherlands Germany, Turkey, Italy, Korea, Greece, Spain, and developing ones like India, Pakistan, Saudi Arabia, Iran, Brazil, Dubai, Egypt, and Thailand. The overall reported colistin resistance was less than 10% but for those 10% cases, we have no alternate antibiotic [3]. The fortunate countries which not yet licensed colistin are in safe zone e.g. Japan and South Africa; we also have no resistant study reported from these countries [32, 33]. Some countries have restrictions towards colistin formulations availability; they used only parenteral formulation e.g. Europe, and Australia [33]. However, this strategy won't help in colistin resistance prevalence. We have reportedly high resistance of colistin from both of these continents [9, 23]. The countries that used both formulations of colistin either parenteral or topical are more in danger for its resistance escalation e.g. The United States, Brazil, Malaysia, and Singapore. Although, the pattern of colistin utilization is also varied between different states [33, 34]. However, our included studies did not have any clinical resistance reported from Malaysia, based on our inclusion criteria. Though, Malaysia has colistin-resistant isolates reported from pigs, chickens, chicken feed, water, and humans [34].

The mcr-1 gene (Mobilized Colistin Resistance) was responsible for colistin resistance and first isolated from China in 2011. Later, this mcr-1 gene was reported from Asia, Europe, Africa, North America, South America, and Oceania [35]. We did not analyze the genetic transfer of colistin resistance in our study, our included studies reported only colistin-resistant prevalence globally, leading one was from Asia and Mediterranean countries followed by Europe. We included 28 studies in our review from which 14 were reported from Asian countries.

Seven studies among the selected ones were reported from Europe. Our first included study was reported from Hungary, central Europe published in 2010. This study collected the non-susceptible carbapenem *Klebsiella pneumoniae* isolates from three different centers of Hungary, and reported the very first hyperepidemic clonal complex of MDR *Klebsiella pneumonia* with the possibility of global spread [9]. Later on, the prevalence of colistin resistance was escalated in Europe and reported in some large-scale studies. A study from Switzerland of 2049 urinary tract clinical isolates [19], 13579 isolates based study in 2017 [22], and 3902 evaluated isolates for colistin resistance in 2018 was reported from Europe [26].

Korea, Germany, Turkey, Greece, Singapore, Turkey and China also conducted small-scale studies and reported 109 colistin-resistant *Enterobacteriaceae* isolates from 2011-2016, see Table 1. The Netherlands reported the emergence of colistin-resistant isolates in ICU (intensive care unit) patients after Selective Digestive Tract Decontamination. This study reported 74 colistin-resistant isolates among ESBL-producing *Klebsiella pneumonia* from patients with the long treatment course of colistin. Data were collected from 2001 – 2008 [4].

The USA is one of the developed countries, also at great risk of colistin resistance. A large-scale retrospective study from Los Angeles, California, USA was published in 2018 with the included data of 10 years from 2006-2016 of 28,512 isolates [29], other small scale studies from Mexico and Michigan of 2012 and 2014 reported overall 17 resistant colistin isolates [11, 14]. A 13579 clinical isolate based study was reported from Spain in 2017, based on four-year data from 2012-2015. This study reported 0.7% colistin resistance among *Enterobacteriaceae* clinical isolates. The surprising fact was that the colistin resistance was not only restricted to MDR strains, and resistance was reported in even those patients who did not prescribe colistin therapy. This study found the mcr-1 gene only in *Escherichia coli* [22].

Among developing countries, Brazil reported a colistin resistance study based on 16533 isolates. The study was published in 2017, whereas data were analyzed from 2010-2014. The study was reported an alarming escalation of colistin-resistant isolates from 2010-2014 among *Enterobacteriaceae* especially in *Klebsiella pneumonia* from 82 resistant isolates to 347 isolates in a five-year period. [24]. Pakistan has reported two colistin-resistant *Enterobacteriaceae* isolates in 2016 based on 2014 isolated organisms [5]. Later on, 40 colistin resistant *Enterobacteriaceae* isolates were reported in 2017 from Pakistan [17]. A study from Cairo, Egypt published in 2019 reported 40 colistin resistant isolates from total of 434. This study reported a very high frequency of colistin resistance among *Enterobacteriaceae* [31]. The most recent publication was reported by Thailand in 2020 with 26 *Klebsiella pneumoniae* and 10 *Escherichia coli* [8].

Another interesting fact among the selected studies is colistin resistance in Anaerobes, not only aerobic strains of *Enterobacteriaceae* are at risk of colistin resistance but this resistance also reported in anaerobic organisms. *Hafnia alvei, Citrobacter freundii*, and *Pantoea species* were the reported colistin-resistant anaerobic organisms [19, 23, 24].

We concluded the prevalence of colistin resistance from all over the world including Asia, Europe, North America, Australia, South America, and Africa in the last ten years, see Figure 1. There are still no strict policies implemented to control this threat, and in the future, we have no therapeutic option available in replacement of colistin [1].

5. Conclusion

This study reported the important fact that colistin-resistant isolate is a threat to the health care community. There is no antibiotic available in replacement of colistin. This year 2020 was reportedly the "COVID year", but colistin-resistant isolates is still a worrisome with no alternative therapeutic available yet. Strict infection control and antibiotic policies should be implemented globally to control such resistance, and a new therapeutic is greatly needed with lesser side effects and high potency to overcome the reported threats like "colistin-resistant isolates".

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest reported.

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