Prevalence of different variants of *Klebsiella pneumoniae* in urine samples: A Review

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A thesis submitted to the Department of Mathematics and Natural Sciences in partial fulfillment of the requirements for the degree of
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Declaration

It is hereby declared that,

1. The thesis submitted is my original work while completing the degree at BRAC University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through complete and accurate referencing.
3. The thesis does not contain material that has been accepted or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all the primary sources of help.

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Approval

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Abstract

Klebsiella pneumoniae is a causative agent which is responsible for multiple infections along with pneumonia. Along with pneumonia, Urine infections are another symptom that is caused by to invasion of *Klebsiella*. It also causes blood steam infection (BSI), surgical site infection and pneumonia. *Klebsiella* was responsible for 7.4% of the overall prevalence of bacterial infections. In this study, we have reevaluated, summarized, and analyzed the prevalence of *Klebsiella pneumoniae* among pregnant, newborn, and different age groups all together as well as the extent of *Klebsiella pneumoniae* from urine samples worldwide. For example, Carbapenem-resistant bacteria According to a recent study*,* *Klebsiella pneumoniae* is the leading cause of human mortality owing to antibiotic resistance in Europe. Prevalence of *Klebsiella pneumoniae* is higher in Western, European, and African regions (100%, 98.70% and 91.67% in Ohio, Lisbon, and Algeria respectively). 3.63 % is the lowest percentage of *Klebsiella pneumoniae* found in urine samples in Taiwan. On the other hand, Enoxacin does not exhibit any antibiotic resistance in any of the samples that were obtained from the majority of nations, with the exception of Peshawar, Pakistan, where it exhibits 43.48% resistance. Conversely, urine samples obtained from patients in Saudi Arabia shown no resistance to Ampicillin and lacked multidrug resistance. With the exception of Malabo, patient urine samples from Ethiopia, Kenya, and Nigeria do not reveal multidrug resistance *to Klebsiella pneumoniae*. However, further research from Middle Eastern regions and third-world countries interprets the dangers of pneumonia as the main cause of urinary tract infection (UTI). Other causes of this symptom are inflammation, trouble in urination, Diabetes, hypertension, and many more hazards and consequences. *Klebsiella pneumoniae* causes trouble in breathing, tremor, blood infection, and bloody diarrhea. Different countries show the prevalence of *Klebsiella pneumoniae* and its antibiotic resistance along with risks.

Keywords

Prevalence, Antibiotic susceptibility, Urinary tract infections, microtubules, microfilaments, Hospital-acquired infection, Community-acquired pneumonia, aspiration pneumonia, and blood infection.

Dedication (Optional)

I intend to deliver this letter to my family; expressing gratitude for the motivation and support they have provided me.

Table of contents

List of Tables

List of acronyms

Acronyms	Explanation
BSI	Bloodstream Infection
CAP	Community Associated Pneumonia
HAP	Hospital Associated Pneumonia
MF	Microfilaments
MT	Microtubules
UTI	Urinary Tract Infection
VAP	Ventilator Associated Pneumonia

Chapter-1
Introduction

1.1 Epidemiology

Klebsiella pneumoniae, a well-known opportunistic pathogen that causes nosocomial pneumonia, bacteremia, and septicemia, also causes urinary tract infections (UTI) (Oelschlaeger & Tall,1997). *K.pneumoniae* biotypes are often acknowledged as opportunistic pathogens that function as causative agents of bacteremia's and respiratory and genitourinary infections. These infections are more prevalent in individuals experiencing physiological or psychological stress (Merino et al.,1992).

1.2. Hazards

Over the course of the past several decades, there has been an increase in the level of awareness regarding the role of *K.pneumoniae* as a significant opportunistic pathogen of the urinary tract in compromised individuals and hospitalized patients (Clegg & Murphy,2017). This bacterium is commonly found in the intestinal tract of humans, and rates of fecal carriage can increase threefold during hospitalization. Multiple genetic resistance mechanisms evolve due to the selective use of antibiotics in a hospital setting (Matovina et al.,2021).

1.3. Pathophysiology

Klebsiella invasion in vivo hasn't been looked into yet, so it's not clear if it's another thing that makes *K.pneumoniae* dangerous (Merino et al.,1992). The advent of these bacteria, which display different antibiotic resistance phenotypes, has made treatment and management of *K.pneumoniae* urinary tract infections (UTIs) challenging (Clegg & Murphy,2017). But because more and more papers are talking about how many bacterial pathogens can get into eukaryotic cells, we looked into *K.pneumoniae's* possible ability to do this (Merino et al.,1992). This is because UTIs are caused by *K.pneumoniae* (Clegg & Murphy,2017). In a gentamicin kill-invasion assay, this study shows how a *K.pneumoniae* isolate from a person with a UTI was able to invade the human bladder and ileocecal epithelial cells in a lab setting (Merino et al.,1992). Isolates of *K.pneumoniae* that did not show susceptibility to one or more antibiotics in three or more different antimicrobial groups were categorized as multidrug-resistant *K.pneumoniae* (Filgona et al,2015). We looked at the role of receptor-mediated endocytosis, endosome acidification, and the influence of microtubules (MT) and microfilaments (MF) in the internalization of *K.pneumoniae* using a number of inhibitors that work on eukaryotic cell structures or processes (Merino et al.,1992).

Chapter-2

Research Methodology

2.1 Search strategy

Using databases such as ScienceDirect, Google Scholar, PubMed, and Scopus, pertinent scientific literature was located. *K.pneumoniae*, pneumonia, prevalence, urine sample, urinary tract infection and UTI were used as search terms. Using the Boolean operators "AND", "OR", and "NOT", the search result was kept specific. Authentic research and review articles with a high number of citations were chosen to retrieve subject-related information.

2.2 Inclusion criteria

The literature includes a description of the incidence of *K.pneumoniae* in urine samples from patients, an examination of the risk factors associated with urinary tract infections (UTIs) during pneumonia, and an analysis of the distribution of *Klebsiella* species among individuals of various age groups. Additionally, the literature briefly contained information regarding the symptoms and dangers associated with *K.pneumoniae* during urinary tract infections (UTIs).

2.3. Exclusion criteria

Literature that only stated the prevalence of bacterial nosocomial infection, the antibiotic resistance of *Klebsiella* spp., the diagnosis and treatment of *K.pneumoniae* were excluded. In addition, articles that merely reported the prevalence of *K.pneumoniae* among non-pregnant or men and women of reproductive age were excluded.

Chapter-3

Klebsiella pneumoniae

3.1. Morphology

Klebsiella accounted for 7.4% of the total incidence of bacterial illnesses (Jay, 1983). It ranked as the third most prevalent etiology for lower respiratory tract infections and primary bacteremia across all categories (Jay,1983). *K.pneumoniae*, a member of the order Enterobacterales and widely known as a nosocomial pathogen that is capable of causing a variety of infectious syndromes, is one of the bacteria in this order (Matovina et al.,2021). According to the World Health Organization, new antibiotics are desperately needed to combat *K.pneumoniae*, a bacterium that causes serious infections in both hospitals and the population (David et al., 2019).

3.2. Resistant Strains

In previous extensive surveillance studies, *Klebsiella* has been identified as the predominant etiological agent responsible for nosocomial pneumonia and bacteremia resulting from pneumonia (Jay,1983). Carbapenem-resistant *K.pneumoniae* is the leading cause of human mortality due to antibiotic resistance in Europe, according to a recent study (David et al.,2019). *K.pneumoniae* causes suppurative lesions, bacteremia, and septicemia, which are responsible for a large number of nosocomial infections in newborns, people getting respiratory treatment, and people in the urology and burn wards of hospitals (Nassif & Sansonetti, 1986). The current study found that patients infected with KPC-producing *K.pneumoniae* had a mortality rate significantly higher than the pooled overall mortality rate (47.66 vs. 42.14%). This result may contribute to KPC-producing *K.pneumoniae* having higher invasiveness, and the KPC-encoding black always carries other drug-resistant genes, resulting in a prominent drug-resistant phenotype in the bacteria (Xu et al.,2017). In previous extensive surveillance studies, *Klebsiella* has been identified as the predominant etiological agent responsible for nosocomial pneumonia and bacteremia resulting from pneumonia (Jay,1983). *K.pneumoniae*, which is one of the most prevalent *Klebsiella* species, is the most prevalent cause of hospital-acquired infections, meningitis, pneumonia, bacteremia, wound infections, and urinary tract infections (Pourbaghi et al., 2021).

3.3. Signs and symptoms

According to a survey, *Klebsiella* was identified as the primary etiological agent of pneumonia among those residing in nursing homes, accounting for a substantial 40% of the total reported cases (Jay,1983). It is common knowledge that *K.pneumoniae* is found everywhere in nature. It is considered to be one of the most significant opportunistic pathogens, and it is responsible for a wide variety of human illnesses, including bloodstream infection (BSI), urinary tract infection (UTI), surgical site infection, and pneumonia (Xu et al., 2017). *Klebsiella* species are highly prevalent Gram-negative bacilli that can be detected in various areas of the body, as well as in the environment and normal flora (Pourbaghi et al.,2021). *Klebsiella* is a prominent etiological agent responsible for pneumonia in elderly populations residing in nursing homes, chronic care facilities, and community settings (Jay, 1983).

Chapter-4

Prevalence of *K.pneumoniae* in urine samples

4.1. High prevalence of *K.pneumoniae* in urine samples

Numerous research has been conducted across diverse age groups and geographical regions worldwide, revealing that Ohio, located inside the United States, exhibits the highest prevalence of *K.pneumoniae* compared to other global regions. A study conducted by Brizendine et al. (2015) revealed a notable increase in the prevalence of positive microscopic results in Connecticut (4.89%) (So et al.,2015) and New Jersey (18.90%) (Popejoy et al.,2016) compared to other regions of the United States. Taiwan exhibited the most minimal prevalence rate among all nations, amounting to 3.63% (Lin et al.,2014)

Serial	Country	Area	Year	Sample number of patient	Detection method		Percentage of *K.pneumoniae*	Reference
					PCR	Culture		
1	Bangladesh	Sylhet	2016	108	X	Yes	90%	(Chakraborty et al.,2016)
2	Japan	Tokyo	2022	62	Yes	X	45.16%	(Ikeda et al.,2019)
3	Korea	Seoul	2016	81	X	Yes	12.30%	(Kim et al.,2017)
4	Korea	Seoul	2010	185	Yes	X	45.56%	(Ko et al.,2010)
5	Nepal	Kathmandu	2013	145	X	Yes	2.29%	(Chander & shreshtha, 2013)
6	Nepal	Kathmandu	2017	39	X	Yes	14.60%	(Nepal et al.,2017)
7	Pakistan	Baluchistan	2021	107	X	Yes	20.80%	(Fatima et al.,2021)
8	Pakistan	Lahore	2021	100	X	Yes	37%	(Iqbal et al.,2021)
9	Pakistan	Peshawar	2020	350	Yes	Yes	64.80%	(Naeem et al.,2021)
10	Thailand	Bangkok	2022	49	X	Yes	90.50%	(Nasomsong et al.,2021)
11	Thailand	Songkhla	2020	324	X	Yes	75.50%	(Vachvanichsanong et al., 2021)
12	Taiwan	Tainan	2014	468	Yes	X	3.63%	(Lin et al.,2014)
13	Iran	Ilam, Tabriz,	2011	288	Yes	Yes	39.4%, 50.7%, 45.8%	(Ghafourian et al.,2012)

		Tehran						
14	Iran	Kashan	2015	250	X	Yes	52.60%	(Moini et al.,2015)
15	Iran	Semnan	2018	173	X	Yes	32.94%	(Moghadas et al.,2018)
16	Iraq	Kufa	2016	464	Yes	Yes	12.26%	(Ahmed & Alaa.,2016)
17	Iraq	Kufa	2017	285	Yes	Yes	11.26%	(Ahmed & Haneen.,2017)
18	Saudia Arabia	Riyadh	2016	160	X	Yes	23.50%	(Al Yousef et al., 2016)
19	USA	Connecticu t	2014	143	X	Yes	4.89%	(So et al.,2015)
20	USA	New Jersey	2016	159	X	Yes	18.90%	(Popejoy et al.,2016)
21	USA	Ohio	2014	108	X	Yes	100%	(Brizendine et al.,2015)
22	Colombia	Valledupar	2012	123	Yes	X	12.70%	(Martinez et al.,2012)
23	Norway	Bærum	2012	101	Yes	Yes	44%	(Jørgensen et al.,2017)
24	Portugal	Braga, Vila Real	2022	102	Yes	Yes	39.20%	(Oliveira et al.,2022)
25	Portugal	Lisbon	2018	76	Yes	X	98.70%	(Marques et al.,2019)
26	Russia	Kazan	2018	10	Yes	Yes	100%	(Khaertynov et al.,2018)
27	Algeria	Tlemcen	2013	24	Yes	X	91.67%	(Yandai et al.,2019)
28	Ethiopia	Addis Ababa	2018	342	X	Yes	14.90%	(Abayneh et al.,2018)
29	Sudan	Khartoum	2020	250	Yes	Yes	55.60%	(Osman et al.,2020)
30	TChad	N'Djamena	2019	503	X	Yes	25%	(Bellifa et al.,2013)

Table 1: Prevalence of *K.pneumoniae* in urine samples. Data has been organized geographically.

4.2. Prevalence of *K.pneumoniae* in Asian region

Sylhet shows a rise of *K.pneumoniae* infection among individuals by 90% (Chakraborty et al.,2016). Moreover, moderate invasion of *Klebsiella* infection has been observed Korea by 45.56% (Ko et al.,2010) and 12.30% (Kim et al.,2017). Among the middle eastern regions, Nepal shows the lowest rate of prevalence, 2.29% in urine sample (Chander & shreshtha, 2013). In Iran, different provinces show moderate percentage of *K.pneumoniae* (Ghafourian et al.,2012). In Pakistan, estimation is still moderate in Baluchistan (Fatima et al.,2021) and Lahore (Iqbal et al.,2021). In 2020, percentage began to rise by 64.80% from patients' urine sample (Naeem et al.,2021). In Taiwan, urine samples show lowest percentage of *K.pneumoniae* percentage, 3.63% (Lin et al.,2014). Also, Bangkok shows dramatic rise of *K.pneumoniae* in urine samples which is 90.50% (Nasomsong et al.,2021).

4.3. Prevalence of K.pneumoniae in Western and European Region

However, the highest prevalence is noticed 100% according to Table-1 by (Brizendine et al.,2015) and (Khaertynov et al.,2018). To elaborate, the USA shows 100% prevalence in Ohio (Brizendine et al.,2015) but lowest percentage in Connecticut, 4.89% (So et al.,2015) and New Jersey,18.90% (Popejoy et al.,2016). Similarly, Colombia shows a decrease in percentage compared to other western regions (Martinez et al.,2012). In Norway, percentage of *K.pneumoniae* is moderately lower but observed both in PCR and culture samples (Jørgensen et al.,2017). In Portugal, the percentage of *K.pneumoniae* is 98.70% in Lisbon, PCR detection confirmed by (Marques et al.,2019). Compared to other European regions, Braga and Vila Real samples confirmed *K.pneumoniae* percentage, 39.20% both in PCR and culture method (Oliveira et al.,2022). In Kazan, patients' urine samples confirmed 100% prevalence of *K.pneumoniae* both in PCR and culture detection test (Khaertynov et al.,2018).

In Algeria, 91.67% prevalence is observed in a study conducted by (Yandai et al.,2019) from the PCR samples of patients' urine samples. Among Ethiopia, Sudan and TChad, prevalence is comparatively low in Addis Ababa, 14.90% a study conducted by (Abayneh et al.,2018). Similarly, TChad shows moderately lower percentage of *K.pneumoniae*,25% (Bellifa et al.,2013) than in Sudan, 55.60% (Osman et al.,2020). However, further studies should be administered and carried on for more information as there were very few research done in African regions.

Chapter-5

Antibiotic resistance of *K.pneumoniae* in urine samples

5.1. Highest antibiotic resistance of *K.pneumoniae* in urine samples

Multiple studies had identified the multidrug resistance and antibiotic resistance caused by *K.pneumoniae* from urine samples in which the prevalence of *K.pneumoniae* was the highest in the respective study. Besides, several antibiotics show different percent estimation in different antibiotics. However, the percent estimation of Ampicillin is 100% all the time in urine samples of almost all countries except in some province of Iran such as Shahrekord (Amraie et al.,2014), Shiraz (Mansury et al.,2016), Sari (Shadkam etal.,2021). On the other hand, samples of urine collected from patients in Saudia Arabia showed no resistance to Ampicillin and no multidrug resistance (Kader & Kumar,2005).

5.2. Antibiotics resistant to urine samples in Asian region

Enoxacin shows no antibiotic resistance in any samples collected from maximum countries except in Peshawar, Pakistan, 43.48% (Ullah et al,2009). In Bangladesh, Cefpirome and Cefradine did not show any resistance to *K.pneumoniae,* from samples collected from Dhaka (Aminul et al 2021) and Sylhet (Chakraborty et al 2016). Moreover, 41.30% of antibiotic resistance has been observed from antibiotic Gatifloxacin from urine samples collected from Peshawar, Pakistan (Ullah et al,2009). In Rohtak, a study conducted by (Gupta et al.,2007) shows that *K.pneumoniae* shows 100% multidrug resistance collected from the patient's urine samples. 93.33% antibiotic resistance by Imipenem has been observed in Peshawar, Pakistan (Ullah et al,2009).

Serial	Country	Area	Year	Sample number	Name of Antibiotics															Multi drug Resistance	Reference
					Ampicillin	Amikacin	Amoxicillin + clavulanic acid	Ceftazidime	Ceftriaxone	Cefpirome	Cefradine	Co-trimoxazole	Ciprofloxacin	Doxycycline	Enoxacin	Gentamicin.	Gatifloxacin	Imipenem	Meropenem		
1	Bangladesh	Dhaka	2021	150	-	50.30%	-	75.30%	72.80%	-	-	-	-	-	-	60.30%	-	-	44.70%	82%	(Aminul et al 2021)
2	Bangladesh	Sylhet	2016	500	100%	-	-	-	50%	-	-	44%	37.50%	-	-	31%	-	-	-	56%	(Chakraborty et al 2016)
3	India	Karnataka	2014	417	75.60%	14.60%	-	-	-	-	-	-	36.50%	-	-	36.50%	-	0%	-	90.20%	(Manjula et al.,2014)
4	India	Kolenchery	2016	2202	100%	32.30%	68%	-	-	-	-	60%	-	-	-	40%	-	14.30%	34.30%	-	(Varghese et al 2016)
5	India	Rohtak	2007	57590	-	68%	-	-	60%	-	-	-	-	-	-	40%	-	-	-	100%	(Gupta et al.,2007)
6	Indonesia	Klaten	2019	167	100%	100.00%	36.69%	-	-	-	-	-	38.75%	-	-	-	-	-	-	54.5%	(Nirwati et al.,2019)
7	Pakistan	Peshawar	2009	92	13.04%	63.04%	17.39%	28.26%	32.61%	30.43%	15.22%	6.52%	45.65%	15.22%	43.48%	17.39%	41.30%	93.33%	86.67%	71.73%	(Ullah et al,2009)
8	Iran	Tabriz	2020	421	-	19.70%	-	18.18%	41.8300%	-	-	-	56.970%	-	-	87.80%	-	6.06%	-	53.30%	(Jafari-Sales et al.,2020)
9	Iran	Tehran	2020	88	-	20.40%	29.50%	38.60%	45.40%	-	-	52.20%	26%	-	-	27.20%	-	11.30%	-	48.80%	(Moghadam et al.,2020)
10	Iran	Shahrekord	2014	195	-	21.96%	-	49.71%	41.61%	-	-	54.33%	15.60%	-	-	32.94%	-	20.80%	-	-	(Amraie et al.,2014)
11	Iran	Shiraz	2016	144	-	15.90%	-	43.70%	-	-	-	43.70%	-	-	-	19.40%	-	15.90%	11.80%	21%	(Mansury et al.,2016)

12	Iran	Sari	2021	100	-	10%	-	46.30%	43.30%	-	-	-	65.60%	-	-	-	-	35.80%	41.70%	74.30%	(Shadkam etal.,2021)
13	Iran	Kashan	2015	250	96%	48.10%	46.30%	50%	52%	-	-	-	46%	-	-	59.3%	-	0%	-	46.60%	(Moini et al.,2015) [50]
14	Saudia Arabia	Alkhobar, Dammam	2005	2455	-	38%	-	-	-	-	-	-	43%	-	-	40%	-	7%	7%	-	(Kader & Kumar, 2005)
15	Portugal	Lisbon	2018	76	96.50%	0%	-	8.80%	-	-	-	-	14%	-	-	14%	-	0%	0%	30%	(Marques et al.,2019)
16	Equatorial Guinea	Malabo	2015	785	100%	25.90%	93.30%	-	81.30%	-	-	-	62.50%	85.80%	-	86.20%	-	3.30%	-	91.70%	(Shatalov, 2015)
17	Ethiopia	Jimma	2011	228	100%	-	-	-	25%	-	-	-	0%	-	-	25%	-	-	-	-	(Beyene & Tsegaye, 2011)
18	Kenya	Nairobi	2013	336	100%	-	-	90.60%	-	-	-	-	83%	-	-	63.60%	-	0.60%	0.60%	-	(Maina et al 2013)
19	Nigeria	Anyigba	2021	200	-	-	83.30%	41.70%	-	-	-	-	75%	-	-	66.70%	-	100%	-	-	(Mofolorunsho et al 2021)
20	Uganda	Kampala, Kayunga, Mpigi	2016	1448	100%	-	-	-	3%	-	-	-	11%	-	-	11%	-	-	-	60%	(Najjuka et al 2016)

Table 2: Antibiotic resistance of *K.pneumoniae* in urine samples. Data has been arranged geographically.

5.3 Antibiotic resistance of K.pneumoniae of urine samples in African region.

From urine samples collected from Anyigba, Nigeria, the samples show 100% antibiotic resistance to Imipenem but zero signs of multidrug resistance (Mofolorunsho et al 2021). 85.80% antibiotic resistance by Doxycycline has been observed in Equatorial Guinea, Malabo (Shatalov,2015). A study conducted by (Kader&Kumar,2005) illustrates no multidrug resistance in Saudia Arabia. Except, Malabo (Shatalov,2015), African regions such as Ethiopia (Beyene&Tsegaye,2011), Kenya (Maina et al2013) and Nigeria (Mofolorunsho et al 2021) shows no multidrug resistance to *K.pneumoniae* in urine samples collected from patients.

Chapter- 6

Conclusion:

To recapitulate, *K.pneumoniae* is causing several infections around the globe including Hospital Acquired Pneumonia (HAP), Ventilator Associated Pneumonia (VAP), Community Associated Pneumonia (CAP), and Aspiration Pneumonia. Among the countries, Iran, Iraq, and some countries in Africa showed invasion of Pneumonia more compared to other Western countries. However, the countries are more associated with antibiotic resistance compared to Asian regions as well. *K.pneumoniae* is more invasive and toxic having multiple variants of its own. Hypervirulent *K.pneumoniae* are more susceptible in different healthcare sectors along with the expansion of Carbapenem-Resistant *K.pneumoniae.* Moreover, *K.pneumoniae* are tough to recognize and diagnosis is quite challenging due to its multiple variants and mutative modification in genetic material. Therefore, I think extensive field research needs to be administered more in the public health care sector and more research needs to be done in life science facilities. More life science sectors need to work on their samples and identify the dangers and treatment of disease caused by *K.pneumoniae.* In a nutshell, the prevalence and antibiotic susceptibility of *K.pneumoniae* need to be studied in in broader sense and the dangers of its multiple variants need to be figured out more in general especially in third-world countries to prevent the risk factors and other health hazards.

Chapter-7
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