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Review on Clinical Diseases Caused by Klebsiella

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Klebsiella are one among the group of gram negative rod shaped bacilli of family Enterobacteriaceae. Klebsiella are normal inhabitants of the intestinal tract of humans, animals, and environment. *Klebsiella pneumoniae* subspecies pneumoniae a most common gram negative lactose fermenting non motile, aerobic rod shaped bacilli, is second most common next to *E. coli*. They are facultative anaerobic bacterial vegetation of digestive tract of man and normal medical clinic procured pathogen, causing urinary tract contamination, nosocomial pneumonia and intra-stomach disease. Disease brought about by multidrug safe gram negative bacilli that produce broadened range beta-lactamase (ESBL) proteins have been accounted for with expanding recurrence in escalated care units related with noteworthy grimness and mortality.

Keywords: Klebsiella pneumonia; nosocomial pneumonia.

1. INTRODUCTION

Klebsiella sp. can be established in a broad range of environment. In humans, this species tends to colonize along the mucous membrane of the colon, nasopharynx and skin. It is considered as a commensal of enteric flora. Outbreak can occur in patients with immunodeficient disease and patient treated with antibiotics. *Klebsiella oxytoca* is used in industrial ethanol fuel

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Table 1. Species classification of the genus Klebsiella

COWAN	BASCOMB	ORSKOV
K.areogenes	K.areogenes/oxytoca	K.pneumoniae
K.edwardsii	Edwardsii	Subsp.pneumoniae
Subsp.edwardsii	Pneumoniae	Subsp.ozaenae
Sunsp.atlantae	Sensu stricto	Subsp. Rhinoscleromatis
K.pneumoniae	Sensu lato	K.oxytoca
K.rhinoscleromatis	K. rhinoscleromatis 'unnamed group Enterobacter aerogenes	K. planticola K. trevisanii K.ornithinolytica

production as they ferment xylose that helps to convert biomass into fuel ethanol [1]. Klebsiella accounts for 3 to 7% of all nosocomial bacterial infections, placing them among the eight most important infectious pathogens in hospitals [2]. The classification of Klebsiella was given in Table 1.

2. HISTORY

The German Swiss microbiologists Edwin kleb coined the term "Klebsiella" which was initially named as "*Hyalococcus pneumoniae*". In 1882, the species *Klebsiella pneumoniae* was described by Carl Friedlander.

In 1886, *Klebsiella oxytoca* was earlier named as Bacterium oxytocum by flugge which was frequently isolated from various clinical samples. *Klebsiella pneumoniae* subspecies rhinoscleromatis was described by von Frisch in 1882.

Drancourt and colleagues in 2001, performed a relative examination of the sequences of 16SrRNA and rpoB genes (encoding the bacterial RNA polymerase β-subunit) of the type strains of nine Klebsiella species, based on which they classified Klebsiella into three clusters [3].

2.1 Cluster I: Comprises

(i) *Klebsiella pneumoniae*

(a)pneumoniae
(b) rhinoscleromatis and
(c) ozaenae

(ii) *Klebsiella granulomatis*

2.2 Cluster II: Comprises of Klebsiella Ornitholytica

(a) Planticola
(b) Trevisanii
(c) Terrigena

2.3 Cluster III: Comprises of Klebsiella Oxytoca

In detail, in the early 1980s, Klebsiella isolates from the environment, which had previously been classified as "Klebsiella-like organisms" (groups J, K, L, and M). These groups gave rise to four new species: *K. terrigena, K. ornithinolytica*, *K. planticola*, and *K. trevisanii*. In 1986, the last two species were combined into one species, *K. planticola*, because of their extensive DNA sequence homology. At present it seems possible that in addition to *K. pneumoniae* and *K. oxytoca*, a third Klebsiella species exists that is able to cause human infections [4].

3. EPIDEMIOLOGY AND HABITAT

Klebsiellae probably have two common habitats, one being the environment, where they are found in surface water, sewage, and soil and on plants and the other being the mucosal surfaces of mammals such as humans, horses, or swine, which they colonize [5].

In humans, *K. pneumoniae* is present as a saprophyte in the nasopharynx and in the intestinal tract. Carrier rates differ considerably from study to study. Apart from medical equipment (contaminated due to faulty hygienic procedures) and blood products, the principal reservoirs for transmission of Klebsiella in the hospital setting are the gastrointestinal tract of patients and the hands of hospital personnel.

The ability of this organism to spread rapidly often leads to nosocomial outbreaks, especially in neonatal units. Of the 145 epidemic nosocomial infections reported in the literature published in English between 1983 and 1991, 13 were caused by Klebsiella. According to the statistics of the Centers for Disease Control and Prevention, Klebsiella spp. account for 8% of endemic hospital infections and 3% of epidemic outbreaks [6].

3.1 Morphology and Culture Characteristics

Klebsiella are short, thick rods of 0.3 to 1.5 by 0.5 to 5.0 µ, gram negative bacilli arranged in singles, pairs or in chains. They are non - motile, oxidase negative, embodied, lactose maturing, facultative anaerobic bacilli. Most Klebsiella strains are typified by a polysaccharide case of extensive thickness, answerable for the shimmering, mucoid settlements on agar plates.

Based on presence or absence of capsular (K) somatic (O) and slime (M) antigens, the Klebsiella strains have been divided into four 4 smooth and 4 rough forms [7].

Smooth forms	Rough forms
1.MKO	MKR mucoid capsulated
2.KO	KR non mucoid capsulated
3.MO	MR mucoid non capsulated
4.OR	non mucoid non capsulated

3.1.1 Pathogenicity factors of klebsiella

The flow investigation into the pathogenicity of Klebsiella centers around the gathering of five destructiveness factors. The Virulence components of Klebsiella sps are capsular polysaccharides (CPLs), cell surface lipopolysaccharides (LPSs), adhesins, siderophores and poisons, every one of which assumes basic job in the pathogenesis of these species [8].

3.1.1.1 Capsular antigens

The Capsule is the most significant harmfulness components of Klebsiella sps made out of complex acidic polysaccharides. They are grouped into 77 serological sorts. The strains communicating container antigens K1 and K2 were seen as more harmful than different serotypes. The level of destructiveness gave by a specific k antigen may be expected to mannose content on the CPS.

3.1.1.2 Adhesion

The connection of microorganism to mucosal and epithelial cell surfaces is the initial phase in the advancement of colonization and disease. The attachment properties are interceded by various sorts of pili that jut on the outside of the bacterial cells.

Over 80% of clinical confines of *K. pneumoniae*, however not many *K. oxytoca* strains, express sort 1 fimbriae. Type 1 fimbriae are all around described and found in the a large portion of enterobacterial species. Various examinations have demonstrated that type 1 fimbriae are a significant harmfulness factor in *K. pneumoniae* urinary tract infection (1).

3.1.1.3 Siderophor

Iron is fundamental for practically all life for procedures, for example, breath and DNA union (2). The checked impact of iron stock in the host body on the pathogenesis of contaminations has been exhibited for Klebsiella (10). The most popular delegate is enterobactin and aerobactin separately. In the family Klebsiella the generation of both enterobactin and aerobactin has been illustrated [9].

3.1.1.4 Transmission of Klebsiella

From patient to quiet outcomes from sullied medicinal supplies and tainted hands of therapeutic work force and blood items, though, the entries of Klebsiella diseases are careful injuries [10].

3.1.1.5 Risk factors

Risk factors for nosocomial infection of Klebsiella species includes:

- Environmental factors, transmission of *Klebsiella pneumoniae* by means of individual to-individual contact between social insurance laborers and patients, by Contaminated surfaces and instrumentation. Among body destinations, gastrointestinal colonization is likely a typical and critical supply as far as danger of transmission in disease.
- Patients factor, like age, prolonged hospitalization, multiple disease, intubated, surgical drains, wounds, patients on monitoring devices, indwelling catheters and colonization of Klebsiella infections.

- Community gained contaminations that incorporate liquor addiction, diabetes mellitus, constant liver sickness (cirrhosis), interminable renal disappointment, malignancy, organs or tissues transplants, consumes, or potentially utilization of catheters are progressively vulnerable to disease by Klebsiella [11].
- Risk factors related with ESBL colonization and contamination incorporate earlier treatment with anti-microbials, delayed hospitalization, delayed ICU remain, and mechanical ventilation [12].

3.1.2 Clinical manifestation's

3.1.2.1 Pneumonia

Friedlander described a lobar pneumonia caused by *K. pneumoniae* as early as 1882. The anatomic distribution of the infection is usually a consolidation with varying degrees of tissue destruction, including abscesses, cavitations, bronchiectasis, empyema, and pleural adhesions. The lesions may have a slimy appearance due to the mucoid coat of the Klebsiella bacteria.

Chronic forms of this pneumonia may grossly mimic tuberculosis with bronchiectasis and areas of parenchymal scarring [13].

3.1.2.2 Bacteraemia and septicaemia

Bacteraemia is a circulation of bacteria in blood and septicaemia is the condition were bacteria circulates and actively multiply in the blood to form toxic products. The gram negative bacilli commonly causing bacteraemia includes *Klebsiella pneumoniae*, *E. coli*, *P. aeruginosa*, proteus species, salmonella species, Acinetobacter species.

Invasion of such organisms are considered to be one of the most serious condition in infectious disease. Extra vascular infection is most common than intravascular and enters the circulation through the lymphatics. They are secondary to local site of infection such as genitourinary tract, respiratory tract, surgical site infections. Intravascular infection includes infective endocarditis, intravenous and catheter associated bacteraemia [14].

3.1.2.3 Wound infection and Surgical Site Infection (SSI)

Wound infection may be due to surgical procedures, trauma, burns or any disease causing a breach in the mucosal, cutaneous or tissue integrity. A major concern is burns and surgical site infection (SSI). SSI is the disease that happens inside 30 days after an activity and includes skin, subcutaneous tissue and profound delicate tissue of the cuts. The basic pathogens experienced in SSI are gram negative microorganisms. Klebsiella pneumonia's normal living space is the gastrointestinal tract. The greater part of the activities performed were laparotomies and most injuries were either perfect tainted, polluted, or grimy; and spillage from the GIT prompts SSI. Advancement of SSI was related with low serum egg whites, sickliness and kind of suture utilized. Most SSI were brought about by multi-medicate safe (MDR) life forms [15].

3.1.2.4 Pyogenic liver abscess

Klebsiella pneumoniae is a gram-negative living being that can cause pyogenic liver ulcer (PLA) without hepatobiliary malady. Diabetics are at expanded danger of this contamination. A few patients with Klebsiella liver canker can create metastatic contaminations including endophthalmitis, meningitis, mind ulcer, septic aspiratory emboli, lung boil, splenic sore, osteomyelitis [16].

3.1.2.5 Meningitis

Klebsiella meningitis occurs more often in elderly patients and has been reported in patients with alcoholic liver disease, diabetes and transfusion dependent thalassemia major. Co-infection can occur with other pathogens such as Enterobacter. In a series from Taiwan, *K. pneumoniae* and *K. oxytoca* accounted for 13 and 2.3 percent of culture positive meningitis respectively. It is also known that in Asian countries, Klebsiella meningitis can occur as metastatic infection secondary to liver abscess [17].

Urinary tract infection: Klebsiella accounts for 6 to 17% of all nosocomial urinary tract infections (UTI) and shows an even higher incidence in specific groups of patients at risk, e.g., patients with neuropathic bladders or with diabetes mellitus [18].

3.1.3 Lab diagnosis

3.1.3.1 Specimen collection and transport

Sterile aseptic method is required for collection and transport of samples. The specimens were presented in Table 2.

Table 2. Specimens for klebsiella species isolation

Infections	Specimens
Urinary tract infection	Urine
Wound infection	Pus
Respiratory tract infection	Sputum
Bacteraemia	Blood
Meningitis	CSF
Miscellaneous infection	Sterile body fluids, stool etc

3.1.3.2 Medium of choice

Klebsiella species has no complex wholesome necessity. They promptly develop in a standard medium like Nutrient agar, MacConkey agar medium, the fluid medium like supplement juices medium, TSB medium were utilized [19].

3.1.3.3 Colony morphology on agar medium

Colonies are circular, 2-3mm in diameter, dome shaped, mucoid (due to capsular polysaccharides), Greyish-white, translucent-opaque.

On blood agar the colonies are similar to nutrient agar with no haemolysis.

3.1.3.4 Selective Media

Eosin Methylene Blue medium (EMB), Columbia horse blood agar medium, MacConkey-inositol-carbenicillin agar (MIC), used for isolation of Klebsiella species from human feces. A modified medium of Wong containing potassium nitrate instead of nitrogen source which showed two major colony types either 1-2 mm diameter, convex, mucoid red-pink colony or larger which was waterier and pale red with dark red center [20].

3.1.3.5 Biochemical characteristics

Klebsiella species have a unique characteristic of producing mucoid colonies on agar medium other than Acinetobacter species, the latter is a non-fermenter. Depending on biochemical test, Klebsiella species are differentiated from other Enterobacteriaceae by voges proskauer positive and methyl red negative reactions. Motile Enterobacter are differentiated from non-motile strains of Klebsiella species by motility testing. Klebsiella grown on synthetic alginate medium but Enterobacter fails to grow. The detailed analysis were given in Table 3.

Bio typing: Bio composing dependent on an all-inclusive board of biochemical is unquestionably the most practicable technique for composing for

Table 3. Differentiation of genus klebsiella into species using biochemical tests (23)

Biochemical test	*K. pneumoniae*	*K. ozaenae*	*K. rhinoscleromatis*	*K. oxytoca*
Lysine Decarboxylase	+	-	-	+
Ornithine decarboxylase	-	-	-	-
Arginine dihydrolase	+	-	-	+
Indole	-	-	-	+
Methyl red	-	D	+	-
Voges-proskauer	+	-	-	+
Growth at 10°c	-	-	-	D
Malonate	+	-	+	+
ɳ-arabinose	d	D	d	+
B-gentiobiose	+	+	-	+
ɳ-melizitose	-	-	-	D
2-Deoxy-D-ribose	d	-	d	D
L-sorbose	d	D	d	+
D-tagatose	d	-	d	+
M-hydroxy-benzoate	-	-	-	+
Histamine	-	-	-	-
Hydroxy-l-proline	d	-	d	-

Different typing methods for Klebsiella strains were been reported that includes capsular serotyping, bio typing on its own or in combination with serotyping, bacteriophage typing and bacteriocin typing

littler research facilities that are epidemiologically not ideally equipped. The Vitek2 framework is created on fluorescence-based innovation and intended for the recognizable proof of wide scope of microorganisms including gram-negative and gram positive microscopic organisms yeast. (14).

Serotyping: Serotyping is as of now the most broadly utilized strategy for composing Klebsiella spp. It depends basically on a division as indicated by the capsular antigens (25). In any case, because of specialized constraints, the act of serotyping is declining, and sub-atomic techniques, for example, beat field gel electrophoresis, enhanced part polymorphism investigation (16).

Phage Typing: The presence of affectability to at least one extra phages was depicted numerous years prior by Anderson and Felix as 'the procedure of debasement' which 'may happen in a progression of dynamic stages'(19). In the most exceptional stages, corruption brings about affectability to numerous phages (polysensitivity).

Bacteriocin Typing: This is an additional method used to enable more précised epidemiological analysis for capsule type though capsular typing is most preferred (1). Different methods of typing were applicable, in which stand point bacteriocin typing is superior than growth in broth and cross streaking methods.

4. ANTIBIOTICS COMMONLY USED AND THEIR MODE OF ACTIONS

4.1 Beta Lactam Antibiotics

These are antibiotics, consisting of

- Penicillins
- Cephalosporins
- Monobactams
- Carbapenems

4.1.1 Penicillins

The structure of penicillin is

1. β-lactam ring
2. Thiazolidone ring
3. Site where β-lactamase will act

4.1.1.1 Types of penicillins

I. Natural penicillin. Eg., penicillin v

II.Semi synthetic penicillin

A. Amino penicillin Eg., ampicillin, amoxicillin

B. Carboxyl penicillin Eg., carbenicillin

C. Ureido penicillin Eg., piperacillin, mezlocillin

4.1.2 Cephalosporins

They possess β-lactam ring attached to Dihydro-thiazine ring. By addition of different side chains to dihyro thiazine ring a large number of semi synthesis compound have been produced. They are divided into four generations based on the development of the antibiotic and the antimicrobial spectrum. Newer generation when compared to the previous generation have a greater action against gram negative bacteria.

The new generation cephalosporins with the mention of few of their examples are as follow:

- I-Generation: Cephalothin, cephalexin, cefadroxil, cefazolin
- II-Generation: Ceftriaxone, cefuroxime, cefuroxime axetil, cefactlor, cefoxitin
- III-Generation: cefotaxime, ceftazidime, cefixime, cefoperazone
- IV-Generation: cefepime, cefpirome

The fourth generation cephalosporins have better penetration through porins in the outer membrane of the cell wall. They are stable against hydrolyses by β-lactamases. In case of cephamycins, 7-alpha-methoxyl group is fused with the cephalosporins nucleus. This is responsible for the stability against class A β-lactamases [21].

4.2 Carbapenems

These medications are basically identified with the β-lactam anti-toxins. They are amazingly intense and have exceptionally expansive range of movement against gram positive and gram negative microscopic organisms. Carbapenems like, imipenem, Ertapenem, doripenem, biapenem, meropenem are drugs that are increasingly successful against gram negative creature.

5. CONCLUSION

It is the natural capacity of microorganisms to oppose antimicrobial impact of specific anti-toxin class through its inborn auxiliary or useful qualities. Such obstruction can likewise be called as "heartlessness" as those microorganisms have never been vulnerable to that specific

medication. Distinctive kind of inborn obstruction existing in various class of anti-infection agents. The characteristic obtuseness can be because of absence of medication targets, powerlessness of medication to enter bacterial cell, ejection of antimicrobials by chromosomally encoded efflux siphon and natural generation of anti-toxin inactivating chemicals.

Klebsiella species are intrinsically resistance to ampicillin by production of beta-lactamases that destroy ampicillin before it binds with PBP target (13).

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Podschun R, Ullmann U. Klebsiella spp. as nosocomial pathogens: Epidemiology, taxonomy, typing methods and pathogenicity factors. Clin Microbiol Rev. 1998;11(4):589–603.
2. Koneman EW. Koneman's Color Atlas and Textbook of Diagnostic Microbiology. Lippincott Williams & Wilkins. 2006; 1766.
3. Orskov I, Fife-Asbury MA. New Klebsiella capsular antigen and the deletion of five of those previously assigned. Int. J. Syst. Bacteriol. 1977;27:386-387.
4. Ahmed AR, El-badawy ZH, Mohamed IR, Abdelhameed WA. Rhinoscleroma: A detailed histopathological diagnostic insight. Int J Clin Exp Pathol. 2015;8(7): 8438–45.
5. deShazo RD, Stringer SP. Atrophic rhinosinusitis: Progress toward explanation of an unsolved medical mystery. Curr Opin Allergy Clin Immunol. 2011;11(1):1–7.
6. Sahly H, Podschun R. Clinical, bacteriological and serological aspects of Klebsiella infections and their spondyloarthropathic sequelae. Clin Diagn Lab Immunol. 1997;4(4):393–9.
7. Pan Y-J, Fang H-C, Yang H-C, Lin T-L, Hsieh P-F, Tsai F-C, et al. Capsular polysaccharide synthesis regions in *Klebsiella pneumoniae* serotype K57 and a new capsular serotype. J Clin Microbiol. 2008;46(7):2231–40.
8. Simoons-Smit AM, Verweij-van Vught AM, MacLaren DM. The role of K antigens as virulence factors in Klebsiella. J Med Microbiol. 1986;21(2):133–7.
9. Shon AS, Bajwa RPS, Russo TA. Hypervirulent (hypermucoviscous) *Klebsiella pneumoniae*. Virulence. 2013;4(2):107–18.
10. Masci JR, Wormser GP. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 6th Edition Edited by Gerald L. Mandell, John E. Bennett, and Raphael Dolin Philadelphia: Elsevier Churchill Livingstone, 2005. 3661 pp., illustrated. $329 (cloth). Clin Infect Dis. 2005;41(2):277–277.
11. Colonization, Infection and the Accessory Genome of *Klebsiella pneumoniae* NCBI/PMC5786545.
12. Foxman B, Brown P. Epidemiology of urinary tract infections: Transmission and risk factors, incidence and costs. Infect Dis Clin North Am. 2003;17(2):227–41.
13. Hansen DS, Gottschau A, Kolmos HJ. Epidemiology of Klebsiella bacteraemia: A case control study using *Escherichia coli* bacteraemia as control. J Hosp Infect. 1998;38(2):119–32.
14. Banerjee M, Sahu K, Bhattacharya S, Adhya S, Bhowmick P, Chakraborty P. Outbreak of neonatal septicemia with multidrug resistant *Klebsiella pneumoniae*. Indian J Pediatr. 1993;60(1):25–7.
15. Kamal F, Williams G, Akbar H, Khan MA, Kadaria D. *Klebsiella pneumoniae* liver abscess: A case report and review of literature.
16. Tang L-M, Chen S-T. *Klebsiella pneumoniae* meningitis: Prognostic factors. Scand J Infect Dis. 1994;26(1):95–102.
17. Bruce SK, Schick DG, Tanaka L, Jimenez EM, Montgomerie JZ. Selective medium for isolation of *Klebsiella pneumoniae*; 3.
18. Wong SH, Cullimore DR, Bruce DL. Selective medium for the isolation and enumeration of Klebsiella spp. Appl Environ Microbiol. 1985;49(4):1022–4.
19. Hansen DS, Aucken HM, Abiola T, Podschun R. Recommended test panel for differentiation of Klebsiella Species on the basis of a trilateral

interlaboratory evaluation of 18 biochemical tests. J Clin Microbiol. 2004;42(8):3665–9.

20. Magiorakos A-P, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis. 2012;18(3):268–81.

21. Bradford PA. Extended-spectrum β-lactamases in the 21st Century: Characterization, epidemiology, and detection of this important resistance threat. Clin Microbiol Rev. 2001;14(4):933–51.

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