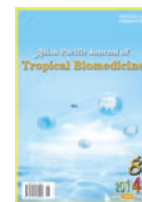


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Adult *Klebsiella pneumoniae* meningitis in Qatar: clinical pattern of ten casesFahmi Yousef Khan<sup>1\*</sup>, Mohammed Abukhattab<sup>2</sup>, Mohammed AbuKamar<sup>2</sup>, Deshmukh Anand<sup>3</sup><sup>1</sup>Department of Medicine, Hamad General Hospital, Doha, Qatar<sup>2</sup>Infectious Diseases Division, Department of Medicine, Hamad General Hospital, Doha, Qatar<sup>3</sup>Microbiology Laboratory, Hamad General Hospital, Doha, Qatar

## PEER REVIEW

## Peer reviewer

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## Comments

It is important for this type of paper to have clear and justifiable definitions for infection *v.s.* colonization, antibiotic resistance and outcome. The authors have carefully done this, so as a case series, the objectives, methods and results have been presented quite well, and the discussion is appropriate. The authors acknowledge that number of patients is small, but it is remarkable that they have even collected 10 cases over a few years. The documentation of the outcome is good for clinical understanding of the condition.  
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## ABSTRACT

**Objective:** To describe the clinical presentation, underlying diseases, antimicrobial susceptibility, treatment and outcome of *Klebsiella pneumoniae* meningitis patients.

**Methods:** This retrospective study involved all patients with 15 years of age or older who admitted to Hamad General Hospital with culture proven *Klebsiella pneumoniae* meningitis from January 1, 2007 to December 31, 2012.

**Results:** A total of ten cases were identified (nine males and one female). Their mean age was (43.3±12.8) years. Eight patients (80%) had nosocomial meningitis with neurosurgery being the most frequent associated condition. Fever and altered consciousness were the most frequent symptom. Cerebrospinal fluid showed elevated protein and glucose levels. Gram stain showed Gram-negative rods in 50% of cases, while positive cerebrospinal fluid culture results were found in all patients. Multidrug resistance was observed in two cases, and all patients had received appropriate empirical and definitive antibiotic treatments. The mean duration of intravenous antimicrobial treatment was (19.3±7.0) d and all patients with external ventricular drains underwent removal of the device, while in-hospital mortality was 50%.

**Conclusions:** The number of cases was too small to come up with therapeutic and prognostic conclusions. Further large-scale prospective study is needed.

## KEYWORDS

Nosocomial meningitis, Community-acquired meningitis, *Klebsiella pneumoniae* meningitis

## 1. Introduction

*Klebsiella pneumoniae* (*K. pneumoniae*) is a Gram-negative, non-motile, encapsulated, lactose-fermenting, facultative anaerobic, bacillus. Although found in the normal flora of the mouth, skin, and intestines, it can cause diverse infections, including pneumonia, genitourinary tract infection, intraabdominal infection, bacteremia and

neonatal meningitis. Recently, it has gained an increasingly important role in adult meningitis both in community acquired and nosocomial settings with significant geographical diversity in its clinical patterns in different parts of the world[1]. In Taiwan, Hong Kong and Thailand, *K. pneumoniae* is increasingly being recognized as important pathogens of community-acquired meningitis[1–4], while it is uncommon in the USA, Cuba, Europe and other

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countries<sup>[5–8]</sup>. *K. pneumoniae* meningitis is seen mostly in patients with diabetes mellitus, debilitating diseases, extrameningeal *K. pneumoniae* infection, *K. pneumoniae* bacteremia, and patients with head injury or who have undergone a neurosurgical procedure<sup>[1]</sup>.

In the state of Qatar, there is lack of information about *K. pneumoniae* meningitis. The aim of this study was to determine the clinical presentation, underlying diseases, antimicrobial susceptibility, treatment and outcome of *K. pneumoniae* meningitis in patients admitted to Hamad general hospital, Qatar.

## 2. Materials and methods

This retrospective study was conducted at Hamad general hospital, a tertiary hospital with eight operating theatres, six intensive care units and 621 beds. It involved all adult patients with 15 years of age or older who admitted to Hamad General Hospital with culture proven *K. pneumoniae* meningitis. To identify the patients, we reviewed the cerebrospinal fluid (CSF) cultures registered in the microbiology laboratory from January 1, 2007 to December 31, 2012. The files of the patients were reviewed retrospectively to retrieve the following data on a standardized data sheet: clinical picture, demographic data, underlying medical conditions, meantime between the surgery and the onset of the infection, susceptibility tests for *K. pneumoniae*, antibiotic therapy used, duration of therapy and patient outcome.

Diagnosis of *K. pneumoniae* meningitis was made if the following criteria were fulfilled: (1) the patient had *K. pneumoniae* cultured from CSF; (2) the patient had at least one of the following with no other apparent cause: fever (38 °C), headache, meningeal signs, cranial nerve signs or irritability; (3) the patient had at least one of the following alterations in CSF: increased white cells, elevated protein and/or decreased glucose. A positive CSF culture or Gram stain with normal levels of glucose, proteins and cell count in the absence of symptoms was considered as contamination/colonization.

Meningitis was considered as nosocomial if the patient had acquired the infection more than 72 h after hospitalization or within one month after discharge from the hospital where the patient received an invasive procedure, especially a neurosurgical one. Otherwise, the patient was considered to have “community-acquired” infection. Mixed-infection was defined as at least two bacterial organisms isolated concomitantly from CSF culture. *K. pneumoniae* isolates were considered as multidrug resistant if they exhibited resistance

to at least two antibiotics used in empirical therapy (third and fourth-generation cephalosporins, carbapenems or piperacillin/tazobactam). Empirical antimicrobial therapy was deemed as inappropriate if the antibiotics were administered more than 24 h of CSF collection and/or when the dosage, route and duration of treatment were not in accordance with hospital guidelines. Definitive therapy was considered as appropriate if antimicrobials were modified and administered not later than two hours after the CSF culture was obtained. Intravenous aminoglycoside monotherapy was considered inappropriate because of low penetration into CSF. In-hospital mortality included all causes of death during admission and considered as the main outcome measure of this series.

The results of analyses of continuous variables are expressed as mean±SD unless otherwise specified.

## 3. Results

There were ten episodes of *K. pneumoniae* meningitis occurring in ten patients during the study period (nine males and one female). The mean age was (43.3±12.8) years (range 20–61 years) and eight were non-Qatari patients. Most patients 80% (8/10) had nosocomial meningitis with neurosurgery being the most frequent associated condition. The mean period between neurosurgery and the onset of the infection was (10.3±3.0) d (range 4–15 d). Table 1 shows the demographic and clinical data of the ten patients.

Fever and altered consciousness were the most frequent symptom (Table 1). Cerebrospinal fluid showed pleocytosis in all cases [mean (1520±2998)] with a polymorphonuclear predominance. Elevated protein levels [mean (210±76) mg/dL] and low glucose levels [(27±8) mg/dL] were also noted. Gram stain showed Gram-negative rods in 50% (5/10) cases, while positive CSF culture results were found in all patients, four (Patients 2, 4, 5, 10) of them had mixed infection.

The antimicrobial susceptibilities of *K. pneumoniae* varied. Multidrug resistance was observed in 2/10 cases, while all isolates were sensitive to gentamicin, meropenem and piperacillin/tazobactam (Table 1). One isolate was extended spectrum beta lactamase (ESBL) producer (detected by the phenotypic confirmatory method). All the patients received appropriate empirical and definitive antibiotic treatments. The mean duration of intravenous antimicrobial treatment was (19.3±7.0) d (range 5–28 d). Intrathecal gentamicin was given for two patients. In addition to medical treatment, all patients with external ventricular drains underwent removal and replacement of the device, while in-hospital mortality was 50% (5/10).

**Table 1**

Describes the demographic and clinical data of the ten patients.

PT-NO	Age	Sex	Infection pattern	Underlying conditions	Other sources of KLP isolates	Clinical picture	Antibiotic treatment			Antibiotics susceptibility						ESBL -KLP	In-hospital mortality	
							Initial therapy	Final therapy	Duration (d)	CTR	GEN	FEP	TAZ	AMC	CIP			MEM
1	46	M	NOCL	Head injury, S/P ventriculostomy and EVD insertion	Sputum, blood	Fever, altered consciousness	MEM	MEM	14	S	S	S	S	S	S	S	No	Died
2	41	M	NOCL	Head injury, S/P ventriculostomy and EVD insertion	wound	Fever, headache and altered consciousness	MEM	MEM	20	S	S	S	S	S	S	S	No	Died
3	61	M	NOCL	HTN, Hg stroke, ventriculostomy and EVD insertion	Sputum, urine	Fever, headache and altered consciousness	MEM	CTR	18	S	S	S	S	S	S	S	No	Cured
4	50	M	NOCL	Ischemic Stroke, S/P craniotomy and EVD insertion	Sputum, blood	Fever, neck pain and altered consciousness	FEP	FEP itGEN	27 24	S	S	S	S	S	S	S	No	Died
5	20	M	NOCL	Head injury, S/P ventriculostomy and EVD insertion	Sputum, wound, blood	Fever, altered consciousness	MEM	MEM itGEN	24 20	R	S	R	S	R	R	S	No	Cured
6	46	M	CA	Br. Asthma, Strongyloidiasis	Blood	Fever, vomiting, headache, SOB, seizures, altered consciousness, neck stiffness	Vanc CTR	MEM	5	S	S	S	S	S	S	S	No	Died
7	56	M	NOCL	Head injury, S/P ventriculostomy and EVD, CAD	Sputum, blood	Fever, seizures	MEM	MEM	30	S	S	S	S	R	S	S	Yes	Died
8	27	M	CA	None	None	Fever, vomiting, headache, neck stiffness	Vanc CTR	CTR	14	S	S	S	S	S	S	S	No	Cured
9	51	F	NOCL	DM, HTN, Hg stroke, S/P ventriculostomy and EVD insertion	Sputum	Fever, headache, altered consciousness	MEM	MEM	19	S	S	S	S	S	S	S	No	Cured
10	35	M	NOCL	HTN, Hg stroke, ventriculostomy and EVD insertion	Sputum, blood	Fever	MEM	MEM	24	R	S	R	S	R	R	S	No	Cured

PT-NO: patient number; M: male; F: female; NOCL: nosocomial; CA: community acquired; S/P: status post; EVD: external ventricular drain; HTN: hypertension; Hg: hemorrhagic; CAD: coronary artery disease; DM: diabetes mellitus; SOB: shortness of breath; CTR: ceftriaxone; GEN: gentamicin; FEP: cefepime; TAZ: Piperacillin/tazobactam; Vanc: vancomycin; AMC: amoxicillin/clavulanate; CIP: ciprofloxacin; MEM: meropenem; itGEN: intrathecal gentamicin; R: resistance; S: sensitive; ESBL-KLP: ESBL *K. pneumoniae*.

**4. Discussion**

In Qatar, *K. pneumoniae* is among the most common Gram-negative bacteria encountered by physicians. However, the prevalence of *K. pneumoniae* meningitis is yet unknown.

As noted in this series the majority of the cases were nosocomial, which is comparable with reports from western countries[6,9], but different from those reported in Taiwan[1,2]. All nosocomial cases in this study had a neurosurgical condition as the preceding event and neurosurgical devices as predisposing factors, which may reflect the expansion of neurosurgical services or inadequate infectious control program in our hospital. This finding coincides with many reports worldwide[1-9]. The interval between neurosurgical procedure and the onset of meningitis is (10.3±3.0) d, which is similar to what was mentioned in the literature. On the other hand, a high incidence of DM among patients with adult community-acquired spontaneous bacterial meningitis (38.5%) has been reported in Taiwan[8,9]. In our study, none

of the two patients with community-acquired meningitis had diabetes mellitus; we found strongyloidiasis as a predisposing factor in one patient, and no obvious factor could be found in the other. Localized strongyloidiasis, as well as disseminated strongyloidiasis, can predispose individuals to bacterial meningitis with enteric organisms such as *K. pneumoniae*, *Escherichia coli* and *Enterococcus* spp. in the absence of evidence for strongyloidiasis outside the gastrointestinal tract[10].

Similar to other reports[1-9], the clinical picture and CSF (biochemistry and cell count) findings in this series were indistinguishable from other forms of bacterial meningitis. These findings make CSF Gram staining and culturing imperative in all patients. However, the examination of Gram stain on admission can be negative or misleading; because of the small number of organisms, patients being partially treated, and culture time of more than one day may be required, thus delaying the final diagnosis of meningeal infection and representing a prognostic factor of mortality.

Thus, the choice of appropriate empiric therapy while

awaiting results of sensitivity is crucial and should be based on the most common pathogen prevalent in a particular geographical area and age group and their antibiotic susceptibility pattern. According to our local policy, ceftriaxone plus vancomycin are the empirical treatment of choice for community-acquired meningitis, while meropenem is the empirical treatment of choice for nosocomial meningitis. Although the empiric treatment in our study was appropriate in all cases, the mortality was high, which could be resulted from the fact that most of our cases had preceding neurosurgical events. Moreover, we think that post-surgical *K. pneumoniae* meningitis might need intrathecal therapy in addition to the parenteral antibiotics in order to decrease the mortality.

Our study has some limitations. First, it is retrospective/hospital based. Second, the number of patient is small.

In conclusion, the clinical picture and CSF findings of *K. pneumoniae* meningitis were not different from those of other bacterial meningitis, and the mortality was high. The number of cases in this series was too small to come up with therapeutic and prognostic conclusions. Further large-scale prospective study is needed for better description of the management and prognosis of adult *K. pneumoniae* meningitis.

### Conflict of interest statement

We declare that we have no conflict of interest.

### Comments

#### Background

This is a descriptive paper on *Klebsiella* meningitis, a rather rare condition, except when occurring in neurosurgical infections. The authors look at the clinical management, progress and outcome of these infections.

#### Research frontiers

This is a descriptive clinical study and cases have been described before. However, it is an uncommon disease to compilation of a series of clinical cases, which will help build up new knowledge on this subject.

#### Related reports

Thigpen *et al.* (2011) has reported the bacterial meningitis in the United States. Ang *et al.* (2011) has study the prognostic factors and outcomes in endogenous *K. pneumoniae* endophthalmitis.

### Applications

The reported cases can be added to the clinical database on this uncommon condition.

### Peer review

It is important for this type of paper to have clear and justifiable definitions for infection *v.s.* colonization, antibiotic resistance and outcome. The authors have carefully done this, so as a case series, the objectives, methods and results have been presented quite well, and the discussion is appropriate. The authors acknowledge that number of patients is small, but it is remarkable that they have even collected 10 cases over a few years. The documentation of the outcome is good for clinical understanding of the condition.

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