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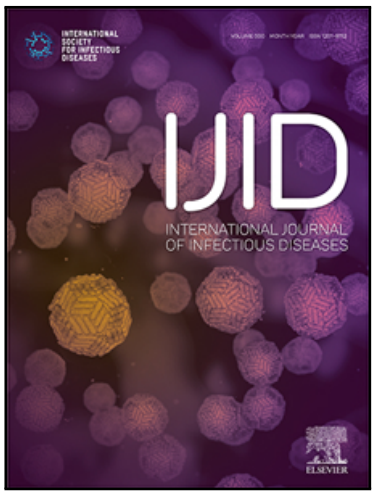

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Highlights

- Spontaneous *K. pneumoniae* meningitis is caused by hypervirulent strains
- Spontaneous *K. pneumoniae* meningitis is a dreadful infection with high mortality
- Post-surgical/traumatic *K. pneumoniae* meningitis has a better prognosis

Spontaneous and post-surgical/traumatic *Klebsiella pneumoniae* meningitis: two distinct clinic-microbiological entities.

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Abstract

Objectives: To analyze and compare the characteristics and outcome of spontaneous meningitis (SM) versus post-surgical/traumatic meningitis (PSTM) due to *Klebsiella pneumoniae*.

Methods: We conducted a retrospective, multicentric, cohort study of all *K. pneumoniae* meningitis cases managed between January 2007 and May 2018 in 7 university hospitals of Paris area. We further analyzed the microbiological characteristics of 16 available *K. pneumoniae* isolates, and sequenced the genome of 7 of them that were isolated from SM.

Results: Among 35 cases, 10 were SM, and 25 were PSTM. SM were more severe than PSTM with higher septic shock (p=0.004) and in-hospital mortality rates (p=0.004). In contrast, 5 patients from the PSTM group versus no patients from the SM group relapsed. All *K. pneumoniae* strains recovered from SM but none of those recovered from PSTM displayed hypervirulent phenotypic (positive string test) and genotypic (genes corresponding to capsular serotypes K1 or K2, virulence genes *rmpA, iutA*) characteristics (p<0.0001). PSTM

tended to be more frequently polymicrobial (p=0.08) and caused by an extended-spectrum β-lactamase producing strain (p=0.08) than SM.

Conclusions: SM and PSTM are two entities differing both from a clinical and a microbiological standpoint. SM appears as a dreadful infection induced by hypervirulent *K. pneumoniae* strains.

Keywords: hypervirulent *Klebsiella pneumoniae* - Meningitis – Spontaneous meningitis – Post-surgical/traumatic meningitis

Introduction

Over the past 3 decades, a syndrome involving community-acquired liver abscesses and septic metastasis associated to *Klebsiella pneumoniae* (KP) has been described (Shon et al., 2013). Strains isolated from patients with this syndrome are referred to as hypervirulent (hvKP). Typically, hvKP strains exhibit an hypermucoviscous phenotype characterized by a positive string test. They also possess virulence genes encoding the hypermucoviscous phenotype (*rmpA*), iron acquisition systems (*iutA*, *ybtS*), and the capsular serotypes K1 or K2 (Holt et al., 2015; Wyres et al., 2016).

Initially limited to Asia, cases of hvKP infections have now been reported in many countries over the world (Decré et al., 2008; Piednoir et al., 2020; Pilmis et al., 2021; Shon et al., 2013).

KP has also been isolated from community acquired central nervous system infections, particularly in Asia where it accounts for 8-40 % of bacteria isolated in Taiwan and South Korea (Hsieh et al., 2021; Lee et al., 2003; Moon et al., 2010). These meningitis have been

associated with hvKP strains (Ku et al., 2017) and their prognosis is poor with a mortality rate of more than 50% (Chang et al., 2010; Jung et al., 2015; Lu et al., 1997; Tang et al., 1997).

In Western countries, no large studies have been conducted on KP meningitis; the epidemiology differs from that of Asia as KP has been mainly, but rarely, isolated in post-surgical/traumatic meningitis (PSTM) (Beer et al., 2008; Pilmis et al., 2021; Zarrouk et al., 2007).

We hypothesized that in France, KP meningitis occurring without any prior meningeal effraction (called spontaneous meningitis, SM) and those occurring after prior trauma or neurological surgery (called post-surgical/traumatic meningitis, PSTM) are two different entities from a clinical, microbiological and genetic standpoint. The aim of our study is therefore to compare the clinical, microbiological, and molecular characteristics of KP meningitis referred to seven university hospitals in the Paris area over an 11-year period.

Methods

Study population

For this retrospective study, patients were recruited based on cerebrospinal fluid (CSF) analytical data. We screened patients' computer files from the microbiology department of the seven participating university hospitals for all CSF samples growing KP in bacteriological culture between January 2007 and May 2018. Participating university hospitals are located in the Paris area. We also analyzed patients whose clinical and biological presentation was compatible with the diagnosis of KP meningitis despite a sterile CSF culture but who had a concomitant blood culture positive for KP. Finally, we asked participating centers to report

any cases of which they were aware, from non-participating centers. All cases were reviewed by an expert panel of 2 infectious disease specialists (BR, AL) to confirm the diagnosis of KP meningitis according to the following criteria. The local ethics committee (Institutional Review Board -IRB 00006477) approved the study protocol.

Definition of KP meningitis

KP meningitis was defined in the absence of a ventricular or lumbar catheter by (i) a KP positive CSF culture; OR (ii) in case of a negative CSF culture, by the presence of clinical and biological signs of meningitis (defined by a CSF leukocytes count > 5 /mm^3) (Société de pathologie infectieuse de langue française, 2009) and a concomitant KP positive blood culture without an alternative diagnosis according to our expert panel. In patients with a ventricular or lumbar catheter, KP meningitis was defined by (i) two consecutive KP positive CSF cultures separated by at least 24 hours; OR (ii) a KP positive CSF culture AND radiological or clinical signs of central nervous system infection without an alternative diagnosis according to our expert panel. This definition was adapted from the Infectious Diseases Society of America (IDSA) guidelines for healthcare-associated ventriculitis and meningitis (Tunkel et al., 2017). In case of multiple episodes, patients were included only once and the first documented episode was considered.

After inclusion, patients were divided into two groups: patients with PSTM and patients with SM. PSTM was considered if the patient had a history of possible surgical meningeal effraction (neurosurgery, middle or internal ear surgery, external lumbar catheter) or a history of traumatic skull fracture confirmed by Computed tomography (CT) scan. Meningitis was considered as SM in all other case.

More details on clinical and biological data collection are available in the Supplementary Material.

Bacteriological analyses

For all isolates, antibiotic susceptibility testing and search for extended spectrum β-lactamase (ESBL) production were performed in the microbiology departments of each hospital according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines (European Committee on Antimicrobial Susceptibility Testing. 2009. Breakpoint tables for interpretation of MICs and zone diameters, version 1.0, 2009). For each available KP isolate the hypermucoviscous phenotype was defined by a positive string test (i.e. >5mm) performed on a colony grown on agar plate (Shon et al., 2013).

For each available KP isolate, we determined the capsular serotypes K1 or K2 and the presence of 4 virulence genes using a multiplex PCR, as described by Compain *et al* (Compain et al., 2014). The whole genome of each available KP isolate from SM was sequenced.

The genomes are publicly available under Bioproject PRJEB38788. Strains T88 and BCKP01 have been described in other studies (Bialek-Davenet et al., 2014; Rodrigues et al., 2020) their genomes are publicly available in the European Nucleotide Archive (ENA). T88 has been deposited under the secondary accession number ERS500945 and BCKP01 under the BioProject number PRJEB37472.

Statistical analyses

We used Fisher's exact test for categorical variables and the Mann-Whitney test for continuous variables. Median value and interquartile range values 25 and 75 are provided for continuous variables. Patients' survival was estimated using the Kaplan-Meier method and a log-rank (Mantel-Cox) test was performed to assess the difference in survival between SM and PSTM groups.

More details on the methods used for the molecular and the statistical analyses are available in the Supplementary Material.

Results

From January 2007 to May 2018, we identified 35 patients with at least one episode of KP meningitis (Fig. 1): 10 patients (29%, patients n°1 to 10) with a KP SM and 25 patients (71%, patients n°11 to 35) with a KP PSTM.

SM and PSTM characteristics

SM and PSTM characteristics are provided in Tables 1, 2, and 3.

Among the patients with SM, only one patient was of Asian origin (Table 2); three patients had radiological images consistent with acute mastoiditis or sinusitis, and one patient was treated for cavum neoplasia.

Among the 25 patients with PSTM, the most frequent indication for surgery was a brain or a spinal tumor (n=11/25, 44%) (Table S1). Fifteen patients (60%) had ventricular or lumbar catheter placed during surgery. The catheter was still present at the time of onset in 10 patients (40%). In 3 cases, meningitis occurred more than one year after the last surgery: chronic CSF leakage was present in 2 cases.

Comparison of SM and PSTM (Table 1)

Demographic and clinical data

There were no differences between the two groups regarding age, gender, Charlson score (Charlson et al., 1987), and Rankin score (van Swieten et al., 1988) before hospitalization. Significantly more patients in the SM group reported alcoholism as a previous condition

(30% versus 0%, p=0.02). Meningitis occurred while the patient was already hospitalized in ICU for another cause in 14 cases (56%) in the PSTM group and in no case in the SM group (p=0.002).

Septic shock occurred significantly more often in the SM group than in the PSTM group (50% vs 4% respectively, p=0.004).

Brain abscesses were found in three patients with PSTM and one patient with SM. Distant bacterial localizations tended to be more numerous with SM (p=0.06). Liver abscesses were found in two patients with SM and one patient with PSTM.

Treatment

All patients were treated with either a third-generation cephalosporin or meropenem as definitive therapy. Only patients with an ESBL-producing KP meningitis were treated with meropenem as definitive therapy. Duration of treatment was available for 21 surviving patients: there was no difference between SM and PSTM with regard to treatment duration.

Outcome

The 28-day mortality rate was significantly higher in the SM group (Fig. 2). Similarly, the in-hospital mortality rate was higher in the SM group than in the PSTM group (70% versus 16% respectively, p<0.004).

PSTM relapsed in five cases and SM in none (p=0.29). Relapses occurred in one patient with chronic CSF leakage and in four patients with an external ventricular catheter (EVC). All three patients who received intra-ventricular aminoglycoside during the first PSTM episode relapsed.

Microbiological analysis

We found a trend toward a higher rate of polymicrobial meningitis (28% versus 0% respectively, p=0.08) and a higher rate of ESBL-producing strains (28% versus 0% respectively, p=0.08) in the PSTM group. Looking at polymicrobial meningitis, associated bacteria were *Enterobacteriaceae* (4 patients), *Pseudomonas aeruginosa* (3 patients) and *Streptococcus oralis* (1 patient). Meningitis induced by ESBL-producing KP was not associated with a higher mortality rate (29% for ESBL-producing KP versus 32% for non-ESBL-producing KP, p>0.99). No strain was resistant to carbapenems.

A total of 16 strains from patients in our cohort had been maintained in the microbiology laboratories and could be further analyzed (Table 3). All strains isolated from SM had (1) a hypermucoviscous phenotype; (2) genes corresponding to capsular serotypes K1 or K2; (3) both *rmpA* and *iutA* virulence genes. No strains from the PSTM group had any of these characteristics (p<0.0001).

We then sequenced the genome of the seven strains isolated from the patients with SM (Table 3).

The two strains with the K1 capsular serotype gene cluster belonged to the sequence type ST23, and the five strains with the K2 capsular serotype belonged to ST66 (n=2), ST86 (n=2) and ST380 (n=1).

A allelic profile comparisons and minimum spanning tree analysis showed that the KP strains isolated from SM were epidemiologically unrelated, as they differed among themselves by cgMLST 14 alleles or more (Fig. S1).

Discussion

In our study, we identified two different patterns of KP meningitis, differing in clinical, microbiological and molecular presentation. On the one hand, spontaneous KP meningitis is a rare but dreadful infection induced by hypervirulent KP strains that frequently leads to severe invasive and disseminated infections resulting in septic shock (50%), multiple bacterial localizations (60%) and death (70%); SM likely occurs in patients with little prior conditions. On the other hand, post-surgical/traumatic KP meningitis is frequently induced by ESBL-producing strains (28%), and less frequently lead to septic shock (4%), and death (16%). PSTM occurs mainly in patients hospitalized in ICU for a neurosurgical condition (56%) which affects prognosis more than PSTM. The in-hospital mortality rate was significantly higher in the SM group (70% versus 16%, p=.004) than in the PSTM group. This observation contrasts with the much poorer health status at the onset of meningitis in patients with PSTM. A higher mortality rate in patients with SM has also been reported elsewhere (Pilmis et al., 2021; Tang and Chen, 1994). Several factors may contribute to the difference in mortality between SM and PSTM: (i) 84% of PSTM occurred during hospitalization and may have been detected and treated at an earlier stage; (ii) strains isolated in SM have more virulence genes than those isolated in PSTM, which could explain a more severe clinical picture.

Whether a hypermucoviscous phenotype, a K1/K2 phenotype, or virulence genes *rmpA* and *iutA* alone are sufficient criteria to qualify a KP as hypervirulent is debated. Nonetheless, the association of all these three characteristics in all strains isolated from SM in this study, as well as a concordant clinical phenotype, seem to us to be sufficient arguments to qualify them as hypervirulent strains (Shon et al., 2013; Wyres et al., 2019).

As traditionally reported, we observed that patients with SM were mainly men (80%) with a mean age in the 6th decade (Chang et al., 2010; Jung et al., 2015; Tang et al., 1997). Only one patient was from Asia. We found a diversity of geographical origin of the patients similar to the observations of other studies on hvKP infections in the Paris region (Decré et al., 2008;

Rossi et al., 2018). Unfortunately, no data were available in our work on patients' travel history. In accordance with the literature (Chang et al., 2010; Jang et al., 1993; Jung et al., 2015; Lee et al., 2003; Pilmis et al., 2021; Su et al., 2010; Tang et al., 1997), 30% of patients with SM had diabetes mellitus and 30% reported current alcoholism; no patient had cirrhosis. We also found concomitant otorhinolaryngologic disease as a possible source of meningitis in 4/10 SM. Similarly, Chang *et al.* reported a concomitant ear infection in 14% of SM (Chang et al., 2010). We observed bacteremia in 66% of patients with SM, which is consistent with what has been reported elsewhere (Chang et al., 2010; Jung et al., 2015).

All strains we recovered from the SM group belonged to the K1 or K2 serotypes. In a recent study conducted by Ku *et al.* in Taiwan and analyzing phenotypic and genotypic characteristics of 20 KP strains isolated from SM, K1 and K2 were the most frequent serotypes but other serotypes (including K5, K20, K54, K57) were also identified (Ku et al., 2017). However, in the Paris region, all hvKP strains isolated in previous studies belonged to K1/K2 serotypes (Decré et al., 2008; Rossi et al., 2018). In our study, we observed a predominance of K2 serotype in SM isolates, which was also described by Ku *et al*.(Ku et al., 2017) and contrasts with hvKP isolated from liver abscesses which predominantly belong to K1 serotype (Rossi et al., 2018).

The mechanisms and virulence factors associated with blood-brain barrier crossing by hvKP in SM are poorly understood. Recently, Lu *et al.* showed in a mouse model that colibactin was necessary but not sufficient for the meningeal tropism of *pks*+ K1 ST23 (Lu et al., 2017). Colibactin is a small genotoxic molecule synthesized by almost all strains of K1 ST23 and K2 ST380 (Bialek-Davenet et al., 2014; Holt et al., 2015). In our study, the colibactin encoding gene was identified in K1 and K2 ST380 strains as well as in one ST66 strain, but it was absent in three K2 strains. This observation demonstrates that, at least for some K2

strains, the colibactin is not necessary to cross the blood-brain barrier. Further studies are needed to understand how hypervirulent KP strains cross this barrier.

Most KP strains isolated in spontaneous meningitis do not produce ESBL (Ku et al., 2017). In this study, no strains in the SM group produced ESBL, whereas seven strains in the PSTM group (28%) did. In our study, ESBL-producing status of the KP strain was not associated with a higher mortality rate (p>0.99), Pilmis *et al.* have recently reported a similar result(Pilmis et al., 2021). . In our work, this observation could be explained firstly by the strong impact of hvKP strains on the mortality rate of non-ESBL KP meningitis, and secondly by the systematic use of meropenem as empiric treatment for suspected nosocomial meningitis. Nevertheless, although antibiotic resistance does not represent an issue in hvKP so far (Ku et al., 2017; Piednoir et al., 2020; Rossi et al., 2018; Shon et al., 2013; Siu et al., 2012), some cases of infections with hvKP strains producing ESBL, carbapenemase, or *mcr-1* have been reported (Lee et al., 2017; Siu et al., 2012; Su et al., 2008; Surgers et al., 2016; Wyres et al., 2019).

Our study had several limitations. First, the low number of KP meningitis cases may have negatively affected the robustness of our statistical analyses. Indeed, we could only perform unadjusted analyses. Therefore, we cannot exclude that confounding factors may have affected some of our results. Second, this study was retrospective and information concerning geographic origin and preexisting conditions was declarative. This may undermine the exhaustivity of our data, hence, we had no information concerning patients' travel history. Third, abdominal imagery was reported for only three patients with a KP SM. The lack of standardized procedure to assess distant bacterial localizations may have led to an underestimation of their occurrence in our cohort. Fourth, due to the rarity of the disease, we had to consider a long period of time (11 years) to be able to include a meaningful number of cases. Finally, we were only able to recover 16 KP strains from meningitis, which may have

impacted the representativity of our observation. However, the phenotypic and genotypic characteristics of our strains were consistent with those of other studies on hvKP in the same geographic region.

In conclusion, KP SM accounted for 29% of KP meningitis with a high mortality rate. All available KP strains from spontaneous meningitis had genotypic and phenotypic characteristics associated with hypervirulence, making KP SM a coherent clinical and microbiological entity.

Table 1 : Characteristics of spontaneous and post-surgical/traumatic meningitis

	Whole Population	PSTM	SM	p
Population characteristics				
Men/total	26/35 (74.3%)	18/25 (72%)	8/10 (80%)	NS
Age (years)	54 [43-63]	52 [41-61]	58.3 [45.8-64.3]	NS
Charlson score	0 [0-1]	0 [0-1]	1 [0-2]	NS (.13)
Diabetes mellitus	6/34 (17.6%)	3/24 (12.5%)	3/10 (30%)	NS
Alcoholism	3/34 (8.8%)	0/24	3/10 (30%)	0.02
End stage renal failure	0/35	0/25	0/10	NS
Cirrhosis	0/35	0/25	0/10	NS
Rankin score	0 [0-0]	0 [0-0]	0 [0-0]	NS
Hospitalization in ICU prior to meningitis	14/35 (40%)	14/25 (56%)	0/10	0.002
Clinical and biological presentation				
T°>38°C ou <36°C	25/29 (86.2%)	18/19 (94.7%)	7/10 (70%)	0.11
Altered mental status	16/28 (57.1%)	8/18 (44.4%)	8/10 (80%)	0.11
Septic shock	6/35 (17.1%)	1/25 (4%)	5 /10 (50%)	0.004
CSF leukocytes count (/mm^3)	1300 [290-6300]	1150 [185-6400]	3750 |562.5-9025]	NS
CSF protein level (g/L)	2.7 [1.4-5.9]	2.32 [1.2-4.9]	4.05 [1.7-61]	NS
CSF glucose level (mmol/L)	1.4 [.1-3.03]	1.35 [.25-2.94]	1.57 [0-3.1]	NS
Other bacterial localizations				
Cerebral abscess(es)	4/31 (12.9%)	3/25 (12%)	1/6 (16.7%)	NS
Positive blood culture(s)	13/31 (41.9%)	7/22 (31.8%)	6/9 (66.7%)	NS (0.11)
Number of positive sites	0 [0-1]	0 [0-1]	.5 [0-1.25]	NS
Number of suspected sites of infection	0 [0-1]	0 [0-1]	1 [0-2]	NS (0.06)
Outcome				
Relapse	5/35 (14.3%)	5/25 (20%)	0/10	NS
GOS	4 [1-5]	4 [3-5]	1 [1-5]	0.046
Mortality				
In-hospital mortality	11/35 (31.4%)	4/25 (16%)	7/10 (70%)	0.004
28-day mortality	7/35 (20%)	2/25 (8%)	5/10 (50%)	0.01
Management				
Definitive antibiotic treatment :				
Third-generation cephalosporin	26/34 (76.5%)	17/24 (7.8%)	9/10 (90%)	NS
Meropenem	7/34 (2.6%)	7/24 (29.2%)	0/10	NS (0.08)
Fluoroquinolone	17/34 (50%)	15/24 (62.5%)	3/10 (30%)	NS (0.13)
Aminoglycoside	7/34 (2.6%)	3/24 (12.5%)	4/10 (40%)	NS
Intraventricular	3	3	0	
Intravenous	4	0	4	
Vancomycin	1/34 (2.9%)	0/24	1/10 (10%)	NS
Antibiotic duration (days)	14 [10-4.5]	14 [14-35.3]	14 [1.3-41.5]	NS
Hospital length of stay (days)	48 [24-72]	68 [37-90]	11 [1-33.5]	<0.0001
ICU hospitalization	29/35 (82,8%)	21/25 (84%)	8/10 (80%)	NS
ICU length of stay (days)	36 [5.5-63]	38 [15-66.5]	7 [1-40]	NS (0.24)
Microbiological characteristics				
ESBL	7/35 (20%)	7/25 (28%)	0/10	0.08
Polymicrobial	7/35 (20%)	7/25 (28%)	0/10	0.08
String test	7/16 (43.8%)	0/9	7/7 (100%)	<0.0001
K1/K2 Serotype	7/16 (43.8%)	0/9	7/7 (100%)	<0.0001
K1	2/16 (12.5%)	0/9	2/7 (28.6%)	NS (0.18)
K2	5/16 (31.3%)	0/9	5/7 (71.4%)	0.005
Virulence genes				
rmpA	7/16 (43.8%)	0/9	7/7 (100%)	<.0001
iutA	7/16 (43.8%)	0/9	7/7 (100%)	<.0001
ybtS	9/16 (56.3%)	3/9 (33.3%)	5/7 (71%)	NS
allS	2/16 (12.5%)	0/9	2/7 (29%)	NS (.18)

*Values are no. (%) or no. positive/no. tested, or median [IQR25-75]. CSF=cerebrospinal fluid; ESBL = extended spectrum β-lactamase; ICU = intensive care unit; GOS=Glasgow outcome scale; PSTM=post-surgical/traumatic meningitis; SM=spontaneous meningitis. NS = not significant = p>.05; p-values between .05 and .25 are indicated in brackets. *P* values for categorical variables was calculated using a Fischer exact test. *P* values for continuous variables was calculated using a Mann-Whitney test.

Table 2: Characteristics of patients with spontaneous K. pneumoniae meningitis

N°	Gender	Age (year)	Year	Origin	Comorbidities	Symptoms	Septic shock	PBC	Cerebral complications	Distant bacterial localizations	ENT infection	Antibiotic	LOT (days)	Vital Status[§]
1[a]	M	63	2013	Unk	Alcoholism, ICH, DM, HBP, dyslipidémia	AMS	Yes	Yes	Unk	Urines	No	3GC	7	Deceased
2[a]	M	62	2011	Unk	Active psoriatic arthritis (anti-TNF)	Headache, NS, AMS, cerebellar syndrome, fever	Yes	Yes	Unk	Urines, lung, liver	No	3GC	1	Deceased
3[a]	F	47	2009	SSA	Gougerot-Sjögren	Headache, confusion, fever	No	Unk	Unk	0	No	0[#]	0	Deceased
4[a]	M	56	2014	Caucasian	Alcoholism	AMS, fever	Yes	Yes	Cerebral abscesses	Pericardium, pleura, lung, urines, joint	Sinusitis	3GC, AG	66	Deceased
5[a]	M	61	2018	Caribbean	0	AMS, NS	No	No	No	0	Mastoiditis	3GC, AG, FQ	52	Survived
6[a]	M	71	2015	Unk	Active cavum cancer (chemotherapy), HBP	Headache, nausea, AMS, fever	Yes	No	No	0	No	3GC, AG, vancomycin	1	Deceased
7[a]	M	42	2018	Caucasian	HIV*, chronic pancreatitis, alcoholism, DM	NS, seizure, AMS	No	Yes	No	Urines	Mastoiditis	3GC, FQ	21	Survived
8	M	42	2011	NA	0	Headache, nausea, NS, fever	No	No	No	Liver, lung	No	3GC, AG	42	Survived
9	F	68	2009	SSA	Obesity, DM	Headache, seizure, AMS, fever	Yes	Yes	AH	Lung, urines	No	3GC	2	Deceased
10	M	50	2009	Asian	0	Headache, AMS, fever	No	Yes	AH, ventriculitis	0	No	3GC, FQ	40	Deceased

AG= aminoglycoside; AH= acute hydrocephalus; AMS= altered mental status; 3GC=third-generation cephalosporin; DM= diabetes mellitus; FQ= fluoroquinolone; HBP=high blood pressure; HIV=human immunodeficiency virus; ICB=intracerebral bleeding; LOT=length of treatment; NA=North Africa; NS=neck stiffness; PBC=positive blood culture; SSA=Sub-Saharan Africa; Unk=Unknown.

§Vital status at the end of hospitalization.

*CD4 count = 1200/mm^3, undetectable viral load.

#One patient died before receiving the first dose of antibiotic

[a]= patients for whom KP isolates were still available for further analysis. Each isolate has the corresponding number of his patient in Table 3

Table 3: Microbiological characteristics of 16 K. pneumoniae isolates from meningitis

N°	ESBL	Resistance genes (WGS)	String test	ST	*wzi*	CS	*rmpA**	*rmpA2***	*ybtS**	*allS**	*iutA**	*Kvg***	*Salmochelin***	*Colibactin***	*Microcin***	Isolates‡
Spontaneous meningitis																
1	-	*blaSHV 11*	+	23	1	K1	+	+	+	+	+	-	+	+	+	SAKP02
2	-	*blaSHV 11*	+	23	1	K1	+	+	+	+	+	-	+	+	+	SAKP01
3	-	*blaSHV 1*	+	86	2	K2	+	+	-	-	+	+	-	-	-	T88
4	-	*blaSHV, tetU*	+	380	2	K2	+	-	+	-	+	+	+	+	+	CMKP01
5	-	*blaSHV 77*	+	66	646	K2	+	-	-	-	+	-	+	-	-	HGKP01
6	-	*blaSHV 1*	+	86	2	K2	+	+	+	-	+	+	+	-	-	BJKP01
7	-	None	+	66	257	K2	+	-	+	-	+	-	+	+	-	BCKP01
Post-surgical/traumatic meningitis																
8	-	ND	-	ND	ND	Other	-	ND	-	-	-	ND	ND	ND	ND	ND
9	-	ND	-	ND	ND	Other	-	ND	+	-	-	ND	ND	ND	ND	ND
10	-	ND	-	ND	ND	Other	-	ND	+	-	-	ND	ND	ND	ND	ND
11	+	ND	-	ND	ND	Other	-	ND	+	-	-	ND	ND	ND	ND	ND
12	+	ND	-	ND	ND	Other	-	ND	-	-	-	ND	ND	ND	ND	ND
13	-	ND	-	ND	ND	Other	-	ND	-	-	-	ND	ND	ND	ND	ND
14	+	ND	-	ND	ND	Other	-	ND	-	-	-	ND	ND	ND	ND	ND
15	-	ND	-	ND	ND	Other	-	ND	-	-	-	ND	ND	ND	ND	ND
16	-	ND	-	ND	ND	Other	-	ND	-	-	-	ND	ND	ND	ND	ND

+=positive; -=negative; CS= capsular serotype; ND= Not Done; ST, =sequence type; ‡= Isolate reference in GENBANK. *=WGS and PCR, **=WGS only

Declaration of Competing Interest

The authors do not declare any conflicts of interest.

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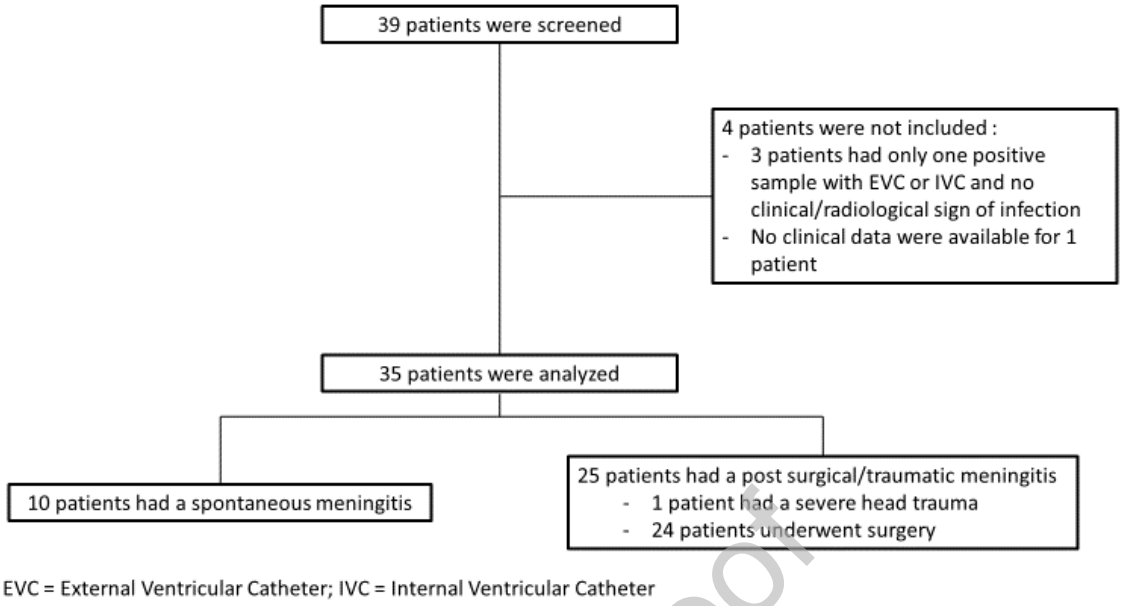
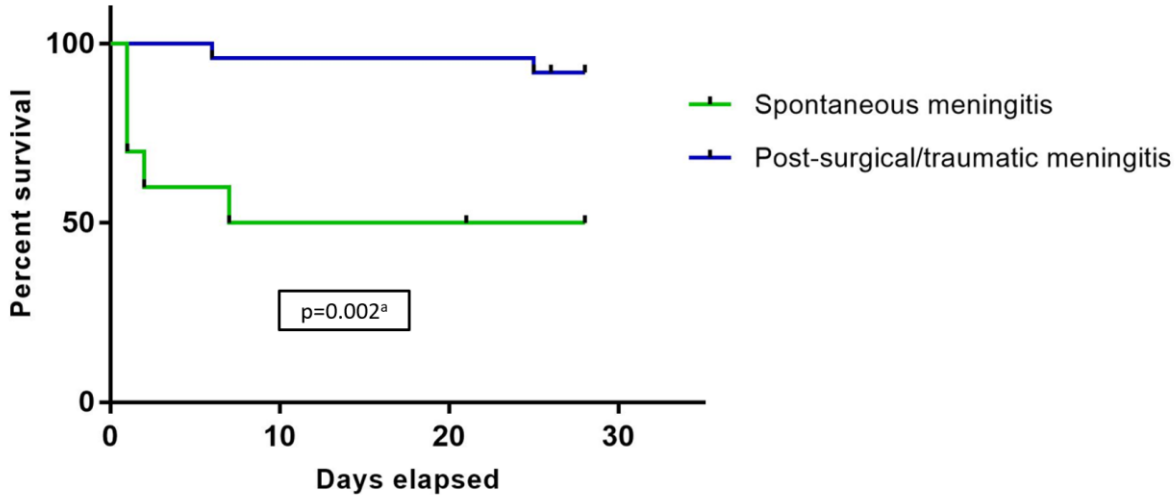


Fig. 1: Flow chart. Selection of patients with a spontaneous or a post-surgical/traumatic *K. pneumoniae* meningitis.



Day	0	1	2	6	7	22	25	28
Spontaneous meningitis (survivors)	10	7	6	6	5	5	5	5
Post-surgical/traumatic meningitis (survivors)	25	25	25	24	24	24	23	23

[a]A log-rank (Mantel-Cox) test was performed to assess the survival difference between SM and PSTM groups.

Fig. 2: 28-day survival in patients with a *K. pneumoniae* meningitis. Kaplan-Meier curves.