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Spontaneous community-acquired bacterial meningitis in adults admitted to the intensive care units in the Caribbean French West Indies: Unusual prevalence of *Klebsiella pneumonia*

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1 **Title:** Spontaneous community-acquired bacterial meningitis in adults admitted to the
2 intensive care units in the Caribbean French West Indies: unusual prevalence of *Klebsiella*
3 *pneumoniae*

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25 **Abstract - Word count : 51**

26 An unusual prevalence of *Klebsiella pneumoniae* (24%) was observed in 25 adults admitted to
27 the intensive care units of two University Hospitals from French West Indies for **spontaneous**
28 community-acquired bacterial meningitis. All tested isolates had several prominent features
29 of hypervirulent isolates, including *rmpa* and *iuc* genes, K1 or K2 capsular serotypes.

30 **Running title:** *K. pneumoniae* community-acquired meningitis

31 **Key words:** meningitis – *Klebsiella pneumoniae* - virulence - epidemiology

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38 **Text – Word count : 825**

39 Community-acquired bacterial meningitis (CABM) are rare in Western countries with an
40 incidence of 0.9 per 100 000 per year, associated with unfavorable outcome in
41 approximately 40% of cases (1). Most common involved pathogens are *Streptococcus*
42 *pneumoniae* and *Neisseria meningitidis*, including CABM requiring an intensive care unit (ICU)
43 admission (1). Guadeloupe and Martinique, two French overseas islands, located in the
44 Caribbean (about 800 000 inhabitants, mostly Caribbean and European) were considered as
45 very high-resource countries in 2013 (<http://hdr.undp.org/>). Very few data are available about
46 CABM epidemiology in this area (2). We report here the clinical and microbiological
47 characteristics, and outcome of **spontaneous** CABM in adults admitted in the ICU of two
48 University Hospitals from Caribbean French West Indies.

49 Over a 6 year-period (January 2012 to December 2017), all patients over 18 years admitted
50 for a diagnosis of CABM with a positive cerebrospinal fluid culture were retrospectively
51 included. **No post neurosurgical nor device-associated meningitis were included.** API
52 biochemical galleries (API, BioMerieuxTM, Marcy l'Etoile, France) were used for bacterial
53 identification. Antibacterial drug susceptibility was determined using the disc diffusion
54 method, according to the 2018 guidelines of CA- SFM/EUCAST ([http://www.sfm-](http://www.sfm-microbiologie.org)
55 [microbiologie.org](http://www.sfm-microbiologie.org)). Detection of *iuc* (coding for aerobactin) and *rmpA* (upregulator of capsule
56 expression) genes, and capsule serotyping of *Klebsiella pneumoniae* isolates were performed
57 as previously described (3). A standardized specific questionnaire was fulfilled to get
58 demographic, clinical and biological data, and outcome.

59 Chi-2 or Fisher's exact tests (if required) and Student's t test were used to compare categorical
60 and continuous variables, respectively. A p-value under 0.05 was significant. The ethical
61 committee of the University Hospital in Guadeloupe approved the protocol (registration
62 number: n° A1_18_06-01_MEN).

63 After exclusion of 7 patients because alternative diagnosis or lack of microbiological
64 confirmation, a total of 25 patients with culture-proven bacterial meningitis were included.

65 General data including underlying comorbidities for 17 (68%) patients are reported in the
66 Table. Main involved bacteria were *S. pneumoniae* (n=7, 28%), *K. pneumoniae* (n=6, 24%), *S.*
67 *aureus* (n=5, 20%) and *E. coli* (n=3, 12%). One patient displayed a mixed infection with *E. coli*
68 and *Streptococcus* spp. No difference has been shown regarding the bacterial epidemiology
69 between the two hospitals (p>0.05). Suppurative complications of the CABM-related bacteria
70 occurred in 4 patients: a cerebral abscess in two patients (due to *S. aureus* and a combination
71 of *E. coli* and *Streptococcus* spp., respectively), a *K. pneumoniae* liver abscess in one patient
72 and a *S. aureus* pulmonary abscess in another one. Moreover, an endocarditis was diagnosed
73 for 4 out of the 5 *S. aureus* CABM. The overall mortality was 52% (13 patients).

74 According to previous data (1,2), *S. pneumoniae* was the most frequent pathogen (28%) in our
75 study. Unexpectedly for CABM, we described a high prevalence of CABM- associated *K.*
76 *pneumoniae* (24%), mostly described as one of the main CABM-related pathogens in Asia (4,
77 5). In Taiwan, *K. pneumoniae* was even the first involved pathogen in adult CABM with
78 prevalence rates up to 50% (6). The identification of Gram negative bacillary and *S. aureus*
79 among the leading cause of bacterial adult's CABM is unusual and several hypothesis could be
80 considered: specific local epidemiology in the Caribbean with high frequency of *K. pneumoniae*-

81 related infections (reservoir issue), the role of the introduction of conjugated vaccines for *S.*
82 *pneumoniae* and *Neisseria meningitidis* as suggested elsewhere (7).

83 The emergence of severe community-acquired hypervirulent *K. pneumoniae* (CA-HvKp)
84 disease has been reported during the past three decades, usually pyogenic liver abscess, but
85 also meningitis, brain abscess or ophthalmitis, initially in Asia and more recently in Western
86 countries (8). Out of the 4 isolates investigated, all harbored *rmpa* and *iuc* genes. These two
87 genes coding for an increased expression of capsular material and an increased efficiency of
88 iron-acquisition, respectively, are two major hvKp-specific virulence factors (8). In addition, all
89 but one (K2) were assigned to the K1 capsular serotype. This serotype is strongly associated
90 with the Sequence Type 23, the most commonly genetic background recovered worldwide
91 associated to CA-HvKp (9). We did not find any significant difference of the clinical
92 presentation or outcome between patients with *K. pneumoniae* CABM versus others (after
93 exclusion of those displaying *S. aureus* endocarditis), related in part to the small sample size
94 ($p>0.05$) (Table 1). We noticed that 2 of the 4 *K. pneumoniae*-infected patients have
95 predisposing risk factors of CA-HvKp infection in our population (8), i.e. diabetes mellitus and
96 alcoholism. Taking into account that diabetes and alcoholism are overrepresented public
97 health issues in the Caribbean (10), a survey of such infections (CA-HvKp) is urgently needed.
98 The mortality is high (around 50%) with a short delay after admission. In term of antimicrobial
99 resistance, a recent rise of extended spectrum beta-lactamase - and carbapenemase-
100 producing HvKp has been reported. In our study, all isolates were susceptible to all
101 antimicrobials tested except for ampicillin and ticarcillin. Altogether, our data suggests the
102 need for comprehensive epidemiologic studies focused on CA-HvKp infections in the

103 Caribbean. A better understanding of environmental niches that act as reservoirs of these
104 isolates may enable preventive interventions.

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109 **Ethical approval** : The ethical committee of the University Hospital in Guadeloupe approved
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156 **Table:** Demographic characteristics, predisposing factors, clinical features upon hospital admission,
157 outcomes parameters and associated complications among the total population of community-acquired
158 bacterial meningitidis (All CABM) and Klebsiella pneumoniae meningitidis (KP CABM). Categorical
159 variables were expressed as percentages and continuous variables as medians (25th and 75th
160 percentiles).

Characteristics	All CABM		KP CABM	
	n=25		n=6	
Age (years) median [Q1-Q3]	60.0	[54–70]	60	[55–68]
Male, <i>n</i> (%)	16	64.0	4	67.0
Underlying disease				
Remote head trauma <i>n</i> (%)	0	0.0	0	0.0
Otitis/Sinusitis <i>n</i> (%)	3	12.0	2	33.0
Diabetes mellitus <i>n</i> (%)	7	28.0	1	16.0
Chronic alcoholism <i>n</i> (%)	4	16.0	1	16.0
Immunosuppressive status <i>n</i> (%)	5	20.0	0	0.0
Cirrhosis <i>n</i> (%)	0	0.0	0	0.0
Malignancy <i>n</i> (%)	4	16.0	0	0.0
Severe chronic renal insufficiency <i>n</i> (%)	2	8.0	0	0.0
Chronic respiratory insufficiency <i>n</i> (%)	0	0.0	0	0.0
Signs and symptoms upon presentation				
Headaches <i>n</i> (%)	14	56.0	6	100.0
Fever <i>n</i> (%)	25	100.0	6	100.0
Septic shock <i>n</i> (%)	7	28.0	0	0.0
Generalized seizure <i>n</i> (%)	5	20.0	3	33.0
Focal neurological deficit <i>n</i> (%)	0	0.0	0	0.0
Neck stiffness <i>n</i> (%)	13	52.0	4	66.0
Glasgow Coma scale, median [Q1-Q3]	10	[9–14]	9	[7–13]
Severity scores				
IGS II median [Q1-Q3]	56	[36-57]	43	[36-47]
Charlson's Score median [Q1-Q3]	3	[2-4]		
Outcome parameters				
Length of stay in ICU, (days) median [Q1-Q3]	10	[3–17]	13	[16–21]
Mechanical ventilation (VM) <i>n</i> (%)	18	72.0	5	83.0

Total duration of VM (days) median [Q1-Q3]	5	[0–17]	7	[2–21]
In-hospital mortality <i>n</i> (%)	13	52.0	3	50.0
Delay of mortality occurrence (days) median [Q1-Q3]	10	[4–22]	3	[1–24]
Initial cerebrospinal fluid results				
Glucose (mmol/L) median [Q1-Q3]	0.40	[0.02–3.83]	0.25	[0.03-4.75]
Protein (g/L) median [Q1-Q3]	5.25	[2.21–7.50]	6.60	[5.62-8.40]
Leukocytes/mm ³ median [Q1-Q3]	2350	[282–5745]	5990	[4795-6660]
PNN percentage median [Q1-Q3]	94	[90–95]	95	[91-97]
Gram's stain-positive (total) <i>n</i> (%)	20	80.0	6	100.0
Culture-positive <i>n</i> (%)	25	100.0	6	100.0
<i>Streptococcus pneumoniae</i>	7	28.0	-	
<i>Klebsiella pneumoniae</i>	6	24.0	6	
<i>Staphylococcus aureus</i>	5	20.0	-	
<i>Escherichia coli</i>	2	8.0	-	
<i>Neisseria meningitidis</i> B	2	8.0	-	
<i>Streptococcus spp</i>	1	4.0	-	
<i>Pseudomonas aeruginosa</i>	1	4.0	-	
<i>Escherichia coli</i> + <i>Streptococcus spp</i>	1	4.0	-	
Associated Complications				
Bacteremia <i>n</i> (%)	18	72.0	4	66.0
<i>Streptococcus pneumoniae</i>	7			
<i>Klebsiella pneumoniae</i>	4			
<i>Staphylococcus aureus</i>	4			
<i>Escherichia coli</i>	1			
<i>Pseudomonas aeruginosa</i>	1			
Cerebral abscess <i>n</i> (%)	2	8.0	0	0.0
Other abscess <i>n</i> (%)	2	8.0	1	16.0