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RESEARCH LETTER

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Clinical phenotype and outcomes of pneumococcal versus meningococcal purpura fulminans: a multicenter retrospective cohort study

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Purpura fulminans (PF) is a rare cause of septic shock characterized by the association of a sudden and extensive purpuric rash together with an acute circulatory failure [1] leading to high rates of intensive care unit (ICU) mortality [1, 2] and long-term sequelae [3]. Clinical presentation of patients with PF differs from that of patients with meningitis since PF patients are commonly admitted to the ICU for hemodynamic impairment exposing them to early death from refractory circulatory failure, as opposed to patients with meningitis who are usually admitted to the ICU for neurological impairment. Among adult patients, *Neisseria meningitidis* and *Streptococcus pneumoniae* are the most commonly involved microorganisms accounting for more than 80% of PF [1] and meningitis [4]. While clinical features and outcomes widely differ between adult patients with pneumococcal and meningococcal meningitis [4], it remains unclear whether pneumococcal (pPF) and meningococcal (mPF) PF exhibit different clinical phenotypes and outcomes, although pPF was previously shown to predominantly occur in asplenic patients [5] and carries a higher risk of limb amputation [1]. We therefore compared the clinical, biological presentations and outcome of adult patients with pPF and mPF.

We performed an ancillary analysis of a 17-year multicenter retrospective study conducted in 55 centers in France, which included all consecutive patients (≥ 18 years) admitted to the ICU for an infectious PF (2000–2016) [1]. Patients with non-microbiologically documented PF or a bacterial documentation other than *Neisseria meningitidis* and *Streptococcus pneumoniae* were excluded.

During the study period, 195 patients with mPF and 67 with pPF were included. As compared to patients with mPF, those with pPF were older and had higher ICU severity scores. Chronic alcoholism and asplenia were more frequent in pPF, while the proportion of patients without previous comorbid conditions was lower. The time elapsed between disease onset and ICU admission was longer and purpura was less often noticed before ICU admission in pPF than in mPF. pPF patients also had lower platelet counts, higher serum urea and creatinine levels, and more frequent bacteremia. pPF patients needed more frequent invasive mechanical ventilation support, renal replacement therapy, plasma and platelets transfusions and had higher durations of invasive mechanical ventilation and vasopressor support. ICU mortality and rate of limb amputation were higher in patients with pPF (Table 1).

The Kaplan–Meier survival analysis did not show significant difference between pPF and mPF patients ($p = 0.80$ by the log-rank test, Fig. 1).

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Table 1 Comparison between meningococcal ($n=195$) and pneumococcal ($n=67$) purpura fulminans

	Meningococcal purpura fulminans $n=195$	**Pneumococcal purpura fulminans $n=67$**	***p* value**
Patient's characteristics and ICU scores			
Male gender	97 (50)	37 (55)	0.527
Age, years	24 [19–45]	49 [38–60]	< 0.001
SAPS II	50 [35–66]	63 [58–72]	< 0.001
SOFA	11 [8–14]	14 [11–15]	< 0.001
Main comorbidities			
Chronic alcoholism	5 (2)	9 (13)	0.002
Diabetes mellitus	3 (2)	4 (6)	0.073
Asplenia or hyposplenia	3 (2)	34 (51)	< 0.001
Malignant hemopathy	1 (1)	2 (3)	0.162
Chronic respiratory disease	18 (23)	14 (28)	0.625
Immunocompromised status	5 (3)	4 (6)	0.241
No coexisting comorbid conditions	164 (84)	22 (33)	< 0.001
Clinical features upon ICU admission			
Days between disease onset and ICU admission, days	4 [4–5]	5 [4–6]	0.003
Headache	99 (51)	26 (39)	0.121
Myalgia	48 (25)	12 (18)	0.338
Digestive signs	124 (64)	41 (61)	0.839
Coma Glasgow score	15 [13–15]	15 [13–15]	0.751
Temperature, °C	38.5 [37–40]	38.5 [37–39]	0.802
Neck stiffness	52 (27)	6 (9)	0.004
Purpuric rash before ICU admission	168 (86)	38 (57)	< 0.001
β-Lactam antibiotic therapy before ICU admission	157 (81)	46 (69)	0.067
β-Lactam antibiotic therapy at ICU admission	195 (100)	67 (100)	–
Biological data upon ICU admission			
Leukocytes count, 10^3 mm^{-3}	10,700 [4000–20,800]	10,655 [2500–19,750]	0.717
Platelets count, 10^3 mm^{-3}	61,000 [28,500–100,000]	33,000 [19,000–49,500]	< 0.001
C-reactive protein, g/L	148 [90–247]	179 [141–289]	0.095
Procalcitonin, ng/mL	48 [14–100]	102 [55–164]	0.087
Troponin, mg/L	1 [0.10–12]	0.25 [0.13–11]	0.697
Creatine kinase, IU/L	300 [110–852]	812 [365–3460]	0.016
Serum urea, mmol/L	9 [7–11]	13 [11–15]	< 0.001
Serum creatinine, µmoL/L	190 [136–250]	240 [184–310]	< 0.001
Prothrombin time, %	33 [22–44]	29 [15–38]	0.227
Factor V, %	23 [10–49]	21 [9–29]	0.246
Arterial lactate, mmol/L	7.40 [5–11]	8 [6–11]	0.798
Fibrinogen, g/L	1.70 [0.6–3]	1.16 [0.5–2]	0.122
Microbiological data at ICU admission			
Bacteremia	99 (51)	56 (84	< 0.001
Lumbar puncture performed	125 (64)	29 (43)	0.004
Positive cerebro-spinal fluid culture	72/125 (58)	11/29 (38)	0.080
Outcome in the ICU			
Lowest LVEF, %	33 [20–45]	30 [25–50]	0.870
Inotropic agent	91 (64)	35 (61)	0.894
Platelets transfusion	57 (29)	46 (69)	< 0.001
Plasma transfusion	67 (34)	44 (66)	< 0.001
Steroids for septic shock or meningitis	116 (60)	45 (67)	0.333
Activated protein C	33 (17)	9 (13)	0.632
Invasive mechanical ventilation	152 (78)	65 (97)	0.001

Table 1 (continued)

	Meningococcal purpura fulminans $n=195$	Pneumococcal purpura fulminans $n=67$	*p* value
Duration of tracheal intubation, days	4 [2–9]	10 [3–28]	< 0.001
Duration of vasopressors, days	3 [2–5]	5 [3–8]	< 0.001
Renal replacement therapy	69 (36)	45 (67)	< 0.001
Veno-arterial ECMO	7 (4)	6 (9)	0.104
Limb amputation	19 (10)	21 (31)	< 0.001
Limb amputation among ICU survivors	18/125 (14)	19/32 (59)	< 0.001
Death in ICU	70 (36)	35 (52)	0.027
Duration of ICU stay, days	5 [2–11]	14 [3–35]	< 0.001
Duration of hospital stay, days	12 [2–23]	23 [3–78]	0.003

Continuous variables are reported as median [Interquartile range] and compared between groups using the Student *t*-test. Categorical variables are reported as numbers (percentages) and compared using χ^2 test. A *p* value < 0.05 was considered significant

ICU intensive care unit; *IMV* Invasive Mechanical Ventilation, *ECMO* Extracorporeal membrane oxygenation, *LVEF* Left ventricular ejection fraction, *SAPSII* Simplified Acute Physiology Score, *SOFA* Sequential Organ Failure Assessment

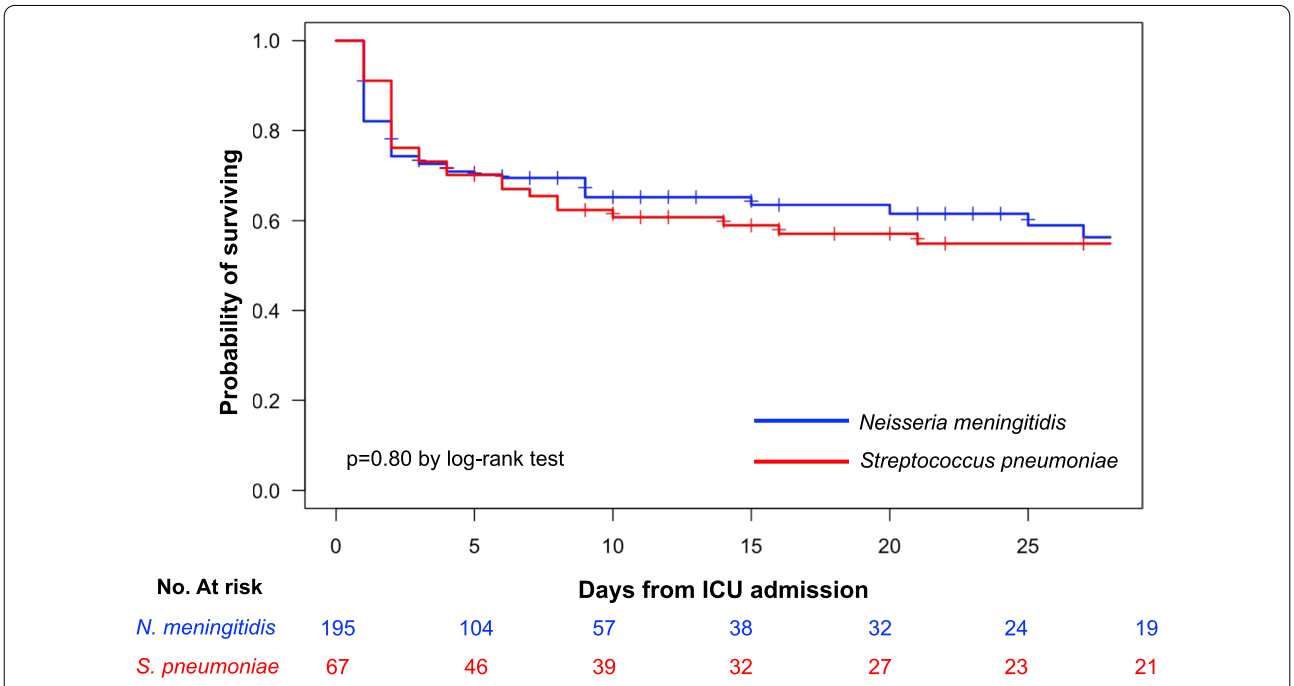

Fig. 1 Kaplan–Meier survival estimates during the 30 days following ICU admission of patients with pneumococcal (red curve) and meningococcal (blue curve) purpura fulminans

By multiple logistic regression adjusting on age, SOFA score, administration of β-lactam antibiotic therapy before ICU admission, platelet counts and arterial lactate levels, pPF was not associated with ICU mortality (adjusted Odds Ratio = 1.15 95% CI 0.45–2.89, $p=0.77$).

As already reported in adults patients with bacterial meningitis [4], this study confirms that significant differences exist between mPF and pPF, regarding both the clinical presentation at ICU admission and outcomes. Patients with pPF showed a different clinical phenotype, with less frequent purpura possibly leading to less frequent antibiotic treatment, more comorbidities with a more severe presentation at ICU admission, resulting in a higher rate of organ failures during ICU stay. Whether this more severe presentation should be ascribed to the level of virulence of the causative pathogen or to host-related characteristics is unsettled.

Our study has several limitations including its retrospective design and its long recruitment period with a high number of centers implying ICU procedures being

inevitably heterogeneous. Nevertheless, the clinical presentation as well as the course in the ICU of patients with PF seem to differ according to the causative bacterium. This clinical observation should encourage researchers to better study the pathophysiology of pPF in order to develop targeted innovative therapies as being done for mPF [6].

Abbreviations
ICU: Intensive care unit; mPF: Meningococcal purpura fulminans; pPF: Pneumococcal purpura fulminans; SOFA: Sequential Organ Failure Assessment.

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Authors' contributions
DC and NDP are responsible for the conception and design. All the authors were responsible for analysis and interpretation of data. All authors read, critically reviewed and approved the final manuscript. DC takes responsibility for the paper as a whole. All authors read and approved the final manuscript.

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Availability of data and materials
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Declarations

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Consent for publication
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Competing interests
The authors declare that they have no competing interests.

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