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

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Keywords: Purpura fulminans, Neisseria meningitidis, Streptococcus pneumoniae, Septic shock, Meningitis

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.

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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).
| Patient's characteristics and ICU scores | Meningococcal purpura fulminans n = 195 | Pneumococcal purpura fulminans n = 67 | p value |
|-----------------------------------------|------------------------------------------|----------------------------------------|---------|
| 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       |                                         |                                        | < 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   |
| Biological data upon ICU admission      |                                         |                                       |         |
| Leukocytes count, 10^9 mm^-3            | 10,700 [4000–20,800]                     | 10,655 [2500–19,750]                   | 0.717   |
| Platelets count, 10^9 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 $\chi^2$ 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, SAPS II Simplified Acute Physiology Score, SOFA Sequential Organ Failure Assessment

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 PF in order to develop targeted innovative therapies as being done for mPF [6].

**Abbreviations**

ICU: Intensive care unit; mPF: Meningococcal purpura fulminans; PF: 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**

The dataset used and analyzed for the current study is available from the corresponding author on reasonable request.

**Declarations**

**Ethics approval and consent to participate**

This study was conducted in accordance with the amended Declaration of Helsinki and was approved by the Institutional Review Board (CE 2016–01) of the French Intensive Care Society in March, 2016.

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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