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Clinical presentation and outcome of twenty cases of Invasive Meningococcal Disease due to Serogroup C — Clonal complex 11 in the Florence province, Italy, 2015—2016

KEYWORDS
Neisseria meningitidis;
Invasive Meningococcal Disease;
Septic shock;
Emergency Departments

Dear Editor,

We read with interest the paper by Lucidarme et al. about geo-temporal localization of Invasive Meningococcal Diseases (IMD) cases due to hyperinvasive ST-11 clonal complex (cc11).[1] In Tuscany, Central Italy, 58 IMD cases, of which 12 deaths, occurred from January 2015 to November 2016, following the emergence of cc-11 *Neisseria meningitidis* Serogroup C.[2] We analyze 20 cases from this outbreak managed in 3 tertiary hospitals in Florence area (S. Maria Annunziata in Bagno a Ripoli, S. Maria Nuova in Florence, and S. Giuseppe in Empoli), in order to describe clinical presentation and outcome determinants. These hospitals have Emergency Departments (EDs) operating on 24-h-basis.

All data derived from the retrospective analysis of electronic clinical charts, and from the laboratory electronic database. All patients consecutively referring to the EDs of these hospitals in the period January 2015—June 2016, and confirmed positive for IMD, were included. A diagnosis of laboratory-confirmed IMD was made, according to National Guidelines,[3] if a patient's samples (blood and/or cerebrospinal fluid) were culture-positive for *N. meningitidis*, or Real Time-PCR (RT-PCR) positive for the *ctrA* gene, or both.[4] All samples in which the *ctrA* gene was detected by RT-PCR were included in a serogrouping analysis. The serogroups were identified by RT-PCR or end-point PCR by using appropriate primers and probes.[4] Diagnosis and clonal-complex analysis were performed by the Laboratory of Immunology and Infectious Diseases, Meyer Children's Hospital, and the genomic analysis was confirmed by the National Reference Laboratory of the National Institute of Health in Rome. Statistical univariate analysis have been conducted using contingency tables with calculation of chi-squared test, and Mann—Whitney U test.

As used in clinical practice,[5,6] we classified our IMD cases as bacteraemia if only mild symptoms were present, as meningitis or sepsis if, respectively, meningeal or systemic symptoms were predominant, and as sepsis/meningitis in case of combination of both clinical presentations. We define as having septic shock with *Purpura fulminans* the patients with shock and acute thrombotic disorder rapidly leading to skin necrosis and disseminated intravascular coagulation. As almost all cases occurred before "Sepsis-3 Consensus", we defined sepsis and septic shock according to previous definitions.[7]

Among the 20 patients included in the study, none had significant co-morbidities. Two adolescent patients were vaccinated in 2007—2008, one 59-year-old patient had been vaccinated 21 days before the onset of symptoms. The average time from the symptoms to the arrival in the ED was 37 h. The clinical symptoms before pointing to ED were: fever in 100%, headache in 94%, confusion in 38%, neck stiffness in 30%, arthralgia in 19%. The 'classic triad' of neck stiffness, fever and altered consciousness was present in 30% of cases. On the contrary, petechiae were always present. The main clinical pictures at ED presentation were: bacteraemia in 2 patients (10%), meningitis in 3 cases (15%), meningitis/sepsis in 6 (30%); and septic shock with *Purpura fulminans* in the remaining 9 (45%). The patient demographic, clinical and bio-chemical characteristics at the time of ED referral are summarized in Table 1.

The average time between the arrival of the patient at ED and the start of antibiotic therapy, available in 14 cases, was 3 h, in 93% of cases this therapy included Ceftriaxone. The aetiological diagnosis was obtained through: PCR on blood (carried out in 18 cases, positive in 17/18), PCR on

Table 1 Demographical and clinical characteristics found at the EDs in 20 patients with IMD due to Serogroup C cc11, by clinical presentation, from January 2015 to June 2016.

Characteristics (n available data/total)[a]	All patients (20 cases)	Meningitis (3 cases)	Meningitis and sepsis (6 cases)	Bacteremia (2 cases)	Septic shock with *Purpura fulminans* (9 cases)
Male sex (%, 20/20)	55%	33%	50%	50%	66%
Years (mean, 20/20)	40 (13—83)	37 (20—69)	45,6 (26—66)	26 (18—34)	39 (13—83)
Main presenting symptoms (20/20)	Fever (Mean 38.7 °C) and petechiae (different degrees) always present	Few petechiae, fever, meningeal signs	Petechiae, fever and meningeal signs. Some unusual secondary localization (2 pericarditis, 1 arthritis)	Few petechiae and low-grade fever	Confluent petechiae, fever
Hours between symptoms onset and referral to ED (mean, 13/20)	24	Data not available	28	15	22
MEWS score at presentation to ED (mean, 13/20)	1,8	2,5	2,2	0,5	1,5
Selected bio-chemistry parameters					
White blood cells (mean, 16/20)	$13{,}1 \times 10^3$	$13{,}8 \times 10^3$	$18{,}0 \times 10^3$	$17{,}0 \times 10^3$	$6{,}3 \times 10^3$
Platelets (mean, 16/20)	119×10^3	134×10^3	136×10^3	170×10^3	68×10^3
C-reactive protein (mean, 14/20)	18	27	19	16,5	11
Procalcitonin (mean, 10/20)	80	55	22	Not performed	127
Cerebrospinal fluid					
Proteins (mean, 13/13)		458 (273—737)	436 (73—840)	25 (23—29)	30 (20—40)[b]
Cells (mean, 13/13)		4790 (248—11,000)	6027 (200—18,000)	5 (1—8)	5 (2—8)[b]
Glucose (mean, 13/13)		41 (3—115)	19 (0—74)	60 (55—65)	55 (50—65)[b]
Need for intensive care (IC) (20/20)	17/20	2/3	6/6	0/2	9/9
Mean length of stay in IC (days)		1,4	10		Not calculable[c]
Letality (20/20)	7/20; 35%	0/3; 0%	0/6; 0%	0/2; 0%	7/9; 77%

[a] Not all data are available for all patients. Number in brackets refer to available data on total data.
[b] Among patients with septic shock with *Purpura fulminans*, cerebrospinal fluid in ED has been collected in 2 cases only.
[c] Average length of stay in the Intensive Care incorrectly calculable for patients with septic shock with *Purpura fulminans*, because for some patients the hospital stay was a few hours.

cerebrospinal fluid (13/13), bacteriological examination of cerebrospinal fluid (12/13), bacterial culture of cerebrospinal fluid (9/13), blood culture (4/8). Genomic analysis has been performed in 19 cases: 17 cases belong to finetype C: P1.5-1,10-8:F3-6: ST-11 (cc11), one patient had been affected by another finetype, while the last strain resulted as not determined.

All cases (except 2 with bacteremia and 1 with meningitis) were admitted in Intensive Care Unit (ICU). All patients with meningitis and meningitis/sepsis were discharged from ICU after a mean stay 6 days. Seven patients (35%) died, all presenting as septic shock with *Purpura fulminans*. In 5 cases, deaths occurred within few hours after presentation to ED, in two cases death occurred after 12 and 18 days, from complications as a result of tissue necrosis. Among those with septic shock with *Purpura fulminans* who survived, one underwent to amputation of a hand phalanx. One sequelae (a stroke) occurred in a patient with sepsis/meningitis during convalescent phase. In Table 2 are presented key parameters among patients deceased or survived. Septic shock is significantly predictive of increased lethality, such as having lower White Blood Cells, or Platelets or C-reactive Protein. Among demographic and epidemiological factors (sex, age, comorbidities, vaccination, clinical onset, time between clinical onset and ED referral, genomic analysis), none resulted predictive of septic shock.

The main limitation of this study is that, in some cases, data were not collected or not registered because of the dramatic clinical presentation of patients: this may introduce a bias, since the lacking data are mostly referred to patient with rapid progression to death.

Despite this limitation, our study suggests interesting remarks. The presentation among our patient confirms that the clinical spectrum is very wide. The use of PCR, recently introduced in EDs among routine analysis for suspected IMD, and the increased awareness among ED clinicians because of the outbreak, led to the diagnosis of different clinical pictures, including mild diseases. As already reported for cc-11, in our study the incidence of septic shock, and