Intensive Care Med (2011) 37:801–807
DOI 10.1007/s00134-011-2163-y

ORIGINAL

Mottling score predicts survival in septic shock

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Received: 27 September 2010
Accepted: 30 November 2010
Published online: 4 March 2011

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Abstract *Background:* Experimental and clinical studies have identified a crucial role of microcirculation impairment in severe infections. We hypothesized that mottling, a sign of microcirculation alterations, was correlated to survival during septic shock. *Methods:* We conducted a prospective observational study in a tertiary teaching hospital. All consecutive patients with septic shock were included during a 7-month period. After initial resuscitation, we recorded hemodynamic parameters and analyzed their predictive value on mortality. The mottling score (from 0 to 5), based on mottling area extension from the knees to the periphery, was very reproducible, with an excellent agreement between independent observers [kappa = 0.87, 95% CI (0.72–0.97)]. *Results:* Sixty patients were included. The SOFA score was 11.5 (8.5–14.5), SAPS II was 59 (45–71) and the 14-day mortality rate 45% [95% CI (33–58)]. Six hours after inclusion, oliguria [OR 10.8 95% CI (2.9, 52.8), $p = 0.001$], arterial lactate level [<1.5 OR 1; between 1.5 and 3 OR 3.8 (0.7–29.5); >3 OR 9.6 (2.1–70.6), $p = 0.01$] and mottling score [score 0–1 OR 1; score 2–3 OR 16, 95% CI (4–81); score 4–5 OR 74, 95% CI (11–1,568), $p < 0.0001$] were strongly associated with 14-day mortality, whereas the mean arterial pressure, central venous pressure and cardiac index were not. The higher the mottling score was, the earlier death occurred ($p < 0.0001$). Patients whose mottling score decreased during the resuscitation period had a better prognosis (14-day mortality 77 vs. 12%, $p = 0.0005$). *Conclusion:* The mottling score is reproducible and easy to evaluate at the bedside. The mottling score as well as its variation during resuscitation is a strong predictor of 14-day survival in patients with septic shock.

Keywords Shock · Microcirculation · Prognosis · Mottling · Intensive care medicine

Introduction

During the last decades, understanding of the physiopathology of septic shock has greatly improved. Abnormal microcirculation has been identified as the main cause of organ damage and death [1, 2]. Accumulating evidence suggests that discordance between systemic hemodynamic parameters and microcirculatory alterations is more preeminent during shock [3]. Moreover, microcirculatory dysfunctions were identified as risk factors of morbidity and mortality, whereas systemic hemodynamic parameters were not [4]. Besides monitoring of global

hemodynamic parameters promoted by international guidelines such as the *Surviving Sepsis Campaign* [5, 6], it is of paramount importance to develop tools at the bedside to assess microcirculation and organ perfusion. Skin examination is an interesting clinical parameter. More than 60 years ago, Ebert et al. [7] described "pale skin often covered with perspiration" during septic shock. Later, Altemeier et al. [8] noted moist and cool skin on septic patients with a bad prognosis. In a mixed surgical population, cool skin temperature was associated with lower cardiac output, lower central venous saturation and higher lactate levels as opposed to warm skin temperature [9].

Mottling, an easy to assess clinical sign, is defined as patchy skin discoloration that usually starts around the knees. It is due to heterogenic small vessel vasoconstriction and is thought to reflect abnormal skin microperfusion. Mottling is widely described and taught in medical school as a sign of shock. More than 40 years ago, Vic-Dupont et al. [10] described clinical patterns of patients with septic shock and noted frequent mottling on the knees (65%). However, to the best of our knowledge, no study has objectively investigated its predictive value.

We aimed to assess the prognostic value of mottling in patients admitted to the intensive care unit (ICU) for septic shock using a newly developed clinical score.

Materials and methods

We conducted a prospective observational study in a 15-bed ICU in a tertiary teaching hospital. During a 7-month period, all consecutive patients older than 18 years admitted for septic shock were included. Septic shock, within 24 h after ICU admission, was defined by the 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions conference [11]. Four patients with black skin were excluded because accurate clinical evaluation of mottling was not possible.

Protocol and data collection

Patients were admitted directly from the emergency department or medical wards. Circulatory support was guided by our local protocol, adapted from international guidelines [5]. Intravenous volume expansion and norepinephrine (epinephrine in case of associated systolic cardiac dysfunction) were used in a stepwise manner to achieve pre-defined endpoints of resuscitation from invasive hemodynamic monitoring: mean arterial pressure (MAP) >65 mmHg, central venous pressure (CVP) between 8 and 12 mmHg, and urinary output >0.5 ml/kg/h. $ScvO_2$ was not routinely used for shock management. All patients were investigated with transthoracic echocardiography (Vivid 7 Dimension '06, GE Healthcare) to evaluate left ventricular function, volemia and cardiac output. Cardiac output was measured using the diameter of the aortic annulus, the velocity time integral (VTI) of the Doppler flow and heart rate.

General characteristics of the patients were recorded: demographic data, diagnoses, severity of illness evaluated by the Sequential Organ Failure Assessment (SOFA) score (within 6 h of admission) [12] and Simplified Acute Physiology Score II (SAPS II)[13]. Six hours after ICU admission (H6), which was required for medical management and global hemodynamic restoration, we collected data that reflected macrocirculation and organ perfusion. Macrocirculation was assessed using MAP, heart rate (HR), CVP and the Cardiac Index. Microcirculatory dysfunction and organ perfusion were assessed by arterial lactate levels, urinary output and mottling [14]. We quantified the extent of mottling on the legs on a 6-degree scale ranging from 0 to 5. The mottling score is based on mottling area extension on legs: score 0 indicates no mottling; score 1, a small mottling area (coin size) localized to the center of the knee; score 2, a mottling area that does not exceed the superior edge of the knee cap; score 3, a mottling area that does not exceed the middle thigh; score 4, a mottling area that does not go beyond the fold of the groin; score 5, an extremely severe mottling area that goes beyond the fold of the groin (Fig. 1).

Statistical analysis

Inter-observer agreement for the mottling score was measured by Fleiss' kappa for multiple raters. We planned the agreement analysis so that the lower CI bound on the κ would be larger than 40% (corresponding to 'moderate agreement' in the Landis and Koch scale), hypothesizing that agreement would be very good in practice (>80%). Twenty-six cases spanning the whole scale, independently assessed by three intensivists, were sufficient in this respect. The 95% confidence interval was determined using the percentile bootstrap.

Patient characteristics were summarized as mean ± standard deviation, median (25th–75th percentiles) for skewed distributions and percentages as appropriate. Differences between groups were compared using the Kruskal-Wallis test. Differences in 14-day survival according to the initial change in the mottling score were tested by Fisher's exact test. Patients' characteristics associated with death by the 14th day following admission in the ICU were determined by logistic regression; results were expressed as odds ratio (OR) (95% CI). Survival curves were computed by the Kaplan-Meier method and compared by the log-rank test.

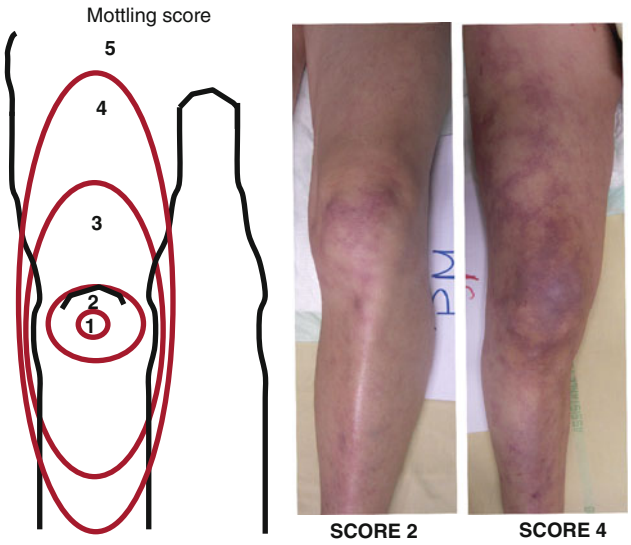

Fig. 1 *Left*: the mottling score is based on a mottling area extension on the legs. Score 0 indicates no mottling; score 1, a modest mottling area (coin size) localized to the center of the knee; score 2, a moderate mottling area that does not exceed the superior edge of the kneecap; score 3, a mild mottling area that does not exceed the middle thigh; score 4, a severe mottling area that does not go beyond the fold of the groin; score 5, an extremely severe mottling area that goes beyond the fold of the groin. *Right*: Examples of the mottling score

From clinical experience, a large difference in mortality according to mottling was expected. Assuming 30% mortality overall at day 14 and a prevalence of severe mottling (score 4 or 5) of 15%, the inclusion of 60 patients was sufficient to detect an OR larger than 10 (i.e., 25 vs. 70%) with 80% power.

Statistical significance was set at $p < 0.05$. All analyses were made using the R software (v. 2.9.1; http://cran.r-project.org).

The observational protocol was approved by the ethics committee of the Société de Réanimation de Langue Française (SRLF). This was an observational study without any specific intervention according to the mottling score. All patients and families were informed on the admission leaflet that anonymous data could be used for academic research.

Results

Mottling score

The mottling score ranged from 0 to 5 based on the extension of the mottling area from the center of the knees to the peripheral areas (see Fig. 1). The reproducibility of this score was excellent between observers [kappa 0.87, 95% CI (0.72–0.97)].

Studied population

Between February and August 2009, 60 consecutive patients were included. Baseline characteristics are summarized in Table 1. All of the patients had septic shock and required vasopressors within 6 h of admission, mainly related to pneumonia (45%) and abdominal infection (32%). The mean SOFA score computed with the worst values during the first 6 h after ICU admission was 11.5 (8.5–14.5) and the SAPS II was 59 (45–71). Most of the patients were treated with norepinephrine [50 patients (83%), dose 0.60 (0.2–1)] during the first 6 h of shock management and others with epinephrine [10 patients (17%), dose 0.4 (0.4–2)]. The day-14 mortality rate was 45% [95% CI (33–58)]. Distribution of the mottling score is detailed in Table 1. To assess the prognostic value of mottling, the scores were pooled as follows: no or modest abnormalities (0–1; 31 patients), mild or moderate [2–3; 17 patients) and severe (4–5; 12 patients).

Risk factors of death

The MAP, CVP, HR and cardiac index at H6 were not significantly associated with 14-day mortality.

Table 1 Baseline characteristics of included population

Patients (*n*)	60	
Age, years, [mean (SD)]	66 (16)	
Gender, female [*n*, (%)]	31 (52)	
Primary site of infection [*n*, (%)]		
Lung	27 (45)	
Abdomen	19 (32)	
Urinary tract	11(18)	
Soft tissue	0	
Unlocalized, positive blood culture	3 (5)	
SOFA at H6 [mean (SD)]	11.5 (8.5–14.5)	
SAPS II [mean (SD)]	59 (5–71)	
Norepinephrine		
n (%)	50 (83)	
Doses µg/kg/min (median, 25–75th percentile)	0.60 (0.2–1)	
Epinephrine		
n (%)	10 (17)	
Doses µg/kg/min (median, 25–75th percentile]	0.4 (0.4–2)	
Mottling score, *n* (%)	Admission	H6 after admission
0	18 (30)	24 (40)
1	4 (7)	7 (12)
2	14 (23)	7 (12)
3	11 (18)	10 (16)
4	4 (7)	4 (7)
5	9 (15)	8 (13)

SOFA Sequential Organ Failure Assessment score was calculated within 6 h of inclusion. *SAPS II* Simplified Acute Physiology Score was calculated within 24 h of admission

Values are given as mean ± standard deviation or median (25th–75th percentiles) according to data distribution

Macrocirculatory parameters reached predefined endpoints in all patients but four, and the values measured at H6 were not different between 14-day survivors and non-survivors: mean MAP was more than 65 mmHg (77 ± 11 vs. 73 ± 11 mmHg, $p = 0.12$), and mean CVP was more than 8 mmHg (12 ± 4 vs. 12 ± 5 mmHg, $p = 0.30$). At H6, the arterial lactate levels, urinary output, and mottling score were predictive of 14-day mortality. Lactate level was associated with an increased risk of death [<1.5 mmol/l OR 1, between 1.5 and 3 OR 3.8 (0.7–29.5), >3 OR 9.6 (2.1–70.6), $p = 0.01$] as well as urinary output <0.5 ml/kg/h [OR 10.8 (2.9–52.8), $p = 0.001$]. Mottling score was the strongest predictor of mortality [score 0–1 OR 1; score 2–3 OR 16 (4–81); score 4–5 OR 74 (11–1,568), $p < 0.0001$] (see Table 2). Fourteen-day mortality according to the H6 mottling score increased from 13% for a score of 0–1 to 70% for a score of 2–3 and 92% for a score of 4–5 (χ^2 test for trend $p < 0.001$). We analyzed time of death according to the mottling score. We found that death occurred earlier in patients with a higher score ($p < 0.0001$). Patients with a mottling score of 4–5 died mostly on day 1, whereas patients with a score of 2–3 died on day 2 and day 3 after admission (see Fig. 2).

At the bedside, we observed rapid changes of skin coloration during shock resuscitation, suggesting that the mottling score changes could be useful. We analyzed the prognosis of patients according to mottling score change between H0 and H6; patients with an initial score of 0–1 were excluded, and we focused on patients with initial moderate or extensive mottling ($n = 38$). Among the 13 patients whose score decreased, 10 survived (77%). Conversely, among the 25 whose score did not change or increased, only 3 survived (12%). The percentage of survivors increased significantly with mottling improvement [OR = 21, 95% CI (3, 208), $p < 0.0005$; see Table 3]. Moreover, in patients with moderate or extensive mottling at admission ($n = 38$), an increase in the mottling score between H0 and H6 was associated with an increase in the lactate arterial level (Spearman's correlation coefficient 0.36, $p = 0.03$) (Fig. 3).

An increase in the mottling score was associated with increasing lactate levels ($p < 0.0001$) and decreasing urinary output ($p < 0.0001$). There was no such trend for the cardiac index according to mottling. Finally, the SOFA score also displayed a positive correlation with the level of mottling ($p = 0.0002$).

Table 2 Analysis of hemodynamic parameters at H6 reflecting macro- and microcirculation and identification of three significant risk factors of 14-day death in univariate analysis, urinary output, arterial lactate level and mottling score

Factor	Univariate analysis OR (95% CI)	Analysis *p* value
MAP (mmHg)		
>65	1	
<65	1.9 (0.4, 10.5)	0.43
Heart rate (beats/min)		
>120	1.6 (0.4, 6.1)	
(90–120)	1	
<90	1.1 (0.3, 4.0)	0.80
Central venous pressure (mmHg)		
>12	1 (0.3, 3.3)	
(8–12)	1	0.21
<8	0.3 (0.1, 1.3)	
Cardiac index (l/min/m2)		
>3	1	
<3	1.4 (0.5, 4.1)	0.53
Urinary output (ml/kg/h)		
>0.5	1	
<0.5	10.8 (2.9, 52.8)	0.001
Arterial lactate (mmol/l)		
<1.5	1	
(1.5–3)	3.8 (0.7, 29.5)	
>3	26 (2.1, 70.6)	0.01
Mottling score		
0–1	1	
2–3	16 (4, 81)	
4–5	74 (11, 1,568)	<0.0001

The cardiac index was measured using transthoracic echocardiography

MAP mean arterial pressure

Discussion

Alterations in microvascular blood flow contribute to the development of multiple organ failure and subsequent mortality in patients admitted for acute circulatory failure [15]. To explore microcirculation at the bedside, we focused on clinical skin perfusion because it is easy to assess and non-invasive. Alterations in skin perfusion have direct effects on skin temperature and color as illustrated by the cold and clammy skin described in shock patients. In 1969, Joly and Weil identified the cold toe as a parameter of circulatory shock severity and reported a correlation between an increase in central-to-toe temperature difference and adverse outcome in a mixed ICU population [16]. More recently, a prolonged capillary refill time was identified as an independent prognostic factor of death in severe malaria [17]. In our study, we focused on skin mottling, an old but unexplored sign of shock. To analyze mottling objectively, we developed a clinical score (from 0 to 5) based on the area of mottling from the knees to periphery. Our mottling score is very easy to learn, and physicians are able to use it within few minutes. In a blind test performed on three independent intensivists, we demonstrated that agreement on the mottling score was excellent [Fleiss'kappa = 0.87 (0.72, 0.97)].

We performed a prospective observational study on patients with septic shock, and exclusion criteria were very limited to reflect "real life." Septic shocks were severe as illustrated by the vasopressor doses, the high

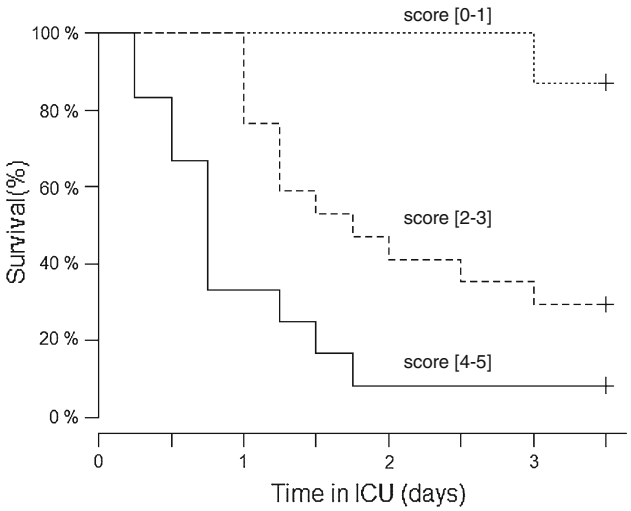

Fig. 2 Kaplan-Meier survival estimates according to the H6 mottling score. Larger mottling scores were associated with earlier death ($p < 0.0001$)

Table 3 Impact of mottling score changes during resuscitation (between H0 and H6) on prognosis

	14-day survivors ($n = 13$)	14-day non-survivors ($n = 25$)
Mottling score decrease ($n = 13$)	10	3*
Mottling score did not decrease ($n = 25$)	3	22*
		*$p = 0.0005$

Patients with moderate and extensive mottling at admission were studied (score 2–5, $n = 38$). A decrease in mottling score was associated with reduced 14-day mortality ($p = 0.0005$)

severity score and the high 14-day mortality rate (see Table 1). In univariate analysis, we identified three risk factors for 14-day mortality after global hemodynamic restoration: urinary output, lactate arterial level and mottling score. Several studies have already reported oliguria to be pejorative [18, 19], but none reported data within 6 h of admission. Arterial lactate level has also been identified as a prognostic factor of mortality [20, 21], and a recent multicenter study showed that resuscitation based on lactate level changes improved outcome [22]. For the first time, we have shown that persistent extensive mottling, evaluated using a newly developed score, is a strong predictor of 14-day mortality. Moreover, the higher the mottling score was, the earlier the mortality occurred, suggesting a direct link among the initial event, severe infection and ICU mortality. In most of the studies, 28-day mortality was the endpoint despite the fact that late mortality could not be directly related to septic shock, but could be due to secondary infections or co-morbidities. These three clinical and biological parameters, which reflect organ perfusion and microcirculatory dysfunction, had a strong prognostic value despite the global hemodynamic restoration underlying the discrepancies between macrocirculation and organ perfusion [23, 24].

Mottling score evolution during resuscitation also provided interesting information. In some cases, the mottling score decreased, suggesting that improvement of macrocirculation also improved microcirculatory dysfunction. However, in other patients, mottling remained extensive despite correction of macroscopic parameters, suggesting that persistent microcirculatory alteration is independent of macrocirculation and could promote organ hypoperfusion *per se*, worsening outcome. Assessing microcirculation with sublingual Orthogonal Polarization Spectral (OPS) imaging, Sakr et al. [25] found similar results; at the onset of shock, survivors and non-survivors had similar sublingual vascular density. After shock correction, despite similar macrocirculatory hemodynamic parameters, patients dying secondary to multiple organ failure had a lower percentage of perfused small vessels than survivors.

Interestingly, we analyzed arterial lactate levels and urinary output according to the mottling score at H6 and found a significant relationship, suggesting that abnormal skin perfusion reflected respectively organ and kidney hypoperfusion. The significant relation between the SOFA score and the mottling score strengthened this conclusion. The higher the mottling score was, the higher the SOFA score. Recently, Lima et al. [26] also reported a significant positive relation between clinical signs of hypoperfusion and arterial lactate level in an ICU population. Furthermore, they showed that patients with clinical signs of hypoperfusion had significantly less SOFA improvement compared to patients with normal peripheral perfusion. In an emergency department, others authors also reported that sublingual microcirculation improvement during the first hours of shock resuscitation was significantly associated with an improvement of SOFA score [27]. We did not observe any difference regarding the cardiac index according to the mottling score. Our results confirmed previous studies by De Backer's group that reported no correlation between changes in the cardiac index and changes in sublingual microperfusion after dobutamine infusion [28].

Several factors could modify clinical evaluation of mottling, such as vasopressors. However, after stratification of drug dosage [norepinephrine, high dose (>0.5 μg/kg/min) and low dose], the association of a high mottling score with mortality remained strong ($p < 0.0001$). More precisely, in those receiving high doses (>0.5 μg/kg/min) at H6, survival was 72% when the mottling score was 0–1 and 0% in the others. In those receiving smaller doses, survival was 95% with the mottling score 0–1 and 55% otherwise. The association of mortality with mottling

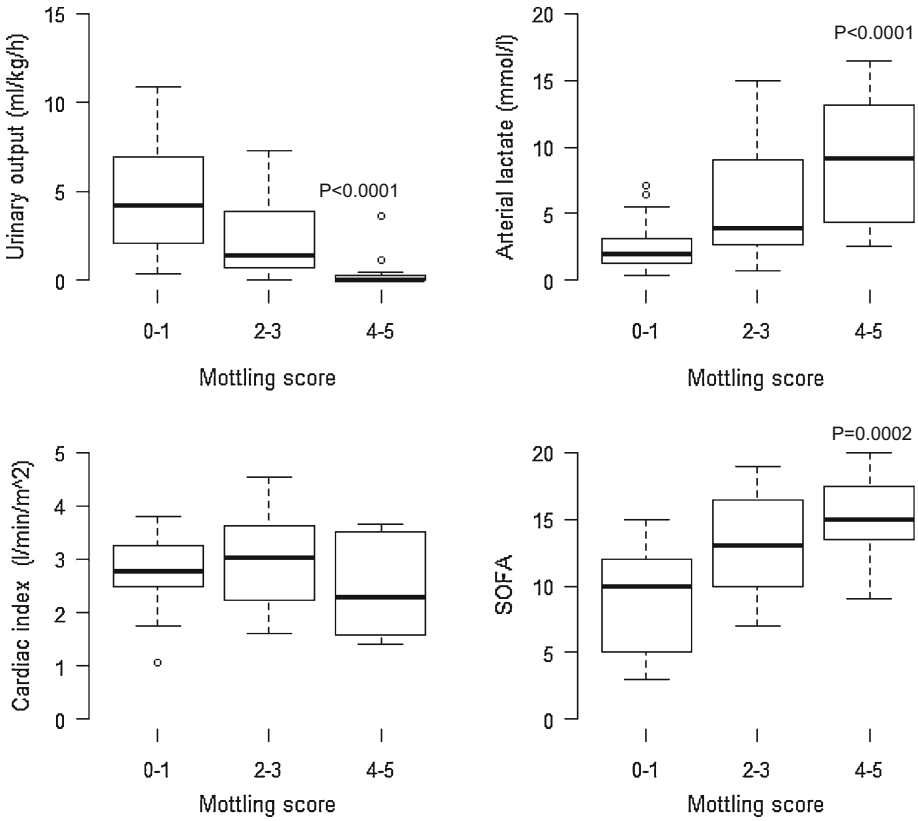

Fig. 3 Urinary output, arterial lactate level, cardiac index and SOFA score according to mottling score at H6 after initial resuscitation. The higher the mottling score was, the smaller the urinary output ($p < 0.0001$), and the larger the lactate level ($p < 0.0001$) and SOFA score ($p = 0.0002$). Boxes show the first and third quantiles, with the median as a thick line. Whiskers extend to 1.5 interquartile range (Q75–Q25)

score was also unaffected by stratification on known arterial disease (defined as a previous vascular event, symptomatic or requiring therapeutic intervention).

Our study has several limitations. It is a monocentric study, and the results need to be confirmed in a larger population. Nevertheless, while the size of this preliminary study was not very large, it was sufficient to highlight significant results. Also, our conclusion was based on patients with severe septic shock and can probably not be extrapolated to patients with severe sepsis who do not require vasopressors. The mottling score could not be used in patients with black skin. In these situations, others clinical signs of peripheral hypoperfusion could be used, such as the central-to-toe temperature difference. Finally, the exact physiopathology of mottling and the link between mottling and microvascular dysfunction remained unproved, and further investigations are necessary.

Conclusion

We developed an original scoring system to objectively evaluate mottling in shock. After initial resuscitation, we identified mottling to be the strongest predictor of death in a septic shock population. The mottling score is easy to assess and could be a new parameter to guide treatments that specifically target organ perfusion and microcirculation.

Conflict of interest The authors had no conflict of interest.

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