Clinical impact of the implementation of monocyte distribution width (MDW) measurement on time to anti-infective administration in sepsis patients in the emergency department: a before/after cohort study

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Critical Care

BRIEF REPORT

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Clinical impact of the implementation of monocyte distribution width (MDW) measurement on time to anti-infective administration in sepsis patients in the emergency department: a before/after cohort study

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Abstract

Background Timely recognition of sepsis in emergency department (ED) is challenging. We evaluated the impact of implementing the biomarker monocyte distribution width (MDW) at bedside, on the time to anti-infective administration.

Methods We conducted a before-and-after cohort study in the ED of an academic hospital in Paris, to compare sepsis patients care and outcomes, before and after the implementation of point of care (POC) MDW measurement in the ED. During post-implementation period (period-2), MDW was measured with complete blood count by ED nurses with results given in 2 min: if above 21.5 units, ED physicians were asked to consider sepsis and to start an anti-infectious as soon as possible. Primary endpoint was time to anti-infectious administration (TTA) from ED arrival, and secondary endpoints were TTA from sepsis onset (TTAS), length of stay, mortality, and hospitalization rates.

Results In total, 255 patients (period-1) and 180 patients (period-2) with sepsis were included. The TTA was 5.4 h (3.5–7.7) period-1 and 4.9 h (IQR 2.5–7.1) in period-2 ($p=0.06$). MDW implementation significantly reduced the median TTAS from to 3.7 h (IQR 1.5–5.8) in period-1, to 2.2 h (IQR 0.5–4.5) in period-2 ($p<0.001$). Mortality rates remained similar between the two periods (18% vs. 16% respectively, $p=0.4$), as did hospitalization rates (93% vs. 91%, $p=0.4$) and ED length of stay (7.2 h (5.3–9.8) vs 7.0 (5.4–9.4), $p=0.7$).

Conclusion Implementing POC MDW measurement in the ED protocols enhances the timeliness of anti-infective administration from sepsis onset, meeting current sepsis management guidelines.

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Introduction

In 2021, the Sepsis Surviving Campaign (SSC) updated [1] the guidelines for sepsis management, recommending time-limited course of rapid investigation and the administration of antimicrobials within 3-h from sepsis recognition. However, timely recognition of sepsis in emergency department (ED) is challenging, due to a large number of patients presenting with unspecific symptoms, often leading to delays in initiating appropriate therapy [2–4]. Furthermore, the performance of screening scores recommended so far are unsatisfactory, urging for more effective tools and notably biomarkers to identify sepsis [5, 6].

Monocyte Distribution Width (MDW), a parameter derived from routine complete blood cell count (CBC), describes the size distribution of circulating monocytes [7, 8], which represents the first line defense against infection. Several authors have reported high MDW values as accurate for early sepsis detection [7–10]. However, to our knowledge, no study has explored the impact of implementing MDW on sepsis management in the ED.

The purpose of this study was to assess if the routine implementation and measurement of MDW in a point-of-care (POC) setting in the ED could improve the time to anti-infectious administration (TTA) in patients with sepsis.

Materials and methods

Study design

We conducted a before-after cohort study in the adult ED of Pitié-Salpêtrière Hospital, in Paris, France, a 1700-beds University hospital with 65,000 ED admissions per year. Study endpoints were compared between January 1st and April 15th (pre-implementation period—"period-1") and May 15th and October 21th 2023 (post-implementation period—"period-2").

During period 1, blood samples for CBC were sent as routine practice, to the central laboratory and tested on Sysmex XN-10™ (Sysmex®, Villepinte, France). Standard care was provided to all patients.

Between both periods, the DxH-900 hematology analyzer (Beckman Coulter Inc., Brea, CA with version 1.0.0.329 software) was implemented in the ED's POC room (ED-POC) for CBC analysis and ED teams were trained.

During period 2, ED nurses were asked to test a K3EDTA tube on the DxH-900 analyzer immediately after sample collection, 24-h a day. The turnaround time was 2 min. In case of MDW measurement above 21.5 units' threshold, they were asked to alert the treating physician and sepsis should be considered. No protocol was imposed for diagnostic and treatment workup. The same tube was sent in parallel to the central laboratory for CBC analysis, as standard of care.

The Infectious Ethic Committee approved the study; according to the French law, it was exempted from informed consent.

Selection of participants

During the study duration, all patients having a CBC test performed in the ED were retrospectively screened by three emergency physicians (blinded to MDW result), selecting those with any suspicion of infection. Patients fulfilling sepsis-3 definition were finally selected for study endpoints. Patients were excluded if pregnancy, if re-visiting the ED for the same reason and if included in other interventional studies on sepsis.

Data collection and outcomes

Data were collected retrospectively by clinical research assistants (CRA) from electronic medical chart into spreadsheet. Sepsis was diagnosed if SOFA score was ≥ 2 and if there was a confirmed infection defined by a positive microbiological result or a documented radiological or clinical source. The "sepsis onset" was defined as the moment at which SOFA score was positive.

The primary endpoint was TTA, defined by the time between ED registration and the first anti-infectious administration.

Secondary outcomes were: time to TTA from "sepsis onset" (TTAS), proportion of sepsis receiving an anti-infectious in the first hour from ED arrival, proportion of sepsis having completed the sepsis bundle [11] in the first and third hour from ED arrival, ED length of stay, in-hospital mortality at 30 days from ED arrival, hospital length of stay and performances of MDW, C-reactive protein (CRP) or procalcitonin (PCT) for sepsis diagnosis.

Statistical analysis

We reviewed our center data from a previous multicenter observational study [7], reporting a TTA of 5.4 h (± 5.9). With the implementation of MDW, we hoped to shorten TTA by 2 h. 300 patients with sepsis (150 per period) were required with a power of 80%.

Continuous variables were described by their median and interquartile range (IQR) and categorical variables, using frequencies and percentages. We then performed a univariate analysis and a multivariable logistic regression using backward elimination, including variables significantly different between periods at a threshold p value ≤ 0.2. All tests were two-sided and a p value less than 0.05 indicated statistical significance.

Lastly, diagnostic performances of MDW, for sepsis diagnosis in patients with a suspicion of infection, were evaluated in terms of the area under the curve (AUC),

sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), along with their 95% confidence intervals (CIs).

The analyses were performed using R (version 2024.04.2).

Results

A total of 15,930 patients having a CBC performed were screened (6765 in period-1 and 9,164 in period-2), out of 1397 and 1795 had a suspicion of infection (Fig. 1), and 255 and 406, had sepsis respectively. From period-2 we included only the 180 septic patients with MDW tested.

The median age was 75 years-old and 64% were male. Table 1 reports patient's characteristics, complementary exams, infection management and outcomes. Median MDW value of septic patients was 24.9 (interquartile rang (IQR) 20.9–27.9). The most common site of the suspected infection was the respiratory tract on both periods.

The median TTA administration from ED arrival was 5.4 h (IQR 3.5–7.7) in period-1 and 4.9 h (IQR 2.5–7.1) in period-2 ($p=0.06$). The TTA from sepsis onset (TTAS) was significatively reduced, from 3.7 h (IQR 1.5–5.8) in period-1 to 2.2 h (IQR 0.5–4.5), in period-2 ($p<0.001$).

Regarding secondary endpoints, there were no significant differences founded (Table 1 and S1). Though, mortality was higher in patients receiving antibiotics in the first hour compared to those receiving antibiotics later (Table S2 supplementary files).

In multivariate analysis (Table 2), TTAS was significatively lower in period-2: OR 0.83 (95% CI 0.71–0.95), as was ICU transfer. In a sub-group analysis in patients without septic shock. (Table S3 and S4 in supplementary files), TTAS was still significatively lower in period-2; however, the proportion of patients being transferred to ICU was not different between periods.

Finally, we investigated which variables were associated with TTAS with a multivariate regression model (Table S5 supplementary file): period-2 was associated with a lower TTAS (OR 0.32 (95% CI 0.11–0.93).

Diagnostic performances of MDW, CRP and PCT are reported in Tables S6 and S7 and Figs. S1 and S2 (supplementary files): MDW ≥ 21.5 had a sensitivity of 70% (95%CI, 63–77%) and specificity of 55% (50–60%);

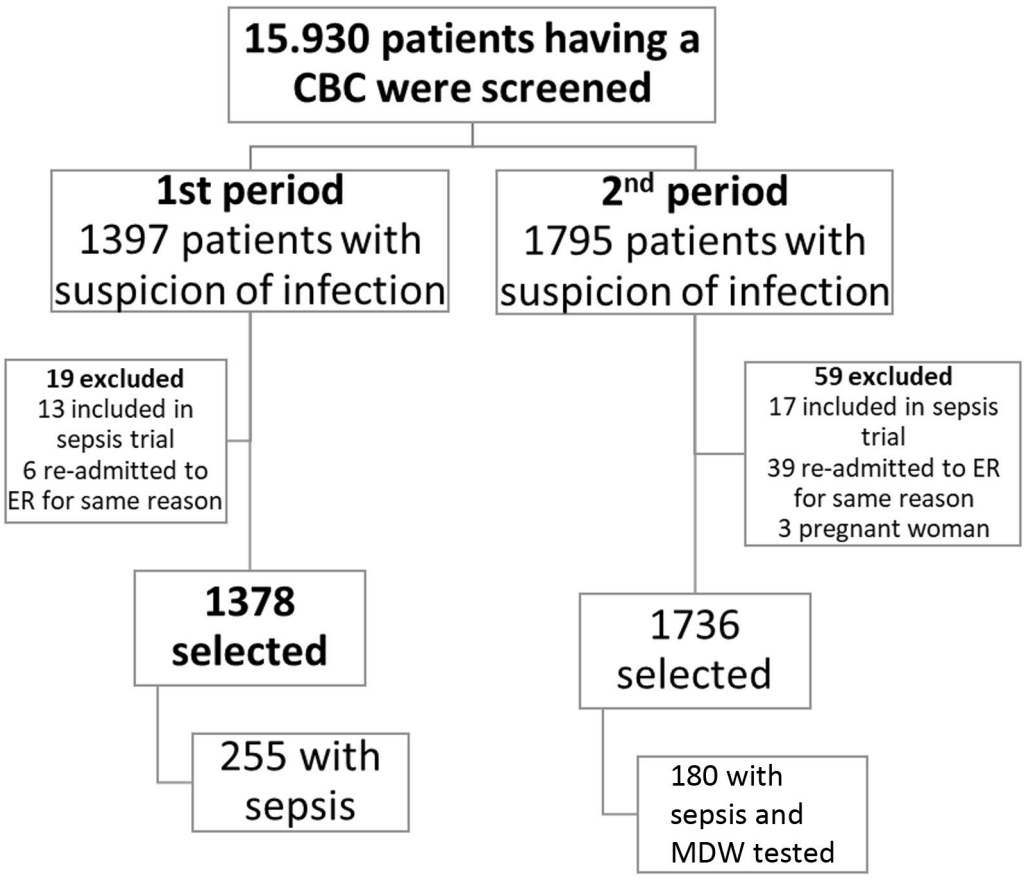

Fig. 1 Flowchart for sepsis-patient's selection procedure. *CBC* cell blood count. *ED* emergency department

Table 1 Characteristics of patients with sepsis, biological results, infection management and outcomes

Characteristics	Overall (n = 435)	Period 1, (n = 255)	Period 2 (n = 180)	*p*-value
Age, years	75 (63–85)	74 (63–85)	76 (63, 86)	0.5
Sex woman	158 (36%)	105 (41%)	53 (29%)	0.012
No past history	41 (9.4%)	26 (10%)	15 (8.3%)	0.5
Significant past history	394 (91%)	229 (90%)	165 (92%)	
Immunosuppression/cancer	106 (24%)	52 (20%)	54 (30%)	0.022
SBP at ED arrival (mmHg) (NA = 1)	120 (99–142)	121 (99–143)	116 (98–139)	0.3
MBP (mmHg)	86 (71–100)	88 (73–101)	85 (70–97)	0.05
MBP < 65 mmHg	59 (14%)	32 (13%)	27 (15%)	0.5
Heart rate (/min)	96 (80–110)	98 (82, 113)	92 (79, 108)	0.008
Respiratory rate (NA = 88)	20 (16–26)	20 (16–27)	18 (16–25)	0.042
Pulse oxymetry (%)	95 (93–97)	95 (93—98)	95 (93.0—97)	0.10
Temperature (°C)	37.2 (36,5- 38,1)	37.2 (36,5–38,2)	37.2 (36,7–38,0)	> 0.9
Glasgow coma score	15 (15–15)	15 (15 -15)	15 (15–15)	0.2
NEWS	5.0 (3.0, 7.0)	5.0 (3.0, 8.0)	4.0 (2.0, 7.0)	0.020
qSOFA score 0	177 (41%)	96 (38%)	81 (45%)	0.2
1	188 (43%)	112 (44%)	76 (42%)	
2	56 (13%)	39 (15%)	17 (9.4%)	
3	14 (3.2%)	8 (3.1%)	6 (3.3%)	
Site of the suspected infection at arrival: None	18 (4.1%)	12 (4.7%)	6 (3.3%)	0.046
Pulmonary	223 (51%)	144 (56%)	79 (44%)	
Urinary	76 (17%)	40 (16%)	36 (20%)	
Digestive	59 (14%)	34 (13%)	25 (14%)	
Cutaneous	28 (6.4%)	12 (4.7%)	16 (8.9%)	
Neurological	9 (2.1%)	4 (1.6%)	5 (2.8%)	
Face and neck	2 (0.5%)	1 (0.4%)	1 (0.6%)	
Leukocytes (*10^9/l)	11 (7–16)	12 (8–16)	11 (7–16)	> 0.9
MDW (U)			24.9 (20.9–27.9)	
CRP (mg/l) (NA = 111)	105 (48–198)	108 (46–202)	105 (51–195)	0.6
PCT µg/l (NA = 151)	1 (0–2)	1 (0–2)	1 (0–3)	0.7
Lactate (mmol/l) (NA = 41)	1.4 (1.0–2.1)	1.4 (1–2.2)	1.4 (1.0–2.1)	0.6
SOFA score	2 (2–3)	2 (2–3)	2 (2–3.25)	0.75
Infection documentation:				0.036
Virus	95 (22%)	64 (25%)	31 (17%)	
Bacteria	163 (37%)	101 (40%)	62 (34%)	
Parasite	16 (3.7%)	7 (2.7%)	9 (5.0%)	
CT-scan or clinical	161 (37%)	83 (33%)	78 (43%)	
Septic shock	20 (4.6%)	16 (6.3%)	4 (2.2%)	0.047
Anti-infectious administered in ED	347 (80%)	208 (82%)	139 (77%)	0.3
TTA from ED arrival (hours) (N = 347)	5.2 (3.1- 7.5)	5.4 (3.5- 7.7)	4.9 (2.5- 7.1)	0.060
TTA from "sepsis onset" (hours) (N = 347)	3.1 (0.9- 5.5)	3.7 (1.5- 5.8)	2.2 (0.5–4.5)	< 0.001
Fluid resuscitation	151 (35%)	81 (32%)	70 (39%)	0.12
Bundle completed	79 (18%)	42 (16%)	37 (21%)	0.3
ICU admission	56 (13%)	40 (16%)	16 (8.9%)	0.037
ED length of stay (hours)	7.1 (5.4–9.6)	7.2 (5.3–9.8)	7.0 (5.4–9.4)	0.7
Hospitalization	400 (92%)	237 (93%)	163 (91%)	0.4
Hospital length of stay (days) (NA = 23)	7 (1–16)	5 (1–14)	9 (3–18)	< 0.001
In Hospital mortality at day-30	75 (17%)	47 (18%)	28 (16%)	0.4

Data are presented with no. (%) or median (interquartile). *ED* emergency department, *SBP* systolic blood pressure, *MBP* mean blood pressure, *NEWS* national early warning score, *qSOFA* quick sequential organ failure assessment. *ICU* intensive care unit. *TTA* time to anti-infectious administration. *NA* not available. Bundle completed consisted of lactate and blood culture measurement + anti-infectious and fluid resuscitation

Table 2 Logistic multivariate model of variables associated to period-2 (post-implementation)

Characteristic	OR	95% CI	*p*-value
Time to anti-infectious from ED arrival	1.10	0.97–1.29	0.2
Time to anti-infectious from "sepsis onset" (hours)	0.83	0.71–0.95	0.013
Genre: man	1.96	1.16–3.36	0.013
Initial O2 Saturation	0.93	0.89–0.98	0.010
Site of the suspected infection at ED arrival: none	—	—	—
Pulmonary	0.69	0.20–2.82	0.6
Urinary	1.50	0.41–6.28	0.6
Digestif	1.92	0.51–8.32	0.4
Cutaneous	1.90	0.43–9.35	0.4
Other	4.61	0.79–30.9	0.10
ICU transfer: no	—	—	0.007
Yes	0.29	0.11–0.67	
No. of patients admitted in ED per day	1.04	1.02–1.05	< 0.001
Time to sepsis	0.99	0.87–1.09	0.8

OR > 1 indicates that the variable is more likely to occur in Period-2. OR < 1 indicates that the variable is less likely to occur in period-2. *ED* emergency department. *ICU* intensive unit care. "Sepsis onset" was defined as the time at which at least 2 items of SOFA score were presented in the ED

PCT > 0.5 µg/l had a sensitivity of 56% (95%CI, 51–61%) and a specificity of 74% (95%CI, 71–77%). The AUC for a receiver operator characteristic (ROC) for MDW, CRP and PCT was, respectively, of 0.682 (0.63–0.73), 0.675 (0.595–0.701) and 0.708 (0.599–0.739).

Discussion

In this cohort study, the POC implementation of MDW measurement for early sepsis detection in the ED was associated with a reduction in the TTAS without significantly reducing TTA from ED registration. The before-and-after cohort design of our study allowed us to assess the clinical utility of MDW in a real-life setting.

To our knowledge, this is the first study showing an improvement in TTAS through the measurement POC of a sepsis biomarker in the ED, with a reduction of 90 min: from 3.7 h (1.5–5.8) to 2.2 h (0.5–4.5). Even though we did not demonstrate an improvement in TTA from ED arrival, we were able to improve adherence with recent sepsis guidelines [11], considering the higher number of emergency department visits per day during period-2.

This reduction agrees with findings from Paoli et al. [12], obtaining a mean reduction from 4-h to 2.1-h with MDW in a simulated model based on results from a multicenter cohort.

Despite the improvement in treatment timeliness, our data did not show significant differences in mortality rates or hospital admissions. The benefits of early antibiotic on mortality remain debatable, especially in patients without shock [13–16]. In this regard, we identified a higher mortality rate in patients receiving antibiotics during the first hour, agreeing with findings of Bisarya et al. [14].

The performance of MDW for sepsis diagnosis in our study was modest (AUC of 0.682). Our main selection criterion (patients with a suspicion of infection) resulted in a more selected population than previous studies [7, 8, 10, 17, 18]. Still, MDW's AUC is consistent with some other studies [9, 19, 20] and is equivalent to other sepsis biomarkers measured routinely (such as CRP and PCT). The main advantages of MDW over other biomarkers are its availability with a CBC (the main blood test performed in ED patients), and the fast time to result, when tested POC.

Our results should be interpreted in the context of certain limitations. First, the before-after cohort design of the study introduces potential biases related to evolving clinical practices and protocols over time. Second, the retrospective collection of data lead to missing data and a possible underdiagnoses of sepsis as some items of the SOFA score were not available. Third, not all patients having a CBC test during period-2 had MDW measured, due to overcrowding and nurse time availability. Fourth, our study did not assess the impact of MDW testing on the appropriateness of antibiotic prescription. Finally, as it was a monocentric study, the results may not be extrapolated to other ED organizations as usual practices may differ.

In conclusion, implementing MDW testing bedside at ED, did not reduced time to antibiotics from ED arrival in sepsis, but improved the time to anti-infectious treatment from sepsis onset to less than three hours, in line with international sepsis guideline.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13054-024-05141-5.

Additional file1 (DOCX 72 KB)

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Author contributions

MCA—conceptualization, methodology, data review and management, formal analysis, investigation, writing. TS—patient's screening. EH—data collection and quality control performance daily. IC—data collection and quality control performance daily. ML—methodology, statistical analysis supervision. PH—conceptualization, methodology, funding acquisition, supervision, patient's screening, writing review and editing. Each author has read and approved the final manuscript.

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Beckman Coulter participated in funding the ED clinical research assistants for data collection. Beckman Coulter provided the DxH-900 analyzer and reagents for measuring MDW and quality controls free of charge. Beckman Coulter did not had a role in the conceptualization, design, data collection and analysis neither on decision to publish nor on preparation of the manuscript.

Availability of data and material
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Infectious Ethic Committee (CER-MIT) (in Paris, France) approved the study. According to the French law, as there were no modifications in standard of care, it was exempted from informed consent. At ED arrival, patients were informed on possible inclusion to this study, in case of sepsis.

Competing interests
MCA, TS, EH, IC and ML have no competing interest. PH—received consultant fees and lecture honorarium from Beckman Coulter.

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References

1. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensiv Care Med. 2021;47(11):1181–247.
2. Le Conte P, Thibergien S, Obellianne JB, Montassier E, Potel G, Roy PM, et al. Recognition and treatment of severe sepsis in the emergency department: retrospective study in two French teaching hospitals. BMC Emerg Med. 2017;17(1):27.
3. Filbin MR, Thorsen JE, Lynch J, Gillingham TD, Pasakarnis CL, Capp R, et al. Challenges and opportunities for Emergency Department sepsis screening at triage. Sci Rep. 2018;8(1):11059.
4. Litell JM, Guirgis F, Driver B, Jones AE, Puskarich MA. Most emergency department patients meeting sepsis criteria are not diagnosed with sepsis at discharge. Acad Emerg Med. 2021;28(7):745–52.
5. Usman OA, Usman AA, Ward MA. Comparison of SIRS, qSOFA, and NEWS for the early identification of sepsis in the Emergency Department. Am J Emerg Med. 2019;37(8):1490–7.
6. Bolanaki M, Winning J, Slagman A, Lehmann T, Kiehntopf M, Stacke A, et al. Biomarkers improve diagnostics of sepsis in adult patients with suspected organ dysfunction based on the quick sepsis-related organ failure assessment (qSOFA) score in the Emergency Department*. Crit Care Med. 2024;52(6):887–99.
7. Hausfater P, Robert Boter N, Morales Indiano C, Cancella De Abreu M, Marin AM, Pernet J, et al. Monocyte distribution width (MDW) performance as an early sepsis indicator in the emergency department: comparison with CRP and procalcitonin in a multicenter international European prospective study. Crit Care. 2021;25(1):227.
8. Agnello L, Iacona A, Lo Sasso B, Scazzone C, Pantuso M, Giglio RV, et al. A new tool for sepsis screening in the Emergency Department. Clin Chem Lab Med CCLM. 2021;59(9):1600–5.
9. Woo AL, Oh DK, Park CJ, Hong SB. Monocyte distribution width compared with C-reactive protein and procalcitonin for early sepsis detection in the emergency department Zivkovic AR, editor. PLOS ONE. 2021;16(4):e0250101.
10. Polilli E, Di Iorio G, Silveri C, Angelini G, Anelli MC, Esposito JE, et al. Monocyte distribution width as a predictor of community acquired sepsis in patients prospectively enrolled at the Emergency Department. BMC Infect Dis. 2022;22(1):849.
11. Levy MM, Evans LE, Rhodes A. The surviving sepsis campaign bundle: 2018 update. Crit Care Med. 2018;46(6):997.
12. Paoli CJ, Reynolds MA, Coles C, Gitlin M, Crouser E. Predicted economic benefits of a novel biomarker for earlier sepsis identification and treatment: a counterfactual analysis. Crit Care Explor. 2019;1(8):e0029.
13. Freund Y, De Abreu MC, Lebal S, Rousseau A, Lafon T, Yordanov Y, et al. Effect of the 1-h bundle on mortality in patients with suspected sepsis in the emergency department: a stepped wedge cluster randomized clinical trial. Intensive Care Med. 2024;50(7):1086–95.
14. Bisarya R, Song X, Salle J, Liu M, Patel A, Simpson SQ. Antibiotic timing and progression to septic shock among patients in the ED with suspected infection. Chest. 2022;161(1):112–20.
15. Liu VX, Fielding-Singh V, Greene JD, Baker JM, Iwashyna TJ, Bhattacharya J, et al. The timing of early antibiotics and hospital mortality in sepsis. Am J Respir Crit Care Med. 2017;196(7):856–63.
16. Im Y, Kang D, Ko RE, Lee YJ, Lim SY, Park S, et al. Time-to-antibiotics and clinical outcomes in patients with sepsis and septic shock: a prospective nationwide multicenter cohort study. Crit Care. 2022;26(1):19.
17. Crouser ED, Parrillo JE, Seymour CW, Angus DC, Bicking K, Esguerra VG, et al. Monocyte distribution width: a novel indicator of sepsis-2 and sepsis-3 in high-risk emergency department patients*. Crit Care Med. 2019;47(8):1018–25.
18. Agnello L, Vidali M, Lo Sasso B, Giglio RV, Gambino CM, Scazzone C, et al. Monocyte distribution width (MDW) as a screening tool for early detecting sepsis: a systematic review and meta-analysis. Clin Chem Lab Med CCLM. 2022;60(5):786–92.
19. Cusinato M, Sivayoham N, Planche T. Sensitivity and specificity of monocyte distribution width (MDW) in detecting patients with infection and sepsis in patients on sepsis pathway in the emergency department. Infection. 2023;51(3):715–27.
20. Li CH, Seak CJ, Chaou CH, Su T, Gao SY, Chien CY, et al. Comparison of the diagnostic accuracy of monocyte distribution width and procalcitonin in sepsis cases in the emergency department: a prospective cohort study. BMC Infect Dis. 2022;22(1):26.

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