MONOCYTE DISTRIBUTION WIDTH (MDW): NOVEL SEPSIS BIOMARKER IN EMERGENCY DEPARTMENT

Detect sepsis earlier, act with more confidence

Melissa Beasley, MT (ASCP), CIC

BECKMAN COULTER

DEFINITIONS

Product Name

Early Sepsis Indicator (ESId)

Parameter Measured

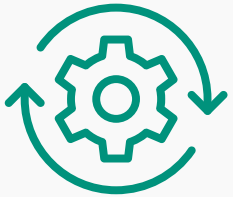
Monocyte Distribution Width (MDW):

distribution of different sizes of Monocytes

4 MAIN POINTS

FDA-cleared and CE Mark

Only hematology based biomarker cleared for sepsis



No Workflow Changes

MDW is part of CBC with Differential Test

MDW is ADDITIVE

Diagnostic Information Coupled with WBC

Additional Information Available EARLY to Increase/ Decrease Probability of Sepsis

Increase your index of suspicion of sepsis to assist with treatment decisions

STUDIED AND PUBLISHED

2017

[Original Research **Critical Care**]

CHEST

Improved Early Detection of Sepsis in the ED With a Novel Monocyte Distribution Width Biomarker

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BACKGROUND: Sepsis most often presents to the ED, and delayed detection is harmful. WBC count is often used to detect sepsis, but changes in WBC count size also correspond to sepsis. We sought to determine if volume increases of circulating immune cells add value to the WBC count for early sepsis detection in the ED.

METHODS: A blinded, prospective cohort study was conducted in two different ED populations within a large academic hospital.

RESULTS: Neutrophil and monocyte volume parameters were measured in conjunction with routine CBC testing on a UniCel DxH 800 analyzer at the time of ED admission and were evaluated for the detection of sepsis. There were 1,320 subjects in the ED consecutively enrolled and categorized as control subjects (n = 879) and those with systemic inflammatory response syndrome (SIRS) (n = 203), infection (n = 140), or sepsis (n = 98). Compared with other parameters, monocyte distribution width (MDW) best discriminated sepsis from all other conditions (area under the curve [AUC], 0.79; 95% CI, 0.73-0.84; sensitivity, 0.77; specificity, 0.73; MDW threshold, 20.50), sepsis from SIRS (AUC, 0.74; 95% CI, 0.67-0.84), and severe sepsis from noninfected patients in the ED (AUC, 0.88; 95% CI, 0.75-0.99; negative predictive value, 99%). The added value of MDW to WBC count was statistically significant (AUC, 0.89 for MDW + WBC vs 0.81 for WBC alone; $P < .01$); a decision curve analysis also showed improved performance compared with WBC count alone.

CONCLUSIONS: The incorporation of MDW with WBC count is shown in this prospective cohort study to improve detection of sepsis compared with WBC count alone at the time of admission in the ED.

TRIAL REGISTRY: ClinicalTrials.gov; No.: NCT02232750; URL: www.clinicaltrials.gov.

CHEST 2017; 152(3):518-526

KEY WORDS: biomarker; blood; cell volume; ED; monocyte; sepsis

ABBREVIATIONS: AUC = area under the curve; CMH = Cochran-Mantel-Haenszel; CRP = C-reactive protein; MDW = monocyte distribution width; MMV = mean monocyte volume; MNV = mean neutrophil volume; NDW = neutrophil distribution width; NPV = negative predictive value; PCT = procalcitonin; PPV = positive predictive value; SIRS = systemic inflammatory response syndrome

AFFILIATIONS: From the Department of Medicine (Drs Crouser and Closser, Mr Herren, and Ms Robart), The Ohio State University Wexner Medical Center, Columbus, OH; the Heart and Vascular Hospital (Drs Parrillo and Bicking), Hackensack University Medical Center, Hackensack, NJ; the Department of Critical Care Medicine (Drs Seymour and Angus), University of Pittsburgh School of Medicine, Pittsburgh, PA; Beckman Coulter, Inc (Drs Tejidor, Magari, Samoszuk, and Chaves and Ms Careaga), Miami, FL; and the Department of Pathology (Dr Williams), The Ohio State University Wexner Medical Center, Columbus, OH.

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2019

Monocyte Distribution Width: A Novel Indicator of Sepsis-2 and Sepsis-3 in High-Risk Emergency Department Patients*

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*See also p. 1152.

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Objectives: Most septic patients are initially encountered in the emergency department where sepsis recognition is often delayed, in part due to the lack of effective biomarkers. This study evaluated the diagnostic accuracy of peripheral blood monocyte distribution width alone and in combination with WBC count for early sepsis detection in the emergency department.

Design: An Institutional Review Board approved, blinded, observational, prospective cohort study conducted between April 2017 and January 2018.

Setting: Subjects were enrolled from emergency departments at three U.S. academic centers.

Patients: Adult patients, 18–89 years, with complete blood count performed upon presentation to the emergency department, and who remained hospitalized for at least 12 hours. A total of 2,212 patients were screened, of whom 2,158 subjects were enrolled and categorized per Sepsis-2 criteria, such as controls (n = 1,088), systemic inflammatory response syndrome (n = 441), infection (n = 244), and sepsis (n = 385), and Sepsis-3 criteria, such as control (n = 1,529), infection (n = 386), and sepsis (n = 243).

Interventions: The primary outcome determined whether an monocyte distribution width of greater than 20.0 U, alone or in combination with WBC, improves early sepsis detection by Sepsis-2 criteria. Secondary endpoints determined monocyte distribution width performance for Sepsis-3 detection.

Measurements and Main Results: Monocyte distribution width greater than 20.0 U distinguished sepsis from all other conditions based on either Sepsis-2 criteria (area under the curve, 0.79; 95% CI, 0.76–0.82) or Sepsis-3 criteria (area under the curve, 0.73; 95% CI, 0.69–0.76). The negative predictive values for monocyte distribution width less than or equal to 20 U for Sepsis-2 and Sepsis-3 were 93% and 94%, respectively. Monocyte distribution width greater than 20.0 U combined with an abnormal WBC further improved Sepsis-2 detection (area under the curve, 0.85; 95% CI, 0.83–0.88) and as reflected by likelihood ratio and

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Journal of Intensive Care

RESEARCH Open Access

Monocyte distribution width enhances early sepsis detection in the emergency department beyond SIRS and qSOFA

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Abstract

Background: The initial presentation of sepsis in the emergency department (ED) is difficult to distinguish from other acute illnesses based upon similar clinical presentations. A new blood parameter, a measurement of increased monocyte volume distribution width (MDW), may be used in combination with other clinical parameters to improve early sepsis detection. We sought to determine if MDW, when combined with other available clinical parameters at the time of ED presentation, improves the early detection of sepsis.

Methods: A retrospective analysis of prospectively collected clinical data available during the initial ED encounter of 2158 adult patients who were enrolled from emergency departments of three major academic centers, of which 385 fulfilled Sepsis-2 criteria, and 243 fulfilled Sepsis-3 criteria within 12 h of admission. Sepsis probabilities were determined based on MDW values, alone or in combination with components of systemic inflammatory response syndrome (SIRS) or quick sepsis-related organ failure assessment (qSOFA) score obtained during the initial patient presentation (i.e., within 2 h of ED admission).

Results: Abnormal MDW (> 20.0) consistently increased sepsis probability, and normal MDW consistently reduced sepsis probability when used in combination with SIRS criteria (tachycardia, tachypnea, abnormal white blood count, or body temperature) or qSOFA criteria (tachypnea, altered mental status, but not hypotension). Overall, and regardless of other SIRS or qSOFA variables, MDW > 20.0 (vs. MDW ≤ 20.0) at the time of the initial ED encounter was associated with an approximately 6-fold increase in the odds of Sepsis-2, and an approximately 4-fold increase in the odds of Sepsis-3.

Conclusions: MDW improves the early detection of sepsis during the initial ED encounter and is complementary to SIRS and qSOFA parameters that are currently used for this purpose. This study supports the incorporation of MDW with other readily available clinical parameters during the initial ED encounter for the early detection of sepsis.

Trial registration: ClinicalTrials.gov, NCT03145428. First posted May 9, 2017. The first subjects were enrolled June 19, 2017, and the study completion date was January 26, 2018.

Keywords: Biomarker, Blood, Sepsis-2, Sepsis-3, Severe sepsis, Infection, ED

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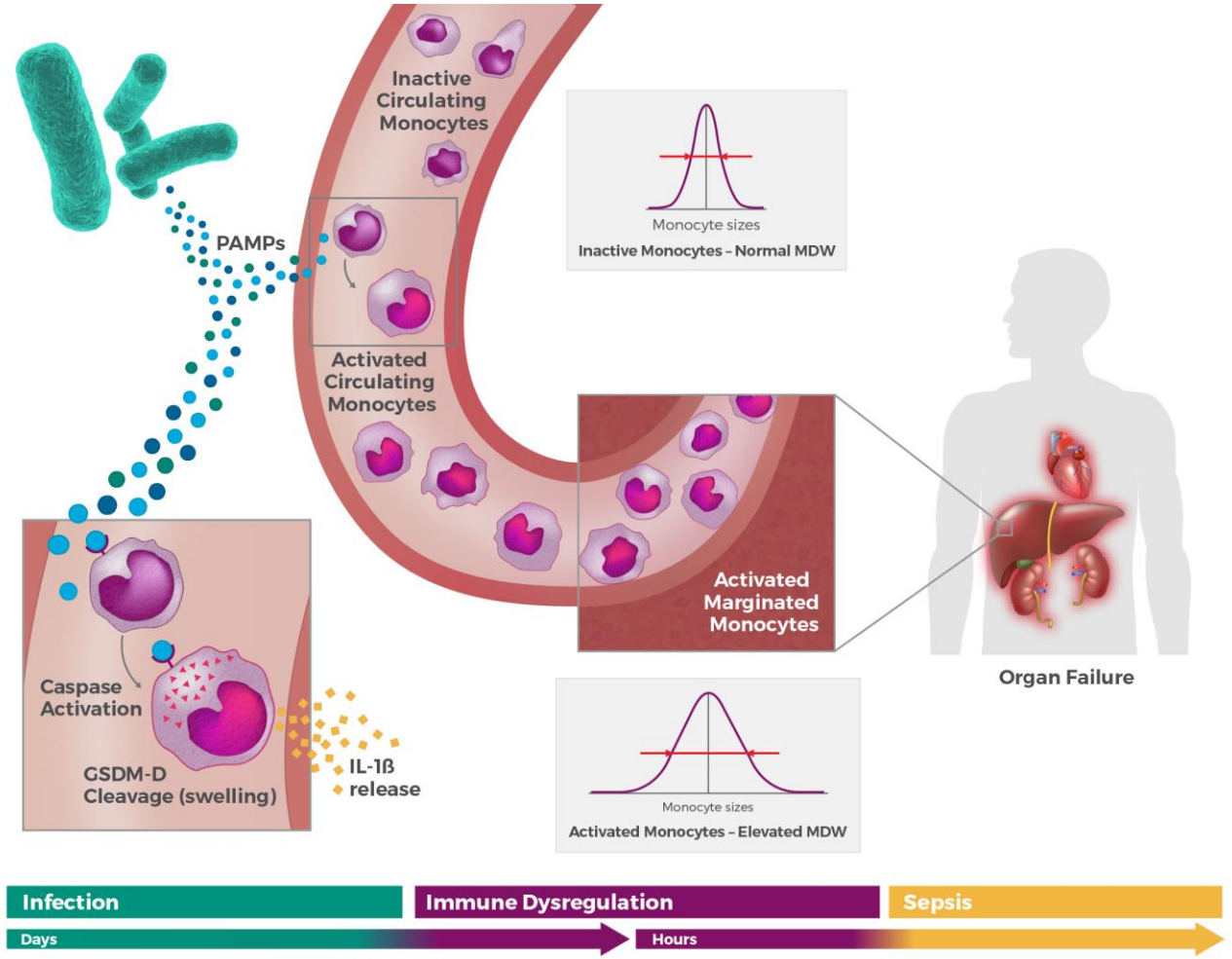
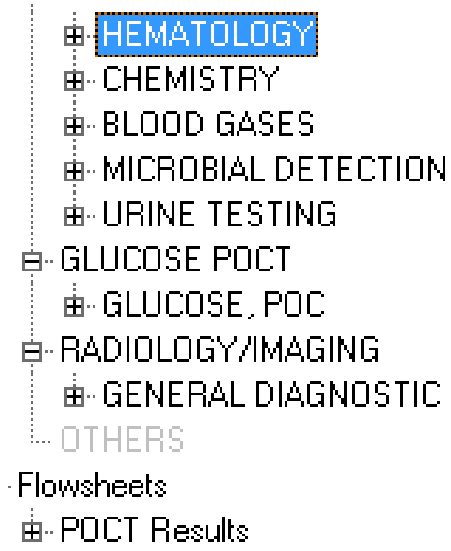
WHAT IS MDW?
Appreciating the role of monocytes



P. Orning et al, J Exp Med 2019;216(11):2458-65
C. Shi and E. Pamer, Nat Rev Immunol 2011;11: 762–774

MDW IS REPORTED AUTOMATICALLY AS A PART OF CBC WITH DIFFERENTIAL TEST IN ADULT PATIENTS SEEN IN ED

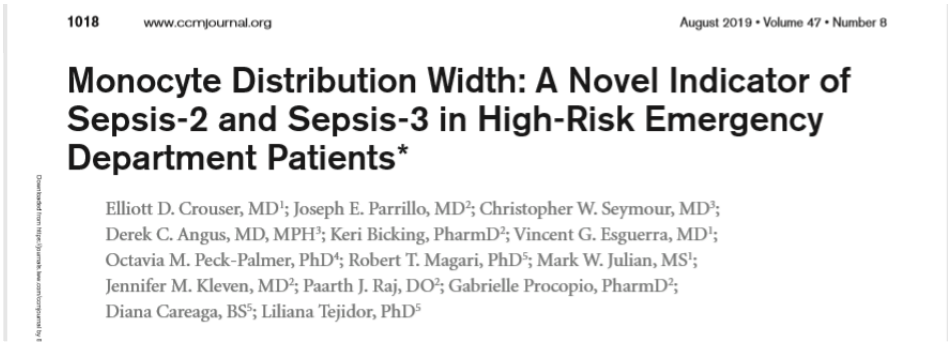


BLOOD COUNTS	
Hemoglobin	15.3
Hematocrit	44.4
Platelet Count	302
White Blood Cells	8.5
Neutrophils	69
Absolute Neutrophi...	6.02
Lymphocytes	22
Absolute Lymph Count	1.86
Monocytes	6
Absolute Monocyte ...	0.49
Eosinophils	1
Absolute Eosinophi...	0.06
Absolute Basophil ...	0.13
MDW (Monocyte Dist...	21.6 *
Basophils	2
RBC	5.24
MCV	84.7
MCH	29.2
MCHC	34.5
MPV	7.5
RDW	13.5

Result includes interpretive text →

"For Adults in ED, MDW >20, may be associated with a higher risk of sepsis during the first 12 hours of hospital admission."

MULTI-CENTER CLINICAL TRIAL PREVALENCE 18%



Monocyte Distribution Width: A Novel Indicator of Sepsis-2 and Sepsis-3 in High-Risk Emergency Department Patients*

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2,158 subjects consecutively enrolled who had CBC drawn at presentation in ED

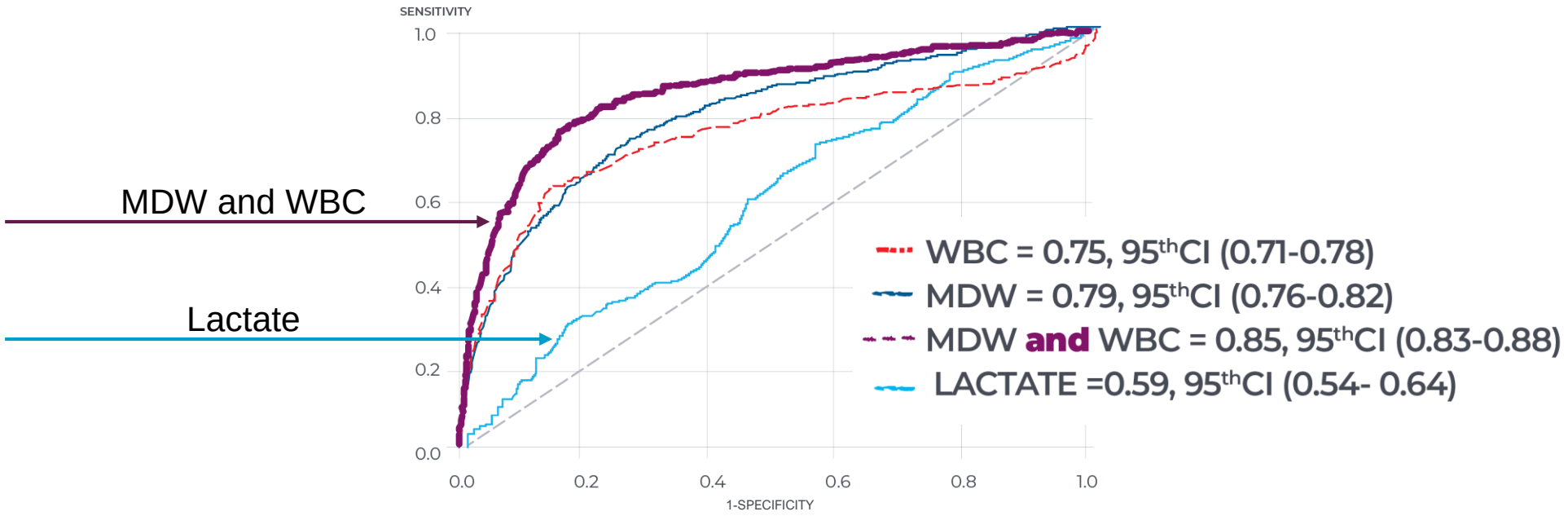
– All subjects presenting to ED – not just those suspected of sepsis
– Subjects not “cherry picked”
– Age 18 – 89 years old

Inclusion Criteria

– Subject must have stayed in ED or hospital for at least 12 hours
– Necessary to collect sufficient medical record data to confirm sepsis or no sepsis
– Due to this inclusion criteria higher percentage of “sick” subjects

MDW: FDA-CLEARED MARKER FOR SEPSIS DETECTION IN EMERGENCY DEPARTMENT

Receiver-Operator Curves for Sepsis-2 Detection



E. Crouser et al. Critical Care Med 2019; 47:1018-1025

Beckman Coulter Data on File Sepsis Pivotal Repository PN C54726 Rev. AB located in CPDM

Early Sepsis Indicator Addendum. P/N C42014AA (US).P/N C21894AC (OUS)
https://www.beckmancoulter.com/download/file/wsr-292218/C42014AA?type=pdf

AT THE TIME OF THE INITIAL EMERGENCY DEPARTMENT ENCOUNTER PERCENTAGE OF SEPTIC SUBJECTS HAD FEW SIRS AND LOW qSOFA

33%

of patients diagnosed with sepsis present with 0-1 **SIRS**

Sepsis 2 & SIRS	No SIRS	1 SIRS	2 SIRS	3 SIRS	4 SIRS	Total
Total patients	930	799	341	79	9	2158
Sepsis patients (#)	14	112	190	61	8	385

Sepsis 3 & qSOFA	No qSOFA	1 qSOFA	2 qSOFA	3 qSOFA	Total
Total patients	1707	398	50	3	2158
Sepsis patients (#)	135	79	26	3	243

88%

of patients diagnosed with sepsis presented with 0-1 qSOFA and might not be identified by **qSOFA**

Increase your index of suspicion of sepsis to assist with faster triage

Crouser et al, Journal of Intensive Care, 2020; 8(1) This is an open access article distributed under the terms of the Creative Commons CC BY license

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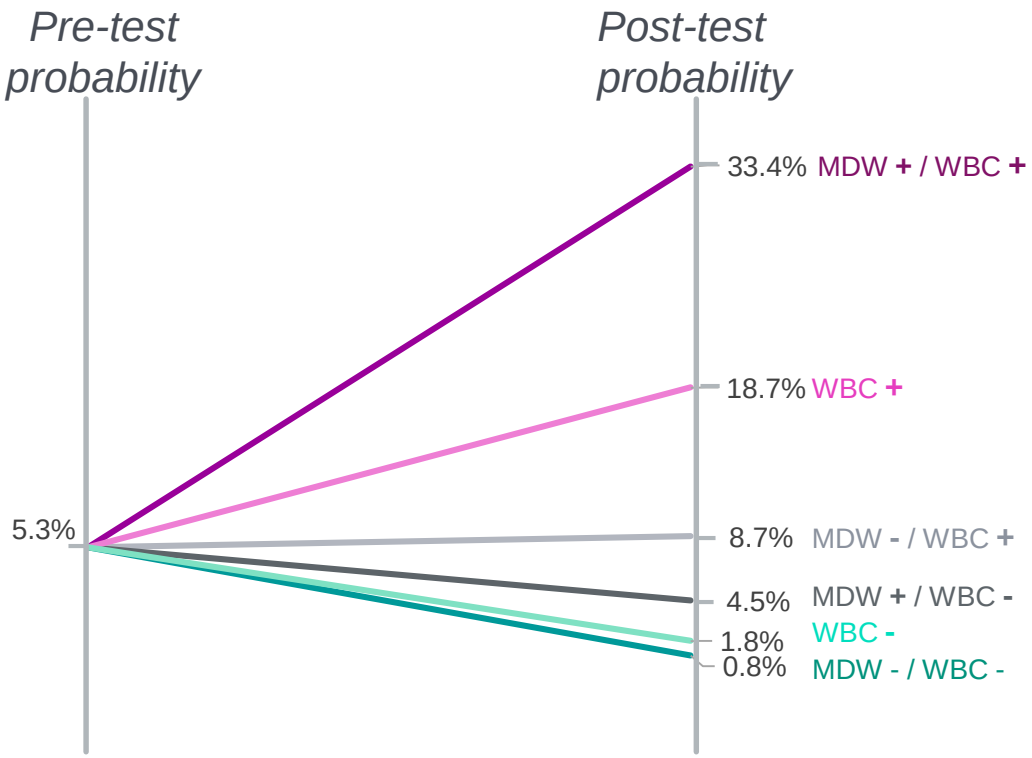
COMBINATIONS OF MDW AND WBC MODULATE SEPSIS PROBABILITY INCLUDING IN PATIENTS WITH ≤1 SEPSIS SYMPTOMS AT PRESENTATION

Sepsis symptoms: abnormal temperature, tachycardia, tachypnea, hypotension, altered mental status

1 or less Symptoms at Presentation SEPSIS-2



60%

of ED patients who were diagnosed with Sepsis in the pivotal study, presented with 0-1 symptom used for Sepsis screening

- Consideration of MDW/WBC combinations may improve specificity of sepsis detection
- Consideration of abnormal MDW may increase sensitivity of sepsis detection

Crouser ED et al. "Monocyte distribution width enhances early sepsis detection in adult patients presenting to the emergency department beyond SIRS and qSOFA., ATS 2020 poster; https://www.atsjournals.org/doi/pdf/10.1164/ajrccm-conference.2020.201.1_MeetingAbstracts.A2600

The performance Monocyte Distribution Width for exclusion of sepsis has not been evaluated and cleared by U.S. FDA

RETROSPECTIVE CASE REVIEW FROM EU TRIAL: 85 Y.O. FEMALE

Presented to ED: Fall in an elderly women. Confusion, no infectious focus, normal auscultation. Hypernatremia 166 mmol/l

CLINICAL HISTORY

Cardio Vascular	HTA
Metabolic	Dyslip.
Genito Urinary	No
Respiratory	No
Hemato Oncology	No
CNS	No
Gastro Intestinal	No
Auto Immune	No
Renal	No
Hepatic	No
Other	No

OTHER LABORATORY

BUN	38.9
CREA	1.81

HEMATOLOGY DATA

WBC	8.76
HgB, g/dL	15.3
PL x 10^9	148
NL x 10^9	7.9

NL %	90.2
LYMPH%	2.9
MONO%	6.8

MDW	22.7

PRESENTING SYMPTOMS

TEMP	36.4
HR	74
RR	16
SBP	128
AMS	No

SYMPTOMS @ 12H

TEMP	36.4
HR	86
RR	16
SBP	104
AMS	16

RESP	0
COAG	1
LIVER	0
CARDIO	0
CNS	0
RENAL	2
SCORE	**3**

ADJUDICATE DIAGNOSIS @ 12H AND HOSPITAL COURSE

Sepsis 2	Sepsis 3	Hospital LOS	ICU LOS	Death
Infection	SEPSIS	Admitted	N/A	N/A

- 12h after ED admission: desaturation 88%, non conclusive Chest X-Ray
- 24h after ED admission: hypotension+ acute respiratory failure →CT-scan → pneumonia -→ ICU

MDW: An additional data point to increase suspicion of sepsis

MDW

Initial Triage:
Acuity Assessment & Vital Signs

Routine Labs:
CBC w/Diff, & Chemistry

Signs & symptoms indicate possible sepsis?

Systemic inflammatory response syndrome (SIRS)

- Temperature >38.3 or <36ºC
- Tachycardia
- Tachypnea or decreased PaCO2
- WBC count >12000/mm3 or <4000/mm3 or >10% bands

qSOFA

- Altered mental status
- Tachypnea
- Hypotension

IL6, PCT, Lactate, CRP

Admission Sepsis Labs Confirmatory Tests Fluids

Empiric antibiotics

Typical Sepsis Care Pathway

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Potential Benefits of ESId

Helps ED Physicians

Providing **insights earlier during the initial ED encounter may aid** physicians in the **risk stratification** of sepsis by:

- **Reducing ambiguity** when working with limited information in a very short amount of time
- **Proper allocation of cognitive attention & hospital resources** for patients most at risk, **improving ED workflow efficiency** [18]

Helps Patients & Hospitals

- Potential to provide quicker treatment
- Potential positive impact to hospital metrics [19]
- Help **strengthen the hospital's perception within the community**; perceived as innovative

Know Sooner, Act Faster with MDW

Novel, regulatory-cleared sepsis biomarker available automatically as part of a CBC with Differential Test

Pivotal study data from large multicenter patient cohort demonstrates:

- Abnormal MDW at presentation increases the odds of sepsis
- Considering MDW together with WBC, MDW may add sensitivity and specificity to sepsis detection, as part of the standard assessment protocol in Emergency Departments

Interpretation of MDW value applies consistently to patients with both high- and low-level symptoms at presentation

Incorporate MDW in your sepsis assessment protocol in the Emergency Department

MORE RESOURCES

Informative references:

- E. Crouser et al, Monocyte distribution width enhances early sepsis detection in the emergency department beyond SIRS and qSOFA, Journal of Intensive Care, 2020; 8(1)
- E. Crouser et al., Monocyte Distribution Width: A Novel Indicator of Sepsis-2 and Sepsis-3 in High-Risk Emergency Department Patients**,** *Critical Care Med 2019; 47:1018-1025*
- E. Crouser et al., Improved Early Detection of Sepsis in the ED With a Novel Monocyte Distribution Width Biomarker *CHEST 2017; 152(3):518-526*

Scientific Presentations on www.beckmancoulter.com:

- ACEP | American College of Emergency Medicine, Expert Theater presented by Tiffany Osborn, MD, MPH and Pr Pierre Hausfater, MD, PhD “MDW: Early Identification of Sepsis in the Emergency Department”
- Sepsis Alliance webinar presented by Angela Craig, APN, MS, CCNS and Dustin Pierce, RN, BSN, CPHQ “No Time To Waste: Early Sepsis Detection using Monocyte Distribution Width (MDW)”
- Compass Group webinar presented by Elliott Crouser, M.D. and Nan West, MT (ASCP), “Monocytes Distribution Width (MDW) New Sepsis Detection Biomarker”
- 360Dx webinar, presented by Tiffany Osborn, MD, MPH and Christopher Farnsworth, PhD, DABCC “Clinical and Laboratory Medicine Collaboration Can Improve Patient Outcomes”