Diagnostic précoce du sepsis: du cabinet du médecin généraliste à l'admission à l'hôpital
Early diagnosis of sepsis: from the general practitioner's office to hospital admission

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Conflicts interest

- Lectures honorarium
  - ThermoFisher Scientific
  - Radiometer
  - bioMerieux
  - Beckman Coulter
- Educational support honorarium
  - bioMérieux
- Clinical research grants
  - bioMérieux
  - Beckman Coulter

What are we talking about....?

Fever

SIRS

Septicemia

Infection

Sepsis

Severe sepsis

Septic shock

Bacteremia

Sepsis 2 *versus* Sepsis 3

A

INFECTION
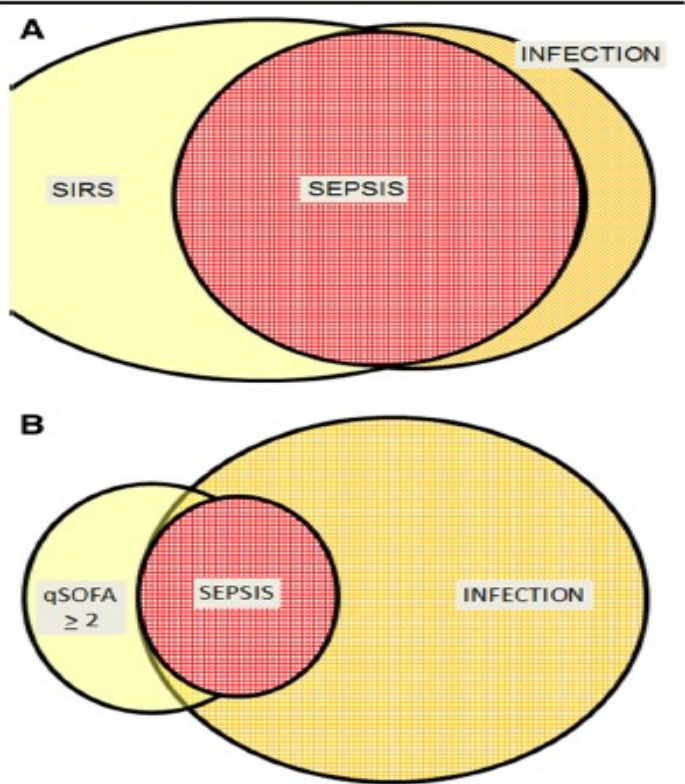
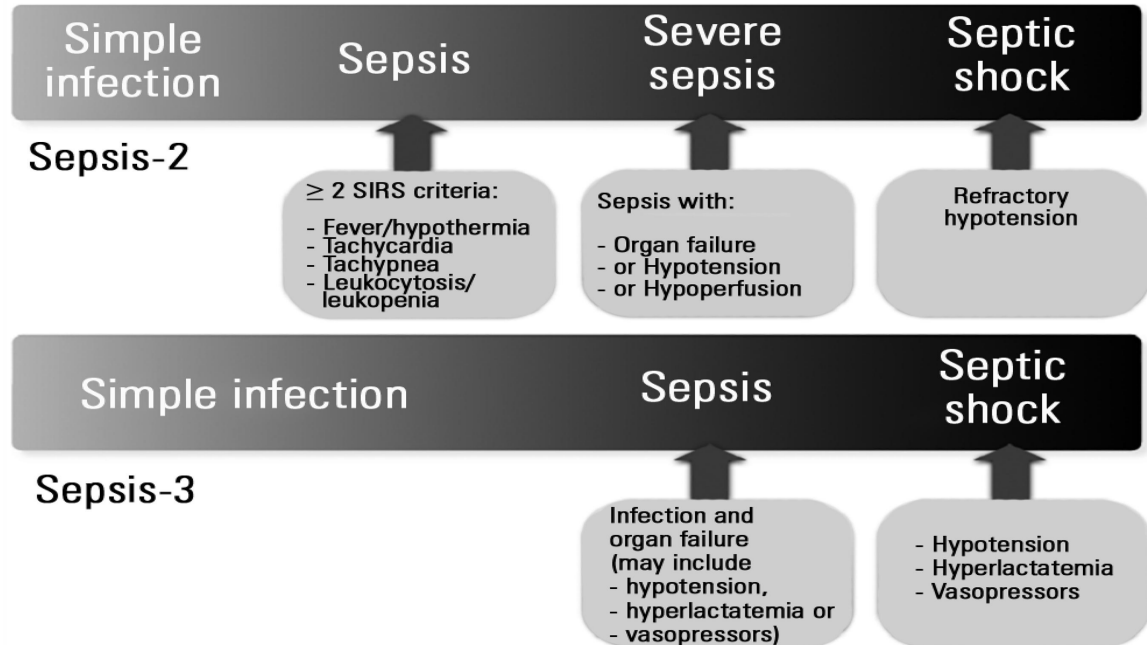SIRS

SEPSIS

B

qSOFA ≥ 2

SEPSIS

INFECTION

Fig. 1 Schematic representation illustrating **a** the almost complete overlap of sepsis and infection when the SIRS criteria of the 1992 criteria [3] are used and **b** the differences between qSOFA and sepsis. *qSOFA* quick sequential organ failure assessment, *SIRS* systemic inflammatory response syndrome

Vincent *et al. Critical Care* (2016) 20:210

Sepsis-2

Simple infection	Sepsis	Severe sepsis	Septic shock
	≥ 2 SIRS criteria: - Fever/hypothermia - Tachycardia - Tachypnea - Leukocytosis/leukopenia	Sepsis with: - Organ failure - or Hypotension - or Hypoperfusion	Refractory hypotension

Sepsis-3

Simple infection	Sepsis	Septic shock
	Infection and organ failure (may include - hypotension, - hyperlactatemia or - vasopressors)	- Hypotension - Hyperlactatemia - Vasopressors

Community-, Healthcare-, and Hospital-Acquired Severe Sepsis Hospitalizations in the University HealthSystem Consortium

David B. Page, MD[1]; John P. Donnelly, MSPH[1,2,3]; Henry E. Wang, MD, MS[1]
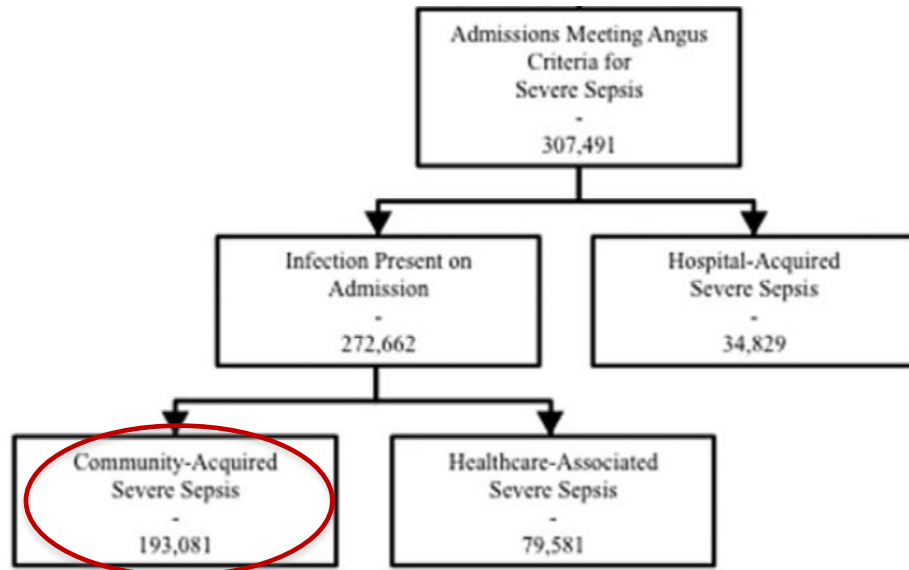
Sepsis Presenting in Hospitals versus Emergency Departments: Demographic, Resuscitation, and Outcome Patterns in a Multicenter Retrospective Cohort

Daniel E Leisman, BS[1,2,3]*; Catalina Angel, MPA[1]; Sandra M Schneider, MD[2,4];
Jason A D'Amore, MD[2]; John K D'Angelo, MD[2]; Martin E Doerfler, MD[5,6]

	Prevalance			
	8,673 (77.8%)	2,509 (22.4%)	1,663 (14.9%)	846 (7.6%)
	EDPS	All HPS	Non-ICU	ICU
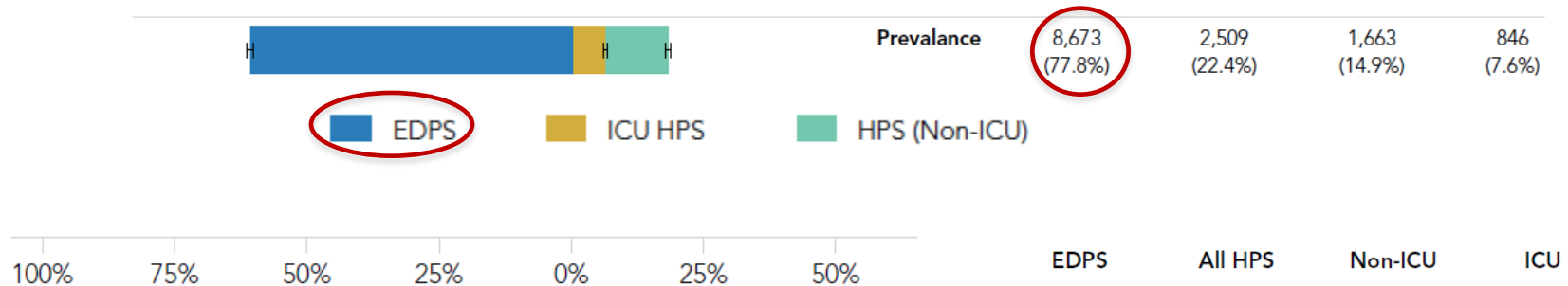
EDPS, ED presenting sepsis; HPS, hospital presenting sepsis; ICU, intensive care unit.

Early and accurate sepsis identification is majoritarily an ED's job !

ED's sepsis mode of presentation through organ dysfunction only

85 year-old dementia, 37.8° C, weakness, agitation
Sepsis ?

In-hospital mortality associated with the misdiagnosis or unidentified site of infection at admission

Toshikazu Abe[1,2,3*], Yasuharu Tokuda[4], Atsushi Shiraishi[5], Seitaro Fujishima[6], Toshihiko Mayumi[7], Takehiro Sugiyama[2,3,8,9], Gautam A. Deshpande[1], Yasukazu Shiino[10], Toru Hifumi[11], Yasuhiro Otomo[12], Kohji Okamoto[13], Joji Kotani[14], Yuichiro Sakamoto[15], Junichi Sasaki[16], Shin-ichiro Shiraishi[17], Kiyotsugu Takuma[18], Akiyoshi Hagiwara[19], Kazuma Yamakawa[20], Naoshi Takeyama[21], Satoshi Gando[22,23] and for the JAAM SPICE Study Group

Characteristics	Misdiagnosed or unidentified site of infection	Correctly diagnosed site of infection	*p* value
	113	861	
In-hospital mortality			
All	28 (24.8)	118 (13.7)	< 0.01
qSOFA ≥ 2 (*n* = 385)	16 (29.6)	69 (20.9)	0.15

Time-to-antibiotics and clinical outcomes in patients with sepsis and septic shock: a prospective nationwidemulticenter cohort study
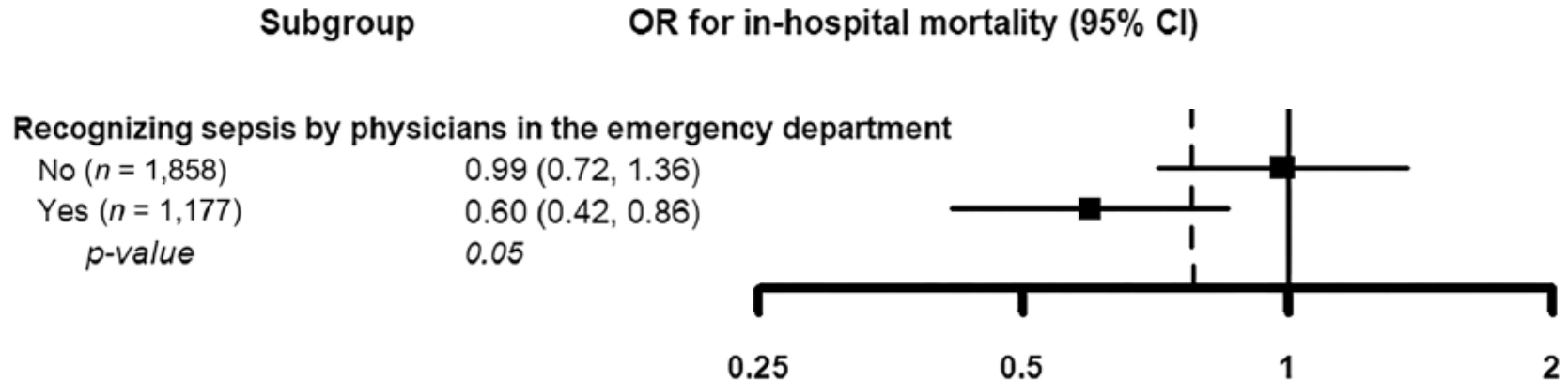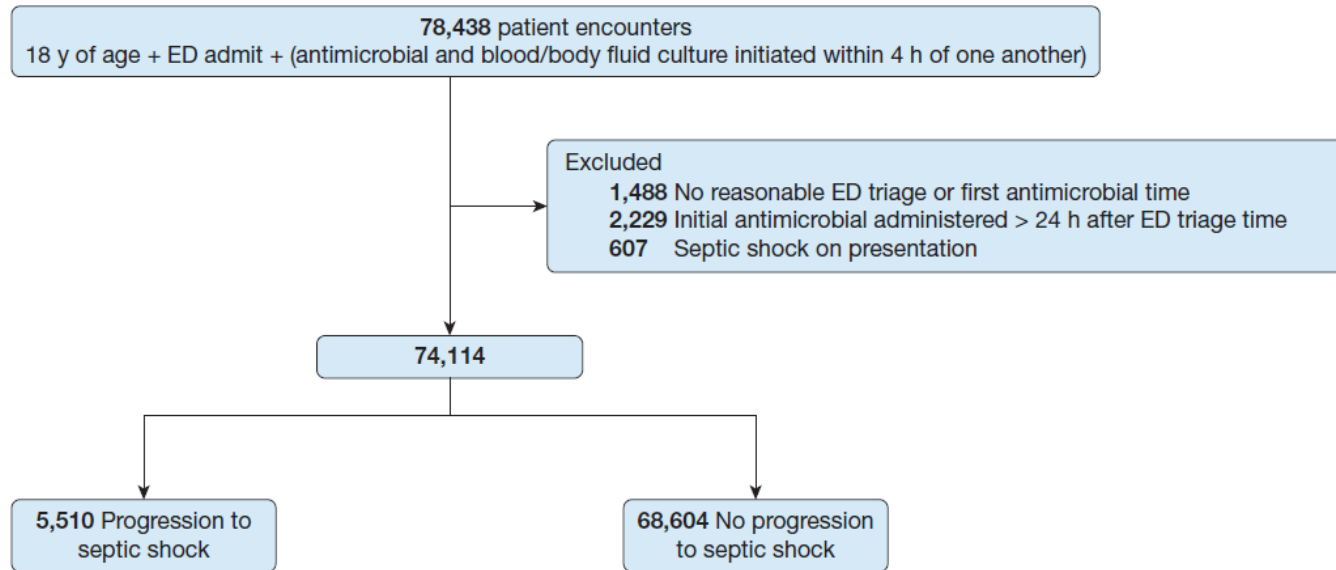
Antibiotic Timing and Progression to Septic Shock Among Patients in the ED With Suspected Infection

Roshan Bisarya, BS; Xing Song, PhD; John Salle, MS; Mei Liu, PhD; Anurag Patel, MD; and Steven Q. Simpson, MD

A
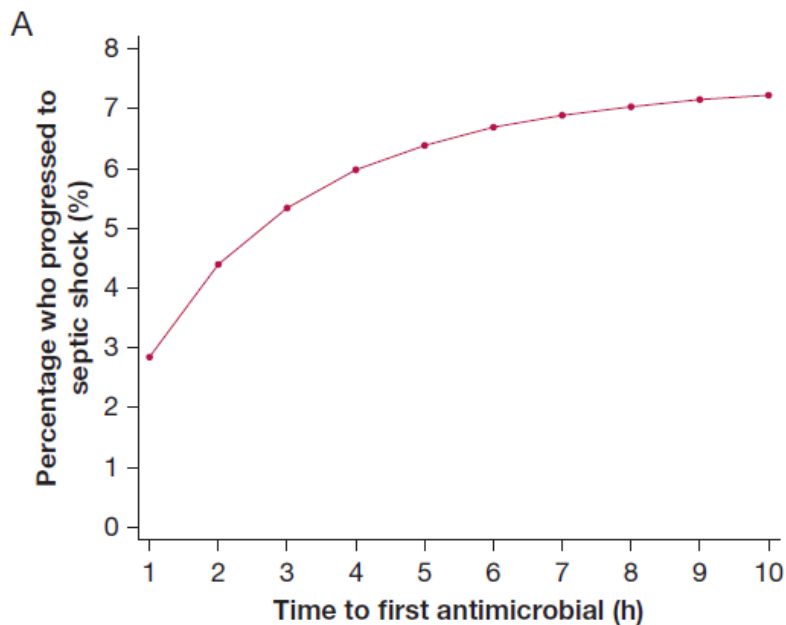
TABLE 4] qSOFA and SIRS Score Septic Shock and Antimicrobial Timing Comparison

Variable	Median Time to Sepsis 2 Septic Shock (h)	Median Time to First Antimicrobial Administration (h)
Negative qSOFA and SIRS scores	44.9 (19.2-111.7)	2.33 (1.1-4.4)
Positive qSOFA score (n = 2,261)[a]	11.2 (5.5-49.7)	0.82 (0.35-2.15)
Positive SIRS score (n = 21,625)[b]	26 (8.4-92.6)	1.2 (0.52-2.69)
Positive qSOFA and SIRS scores (n = 1,607)	9.8 (5.3-39.4)	0.7 (0.32-1.73)

Well, so you just have to treat all the suspicions you have !

😱

Likelihood of Bacterial Infection in Patients Treated With Broad-Spectrum IV Antibiotics in the Emergency Department*

Claire N. Shappell, MD[1,2]
Michael Klompas, MD, MPH[1,3]
Aileen Ochoa, MPH[1]
Chanu Rhee, MD, MPH[1,3]
for the CDC Prevention Epicenters Program

- Retrospective multicentric study

- 300 patients with suspected serious bacterial infections in the ED
  - Defined as blood cultures drawn
  - and the administration of at least one IV broad-spectrum antibiotic

- 196 (65.3%) had definite or likely bacterial infection

- **104 (34.7%) had unlikely or definitely no bacterial infection**
  - 27.9% of them had likely or proven viral infection

ER: the place to diagnose early sepsis

- Not an issue for « easy presenters »
- **Misdiagnosis** for
  - « organ dysfunction only » presenters
  - « not yet » organ dysfunction presenters
  - Apyretic patients

- 🚩 needed… with high specificity ! (rationale ATB use)

~~SIRS~~   ~~qSOFA~~

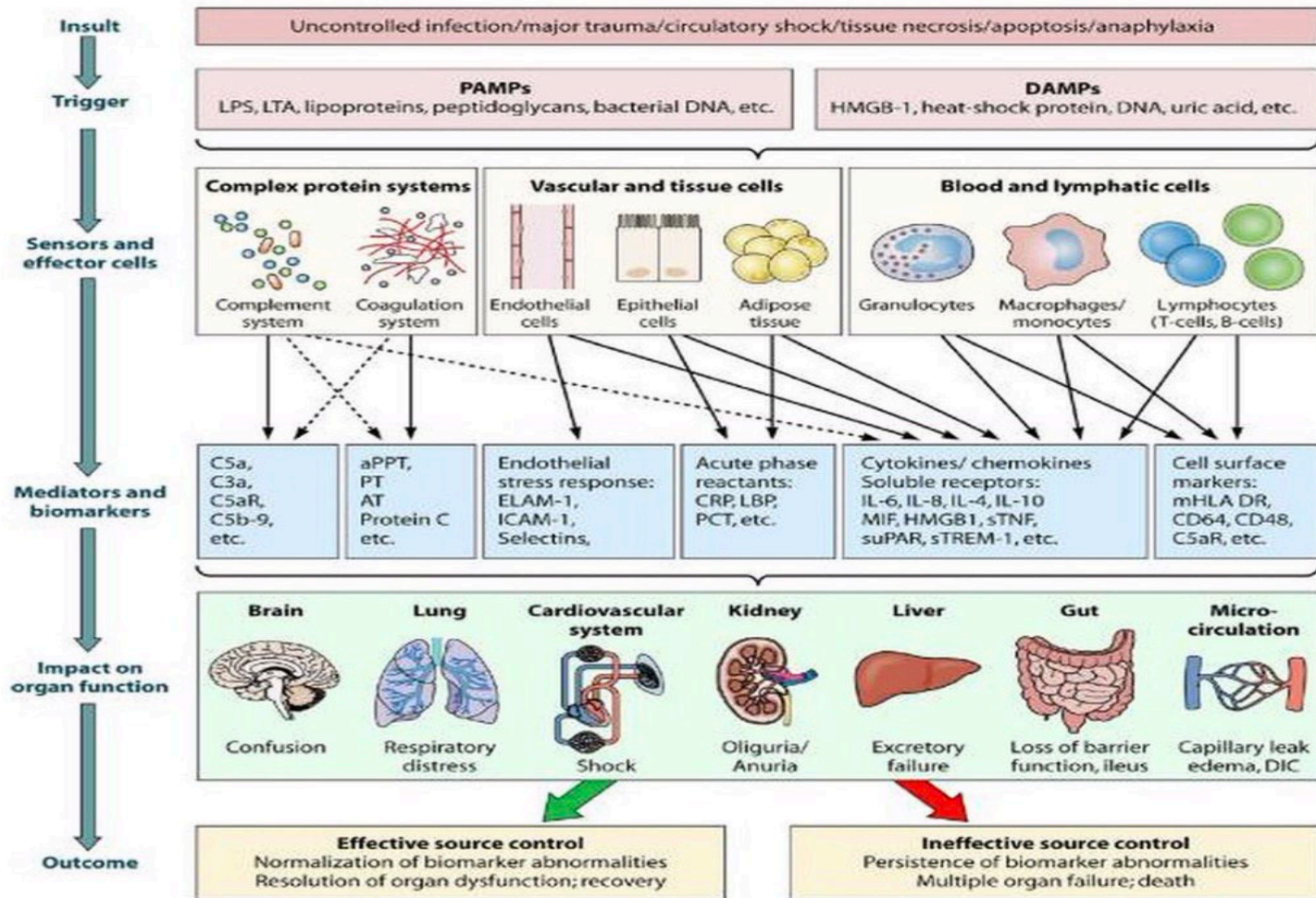**Fig. 5.** Pathophysiology of sepsis induced organ dysfunction. It has been focused attention on immunologic pathways leading to toxic damage on target organs since complement and coagulation cascade activation and endothelial and epitelial damage.

2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference

Infection,[a] documented or suspected, and some of the following:[b]
General variables
    Fever (core temperature >38.3°C)
    Hypothermia (core temperature <36°C)
    Heart rate >90 min^{-1} or >2 SD above the normal value for age
    Tachypnea
    Altered mental status
    Significant edema or positive fluid balance (>20 mL/kg over 24 hrs)
    Hyperglycemia (plasma glucose >120 mg/dL or 7.7 mmol/L) in the absence of diabetes
Inflammatory variables
    Leukocytosis (WBC count >12,000 μL^{-1})
    Leukopenia (WBC count <4000 μL^{-1})
    Normal WBC count with >10% immature forms
    Plasma C-reactive protein >2 SD above the normal value
    Plasma procalcitonin >2 SD above the normal value
Hemodynamic variables
    Arterial hypotension[b] (SBP <90 mm Hg, MAP <70, or an SBP decrease >40 mm Hg in adults
      or <2 SD below normal for age)
    S$\bar{\text{v}}$o$_2$ >70%[b]
    Cardiac index >3.5 L·min^{-1}·M^{-23}
Organ dysfunction variables
    Arterial hypoxemia (Pao$_2$/F$_{IO_2}$ <300)
    Acute oliguria (urine output <0.5 mL·kg^{-1}·hr^{-1} or 45 mmol/L for at least 2 hrs)
    Creatinine increase >0.5 mg/dL
    Coagulation abnormalities (INR >1.5 or aPTT >60 secs)
    Ileus (absent bowel sounds)
    Thrombocytopenia (platelet count <100,000 μL^{-1})
    Hyperbilirubinemia (plasma total bilirubin >4 mg/dL or 70 mmol/L)
Tissue perfusion variables
    Hyperlactatemia (>1 mmol/L)
    Decreased capillary refill or mottling

Serum procalcitonin measurement as diagnostic and prognostic marker in febrile adult patients presenting to the emergency department

Pierre Hausfater[1], Gaëlle Juillien[1], Beatrice Madonna-Py[1], Julien Haroche[2], Maguy Bernard[3] and Bruno Riou[1]

Table 3

Comparison of patients with or without bacterial/parasitic infection (univariate analysis) and identification of variables predictive of bacterial/parasitic infection after stepwise logistic regression analysis (multivariate analysis)

Variable	Univariate analysis			Multivariate analysis	
	Nonbacterial/parasitic ($n = 76$)	Bacterial/parasitic ($n = 167$)	P	Odds ratio [95% CI]	P
Emergency physician diagnosis					
Haemoglobin level (mg/l)					
White blood cell count (/mm³)					
Neutrophil leucocytes (/1500/mm³)					
Platelet count (×1000/l)					
Creatinine (µmol/l)					
PCT (µg/l)					
PCT >1 (µg/l)					
CRP (mg/l)					
CRP >xx (mg/l)					

PCT and sepsis diagnosis in ICU

Méta analysis: 30 publications (3244 patients)
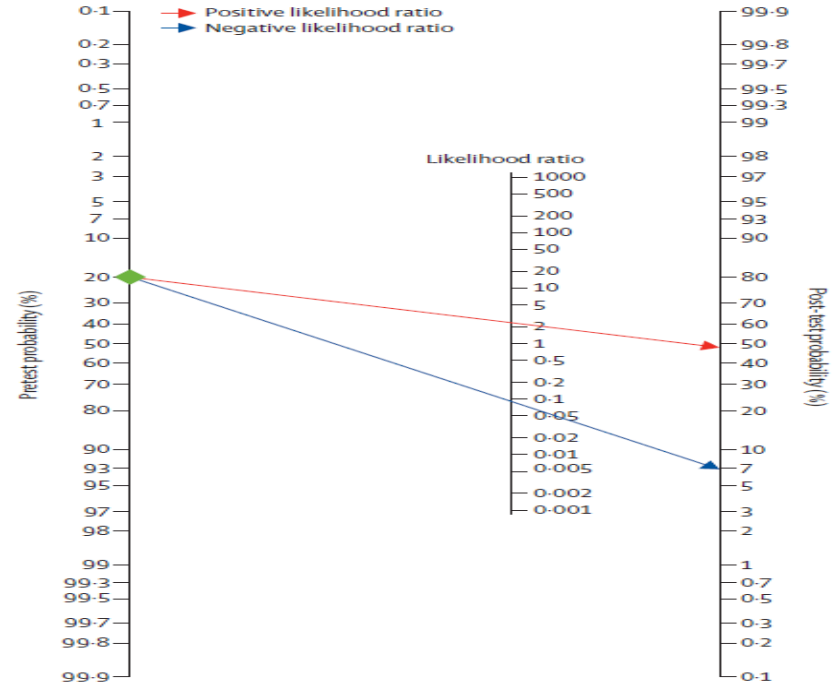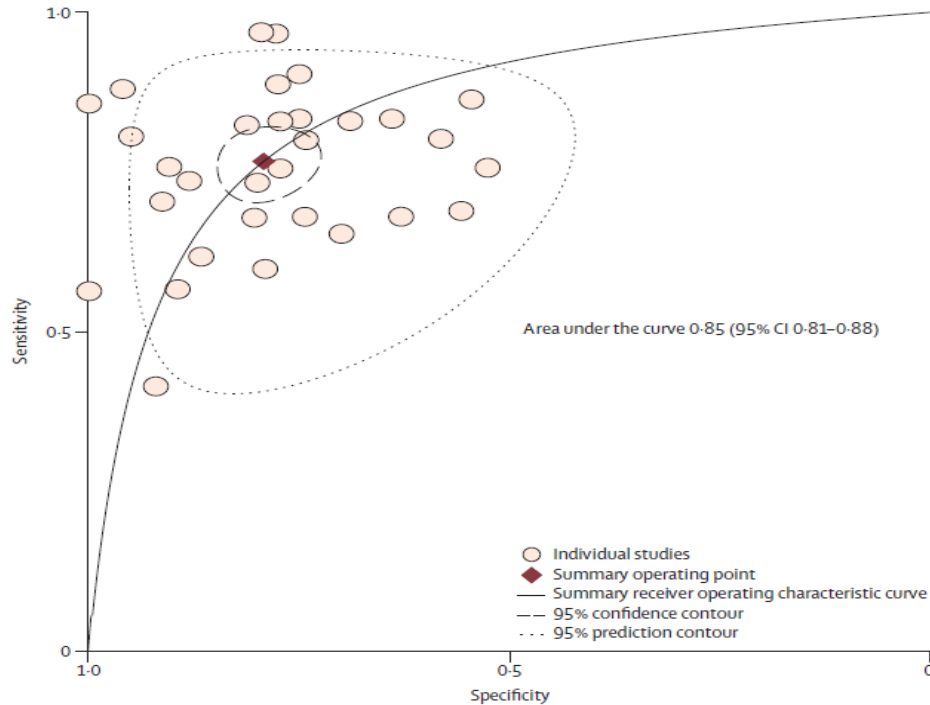
(Wacker, Lancet Inf Dis 2013)

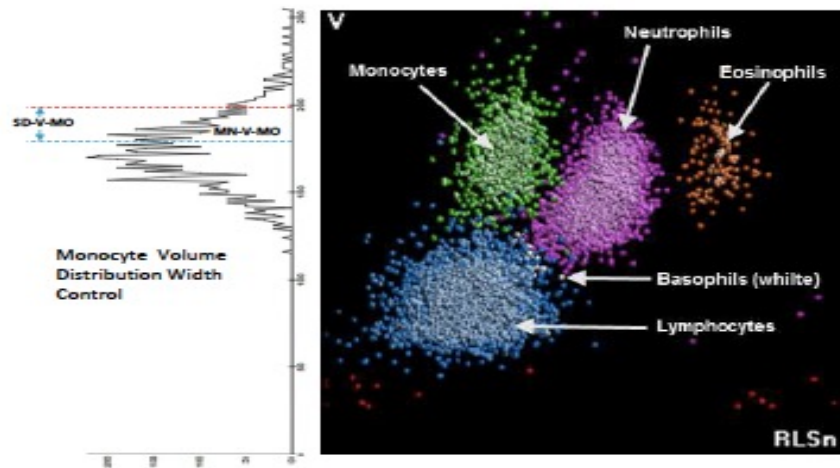# Blood Tests Ordered At Emergency Department Visits: United States 2017

Diagnostic and screening services ordered or provided	Number of visits[1] (standard error) in thousands
All visits	138,977 (10,277)
One or more diagnostic or screening service listed	102,231 (7,941)
None	35,159 (2,876)
Blank	1,587 (368)
Blood tests	
Complete blood count	53,751 (4,572)
Creatinine or renal function panel	5,292 (1,529)
Glucose, serum	8,494 (1,770)
Electrolytes	2,598 (743)
Prothrombin time (PT/PTT/INR)[2]	10,971 (1,337)
Liver enzymes or hepatic function panel	4,841 (792)
Cardiac enzymes	6,790 (1,151)
Comprehensive metabolic panel	40,122 (3,746)
Blood culture	6,523 (811)
Brain natriuretic peptide	4,102 (716)
D-dimer	2,851 (394)
Arterial blood gases	*2,883 (960)
Blood alcohol concentration	2,783 (454)
Basic metabolic panel	12,366 (1,751)
Lactate	3,087 (428)
Other blood test	31,196 (3,117)
Any blood test listed	61,934 (4,887)

National Hospital Ambulatory Medical Care Survey 2017; https://www.cdc.gov/nchs/data/nhamcs/web_tables/2017_ed_web_tables-508.pdf

Monocytes Distribution Width(MDW): a parameter available on CBC-Diff
(on DxH900 analyzer)

Non-septic

MDW = 19.1
WBC cells x10³ = 4.73
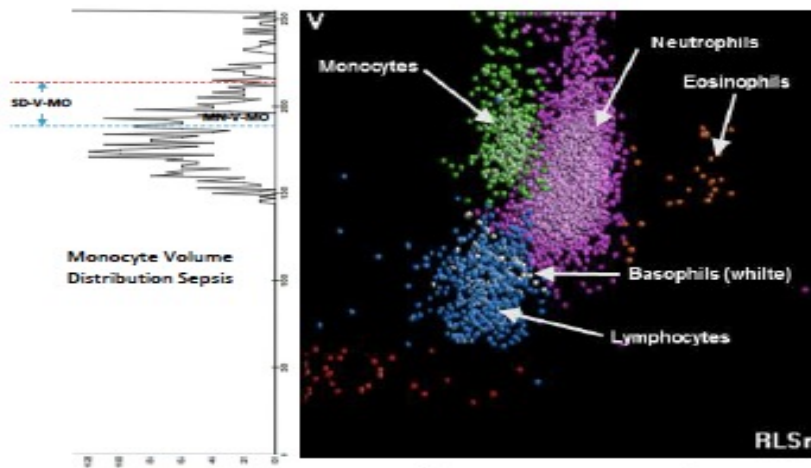
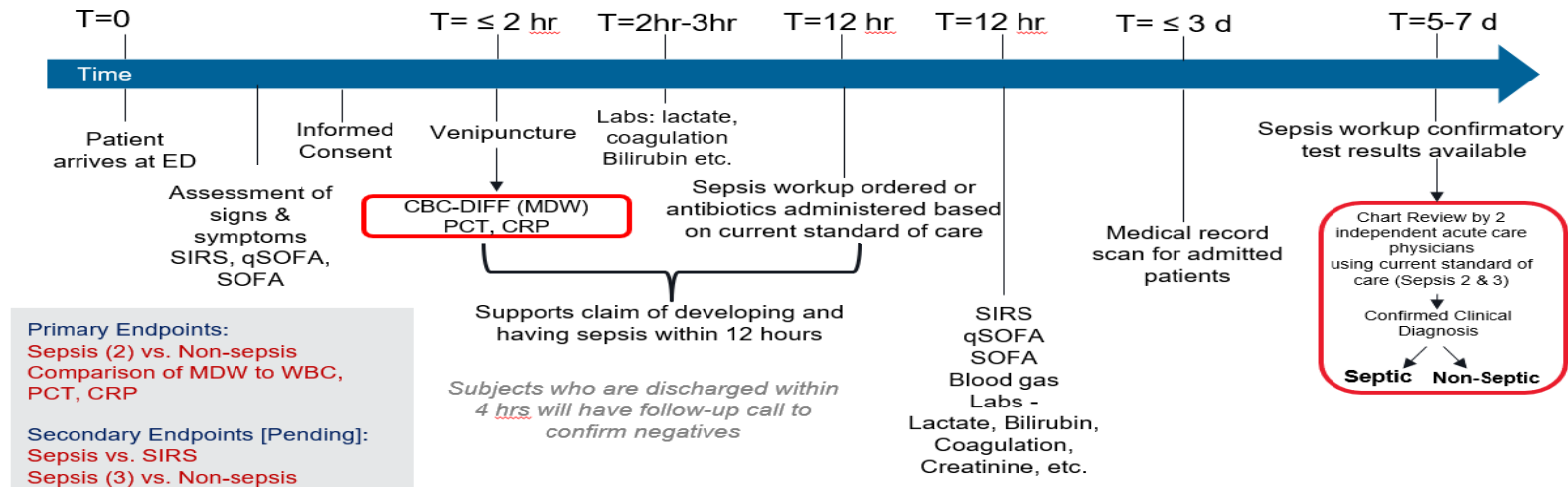Septic

MDW = 24.3
WBC cells x10³ = 10.27
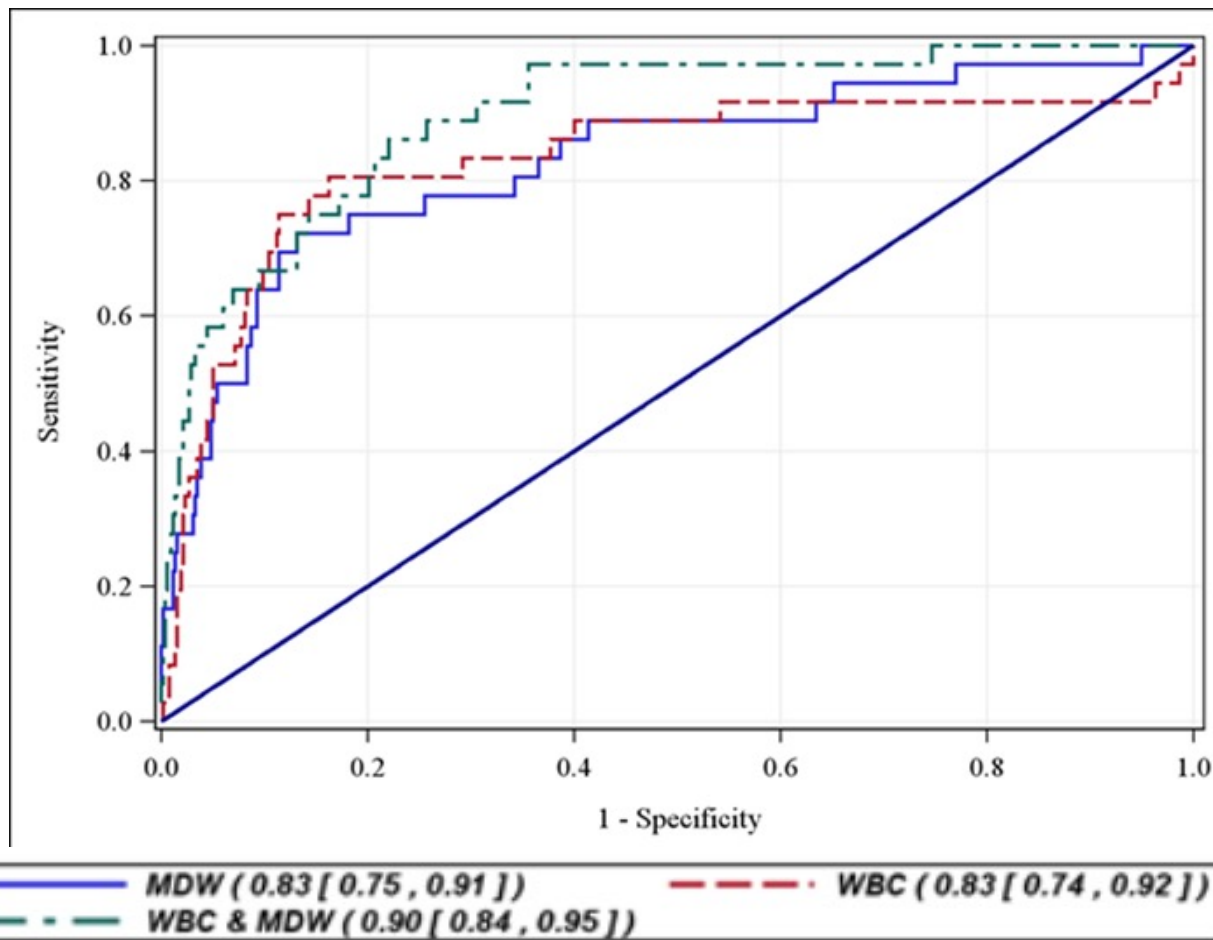
Check for updates

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

Pierre Hausfater[1,2,3*] , Neus Robert Boter[4,5], Cristian Morales Indiano[5,7], Marta Cancella de Abreu[1,2], Adria Mendoza Marin[4,5], Julie Pernet[1], Dolores Quesada[5,8], Iris Castro[9], Diana Careaga[9], Michel Arock[6], Liliana Tejidor[9] and Laetitia Velly[1,2]

| T=0 | T= ≤ 2 hr | T=2hr-3hr | T=12 hr | T=12 hr | T= ≤ 3 d | T=5-7 d |

Time →

Patient arrives at ED

Informed Consent

Venipuncture

Labs: lactate, coagulation Bilirubin etc.

Sepsis workup confirmatory test results available

Assessment of signs & symptoms SIRS, qSOFA, SOFA

CBC-DIFF (MDW) PCT, CRP

Sepsis workup ordered or antibiotics administered based on current standard of care

Medical record scan for admitted patients

Chart Review by 2 independent acute care physicians using current standard of care (Sepsis 2 & 3)

Confirmed Clinical Diagnosis

Septic   Non-Septic

Supports claim of developing and having sepsis within 12 hours

Subjects who are discharged within 4 hrs will have follow-up call to confirm negatives

SIRS
qSOFA
SOFA
Blood gas
Labs -
Lactate, Bilirubin, Coagulation, Creatinine, etc.

Primary Endpoints:
Sepsis (2) vs. Non-sepsis
Comparison of MDW to WBC, PCT, CRP

Secondary Endpoints [Pending]:
Sepsis vs. SIRS
Sepsis (3) vs. Non-sepsis

C : low pre-test probability (no PCT or CRP ordered by ED physician)

MDW (0.83 [0.75 , 0.91])   WBC (0.83 [0.74 , 0.92])
WBC & MDW (0.90 [0.84 , 0.95])

The early identification of disease progression in patients with suspected infection presenting to the emergency department: a multi-centre derivation and validation study

Kordo Saeed[1,2*], Darius Cameron Wilson[3], Frank Bloos[4,5], Philipp Schuetz[6,7], Yuri van der Does[8], Olle Melander[9,10], Pierre Hausfater[11], Jacopo M. Legramante[12,13], Yann-Erick Claessens[14], Deveendra Amin[15], Mari Rosenqvist[10,16], Graham White[17], Beat Mueller[6,7], Maarten Limper[18], Carlota Clemente Callejo[19], Antonella Brandi[12], Marc-Alexis Macchi[14], Nicholas Cortes[1,2,20], Alexander Kutz[6], Peter Patka[8], María Cecilia Yañez[19], Sergio Bernardini[21,22], Nathalie Beau[14], Matthew Dryden[1,2,23], Eric C. M. van Gorp[24,25], Marilena Minieri[21], Louisa Chan[26], Pleunie P. M. Rood[8] and Juan Gonzalez del Castillo[27]

Critical Care   (2019) 23:40

28-day death
ICU admission
H°>10 d

Derivation
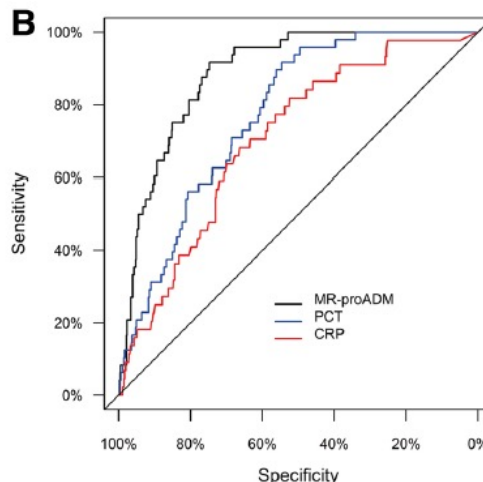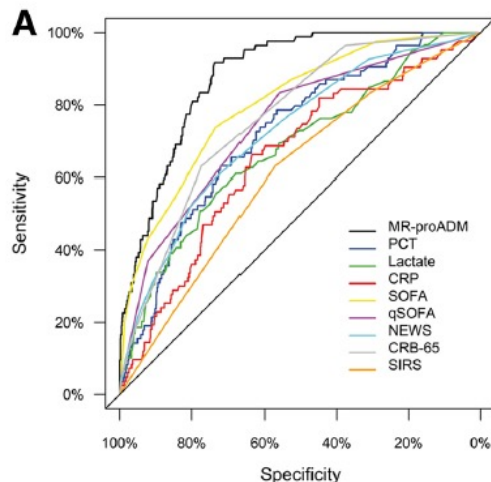
Validation

ROC curve and AUC analysis for 28-day mortality prediction

|	Biomarkers and clinical scores	AUC	Cut-off	Sensitivity	Specificity	PPV	NPV	LR+	LR-	OR
Panel B	MR-proADM	0.89 [0.85 - 0.92]	1.63	0.92 [0.80 - 0.97]	0.75 [0.72 - 0.78]	0.17 [0.13 - 0.22]	0.99 [0.98 - 1.00]	3.63 [3.15 - 4.19]	0.11 [0.04 - 0.29]	32.59 [11.57 - 91.76]
	PCT	0.77 [0.72 - 0.83]	0.15	0.92 [0.80 - 0.97]	0.55 [0.51 - 0.58]	0.10 [0.08 - 0.14]	0.99 [0.98 - 1.00]	2.02 [1.81 - 2.26]	0.15 [0.06 - 0.39]	13.26 [4.72 - 37.25]
	CRP	0.71 [0.63 - 0.78]	106	0.68 [0.53 - 0.80]	0.66 [0.63 - 0.70]	0.11 [0.08 - 0.15]	0.97 [0.95 - 0.98]	2.02 [1.61 - 2.54]	0.48 [0.31 - 0.74]	4.22 [2.20 - 8.10]

Optimal combination of early biomarkers for infection and sepsis diagnosis in the emergency department: The BIPS study

Laetitia Velly[a,b,c], Steven Volant[d], Catherine Fitting[b], Daniel Aiham Ghazali[a,e], Florian Salipante[f], Julien Mayaux[g], Gentiane Monsel[h], Jean-Marc Cavaillon[b], Pierre Hausfater[a,c,*]
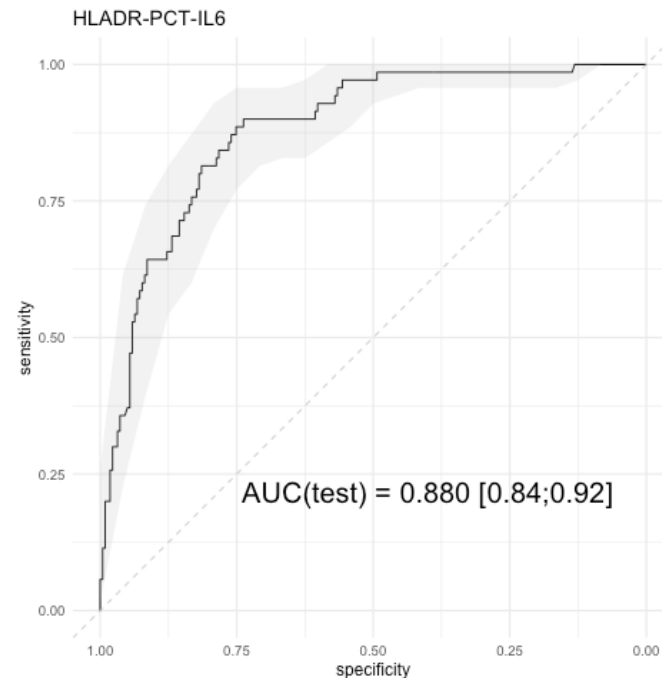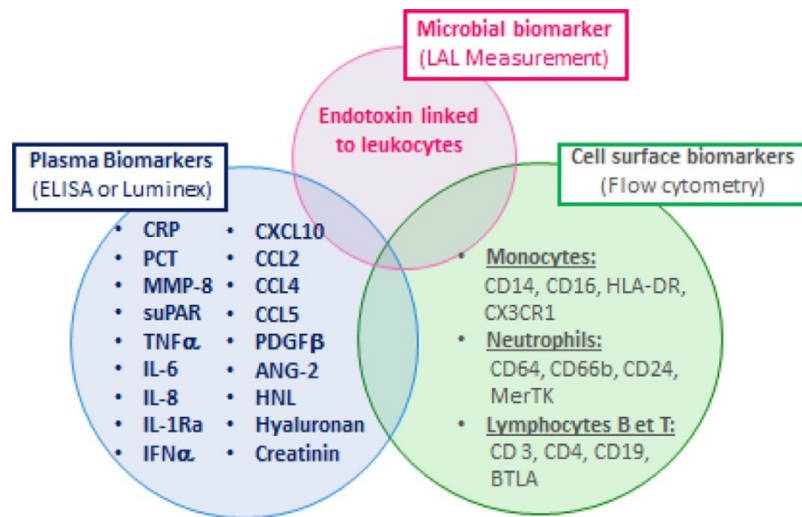
*Research and knowledge have focused on patients **already with sepsis** (ICU) and are hospital-centered and far less on the natural history of cured and self-limited infections in ambulatory medicine*

	Sepsis concern	Sepsis knowledge	Research activity
ICU	+++	+++	+++
ED	++	++	++
GP's Nursing homes	+	+	+/-

Why do they cure without progressing to sepsis ?

What happens the days preceeding sepsis...

The Characteristics and Outcomes of Clinic Visits Immediately Preceding Sepsis Hospitalization

H. Catherine Miller, MD[1], Vincent X. Liu, MD, MS[2,3], Hallie C. Prescott, MD, MSc[1,4]

Of 1,150 patients:

118 (10.3%) seen in clinic

88 (74.6%) on day

30 (25.4%) on the day prior to admission

Figure Distribution of scores on the quick Sequential Organ Failure Assessment (qSOFA) during clinic visit (left side) and at the emergency department (ED)/hospital (right side). A, Of all 118 patients evaluated in clinic before hospitalization for sepsis, 42 (36%) had an increase in qSOFA score, 64 (54%) had no change in qSOFA score, and 12 (10%) had an improvement in qSOFA score. B, Of the 74 patients instructed to present to the ED/hospital from the clinic, 18 (24%) had an increase in qSOFA score, 46 (62%) had no change in qSOFA score, and 10 (14%) had an improvement in qSOFA score. C, Of the 44 patients who were not instructed to present to the ED/hospital, 24 (55%) had an increase in qSOFA score, 18 (41%) had no change in qSOFA score, and 2 (5%) had an improvement in qSOFA score.
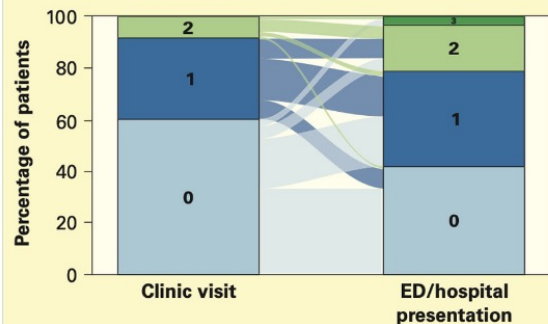
Diagnosing serious infections in older adults presenting to ambulatory care: a systematic review

Thomas Struyf[1], Hanne A. Boon[1], Alma C. van de Pol[2], Jos Tournoy[1], Alexander Schuermans
Theo J. M. Verheij[2], Jan Y. Verbakel[1,3], Ann Van den Bruel[1]

*"Procalcitonin may have potential as a biomarker in ruling out sepsis in **older persons presenting to ambulatory care**, but existing evidence is too scarce. **New diagnostic studies in this setting are clearly needed**..."*

Study reference	Test	Prevalence	Likelihood ratio (95%CI)		Probability of infection (%)
			Positive	Negative	
Sepsis					
28	PCT 0.10ng/ml	22.6%	1.31 (1.24 - 1.38)	0.03 (0.00 - 0.23)	
28	PCT 0.25ng/ml	22.6%	1.91 (1.73 - 2.11)	0.11 (0.05 - 0.22)	
28	PCT 0.50ng/ml	22.6%	2.40 (2.06 - 2.80)	0.28 (0.19 - 0.40)	
28	PCT 2.00ng/ml	22.6%	3.76 (2.84 - 4.98)	0.55 (0.46 - 0.66)	
28	PCT 10.0ng/ml	22.6%	4.34 (2.60 - 7.24)	0.82 (0.75 - 0.90)	
24	CRP 280 mg/l	31.4%	3.03 (1.57 - 5.83)	0.81 (0.70 - 0.94)	
24	Presepsin 312ng/l	31.4%	1.17 (1.08 - 1.27)	0.17 (0.04 - 0.69)	
24	Presepsin 849ng/L	31.4%	3.54 (2.46 - 5.11)	0.41 (0.29 - 0.57)	
24	PCT 0.37ng/ml	31.4%	1.77 (1.48 - 2.10)	0.20 (0.10 - 0.42)	
24	PCT 1.56ng/ml	31.4%	4.11 (2.77 - 6.09)	0.39 (0.28 - 0.55)	
25	CRP 220 mg/l	48.0%	3.03 (1.65 - 5.57)	0.53 (0.37 - 0.75)	
25	LBP 33.9µg/dl	48.0%	1.98 (1.30 - 3.03)	0.49 (0.32 - 0.77)	
25	PCT 1.30ng/ml	48.0%	3.52 (2.10 - 5.90)	0.26 (0.15 - 0.47)	

Probability of infection (%) legend:
- After negative test
- Before test
- After positive test

0 10 20 30 40 50 60 70 80 90 100

Likelihood ratios and pre- and post-test disease probabilities (%) for blood test

Healthcare utilization and Infection in the week prior to sepsis hospitalization

Vincent X Liu, MD, MS[1,2], Gabriel J Escobar, MD[1], Rakesh Chaudhary, MD[2], and Hallie C Prescott, MD, MSc[3,4]

Over 45% of sepsis patients had clinician-based encounters in the week prior to hospitalization with *an increasing incidence of antibiotic use in the outpatient setting*
These pre-sepsis encounters offer several potential opportunities to improve the recognition, risk stratification, and treatment prior to sepsis hospitalization"
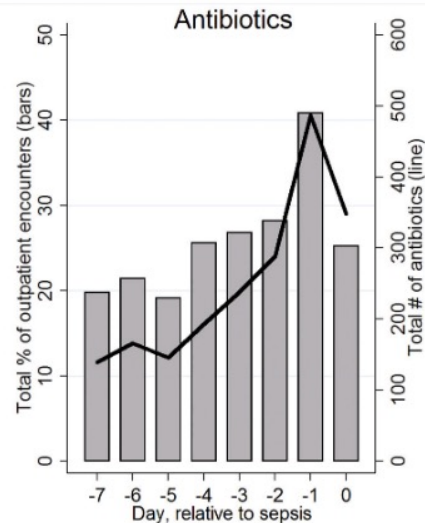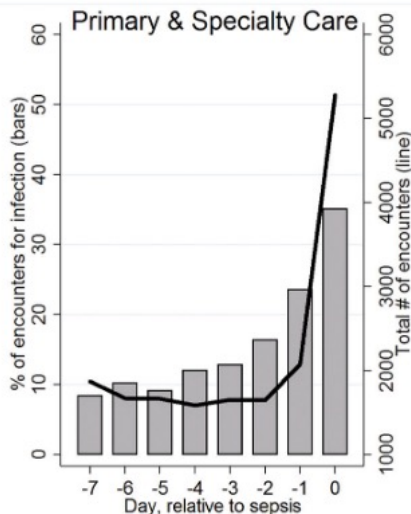
Frequency and Types of Healthcare Encounters in the Week Preceding a Sepsis Hospitalization: A Systematic Review

Alexander H. Flannery, PharmD, PhD[1]

Chad M. Venn, PharmD[2]

Amanda Gusovsky, MPH[1]

Stephanie Henderson, MLS[3]

Adam S. Kiser, BS[1]

Hallie C. Prescott, MD, MSc[4]

Chanu Rhee, MD, MPH[5]

Chris Delcher, PhD[1]

Peter E. Morris, MD[6]

*"In this systematic review, **32.7% of patients** have an **encounter with the healthcare system in the week prior** to a sepsis hospitalization.*

These may present opportunities to improve early sepsis care or potentially prevent the transition from infection to sepsis"
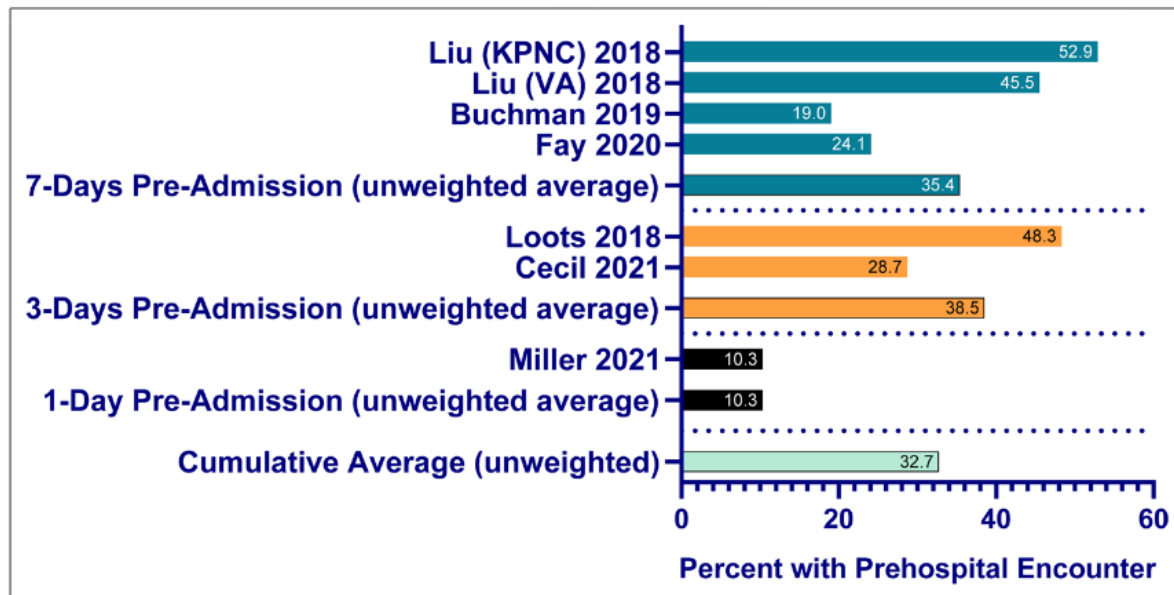

Figure 2. Prehospital encounters by study. KPNC= Kaiser Permanente Northern California; VA=Veterans Health Administration.

Conclusion

- **A small part of sepsis course is explored until now**
- **Atypical mode of presentation is of major concern**
  - Apyretic presenters
  - « Organ dysfunction only » presenters
  - elderly
- **Biomarkers to be validated: both to rule in and rule out sepsis**
  - stringent NPV and PPV
- **Huge research work to promote understanding of upstream mechanisms**
  - Natural history and determinant of self-limited/cured infections
  - Immunological/metabolic course of community infection→ sepsis
  - Emergency room and out-of-hospital/community cohorts
    - Before any therapeutic intervention
  - Longitudinal studies