Sepsis biomarkers ?

Etiologically, any infectious agent that enters the blood-stream of a patient and generates a systemic immune response can cause sepsis. However, the presence of the pathogen in the blood is not a requirement for the clinical symptoms of sepsis to manifest themselves—as the pres-ence of pathogen's signaling molecules or inflammatory mediators, which are released into the circulation from the source of infection, is sufficient for sepsis induction

1 recognition of microorganisms
via binding of pattern-recognition receptors, such as TLRs
to highly conserved molecules:
called pathogen-associated molecular proteins (PAMPs)

2 TLRs recruit adaptor proteins to the cell surface which activate a series of cytoplasmic kinases, initiating cascades that activate various transcription factors .

3 Genes that are induced by these transcription factors prepare the cell to :
fight infection with pro inflammatory molecules

4 Apoptosis is induced in case of cell over- whelmingly infected

5 5 pro inflammatory response vanish if invading micro organisms no longer detected

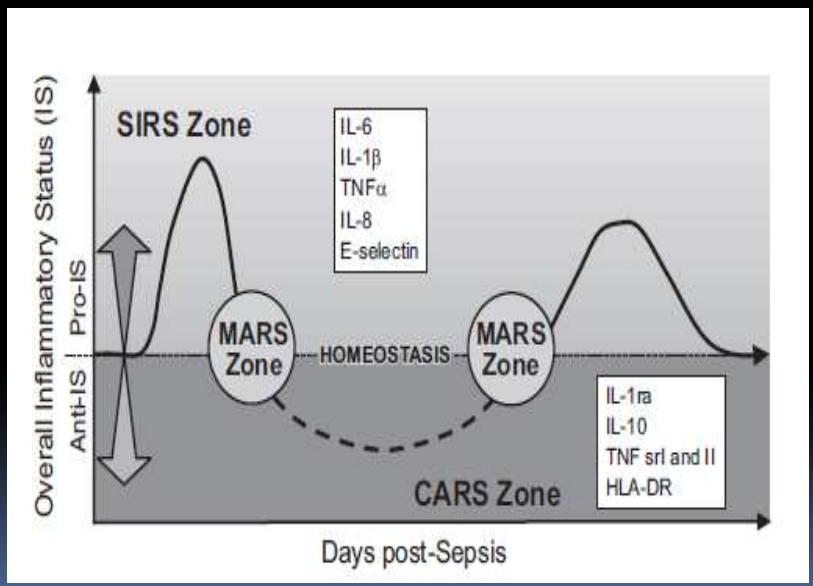
Table 1. Anti-inflammatory/inflammtory cytokines and their functional role in sepsis.

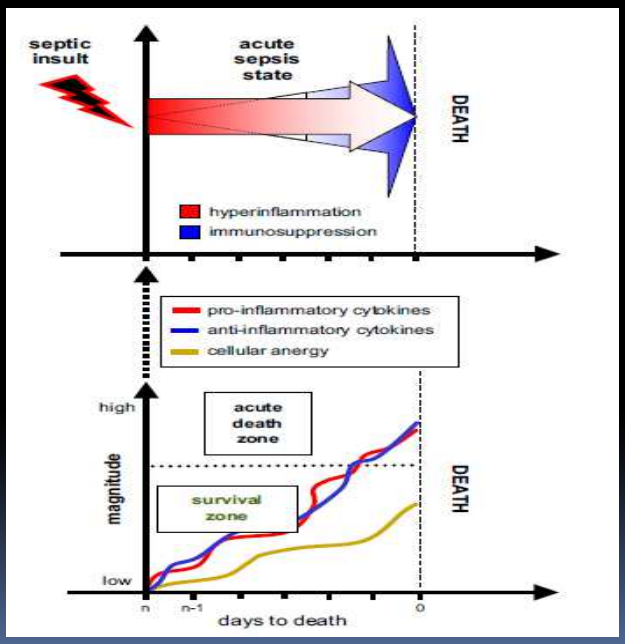
Inflammatory cytokines	Function in sepsis
TNFα	Promotion of inflammation, potent inducer of endothelial adhesion molecules. May act synergistically with IL-1 to promote and initiate inflammatory pathways.
IL-1β	Potent inducer of endothelial adhesion molecules to enable recruitment of immune cells. Involved in promotion of inflammatory signaling pathway, IL-1β can also activate the release of NO by both the endothelial and vascular smooth muscle cells.
IL-6	Important mediator of fever and immno-acute phase responses, involved in differentiating newly defined T helper 17 (TH17) subset of CD4 + T cells. Also involved in production of functional tissue factor complexes.
IL-17/IL-17A	Involved in recruitment of monocytes and neutrophils to inflammation site, also expressed in natural killer (NK) cells. May have indirect chemo-attractive properties due to the upregulation of granulocyte colony stimulaing factor (G-CSF) and CXC chemokines.
Anti-inflammatory cytokines	
TGF-β	Modulates the activity of other cytokines through either enhancing or antagonizing effects. Can diminish the proliferation and differentiation of T cells and B cells. Can also promote a state of resolution and repair.
IL-4	Not released systemically into the bloostream during sepsis. IL-4 suppresses macrophage activity and has general immunosuppressive effects.
IL-10	Involved in modulation of the pro-inflammatory response, serves to move the immune system from a cell mediated response to a humoral response. Blocks the innate immune response. Can also indirectly block pro-inflammatory cytokine activity.
IL-13	Affects cell surface expression of different receptors in macrophages and monocytes. Down regulates CD-14 receptor expression, also down regulates the expression of many pro-inflammatory cytokines such as TNFα & IL-1 in monocytes.

Table 5. *Selected circulating biomarkers assessed in clinical studies for diagnosis of sepsis. At least 49 patients enrolled in any of the studies. Studies listed in the reversed chronological order starting with the most recent, maximally 4 studies per biomarker listed. Selected multiple-biomarker studies listed more than once for separate biomarkers*

Biomarker*	Number/Type* of Patients	Comment
aPTT	All adult:	
	Study 1: 200 patients	Study 1: combination with PCT increased specificity (450)
	Study 2: 49 patients	Study 2: neutropenic hemato-oncology patients (172)
CD64	All adult:	
	S1: 293 patients	S1: sepsis versus SIRS (138)
	S2: 156 patients	S2: bacterial versus viral versus SIRS; CD35 also assessed (180)
	S3: 112 patients	S3: septic versus healthy controls; PCT also assessed (57)
	S4: 135 patients	S4: bacterial versus viral infection (272)
EA Complex	Pediatric: 74 patients	Diagnosis of neonatal sepsis; combination with immature to total neutrophil count ratio improved accuracy; CRP also assessed (377)
G-CSF	All pediatric	
	S1:156 patients	S1: diagnosis of bacterial and fungal sepsis; high negative predictive value (184)
	S2:190 patients	S2: confirmed versus suspected sepsis versus local infections; combination with IL-8 improved accuracy; IL-1ra also assessed (108)
IL-1ra	All pediatric	
	S1: 182 patients	S1: an increase 2 days before the sepsis onset; IL-6 and ICAM-1 also assessed (203)
	S2:190 patients	S2: confirmed versus suspected sepsis versus local infections poor performance, G-CSF and IL-8 also assessed (108)
IL-12	Pediatric: 112 patients	Diagnosis of neonatal sepsis, high specificity, low sensitivity; IL-10 also assessed (353)
IL-8	All pediatric	
	S1: 123 patients	S1: confirmed versus suspected sepsis; IL-6, IL-10, IL-1B, INF-γ, TNF-α, PCT, CRP also assessed (35)
	S2: 92 patients	S2: confirmed versus suspected sepsis; IL-6, PCT, CRP also assessed (408)
	S3: 190 patients	S3: confirmed versus suspected sepsis versus local infections; IL-1ra, G-CSF also assessed (108)
IP-10	Pediatric: 155 patients	Recognition of bacterial sepsis and necrotizing enterocolitis; TNF-α, IL-1β, 6, 8,10, 12 and MCP-1, GROα, RANTES also assessed (265)
LBP	S1: Adult/Pediatric: 57 patients	S1: cancer patients with febrile neutropenia; CRP also assessed (289)
	S2: Pediatric: 140 patients	S2: bacteremia versus no bacteremia; IL-6, CRP, HMGB-1 also assessed (295)
	S3: Pediatric: 92 patients	S3: patients with versus without bacterial sepsis; CD46 and PCT also assessed (139)
	S4: Adult: 185 patients	S4: bacteraemia versus no bacteremia; PCT and HMGB-1 also assessed (125)
MCP-1	Pediatric: 76 patients	Patients with hematologic malignancies; CRP and IL-8 also assessed (95)
neopterin	S1: Adult: 208 patients	S1: SIRS versus septic shock in ICU patients; PCT also assessed (336)
	S2: Adult: 56 patients	S2: postoperative SIRS versus sepsis; EA also assessed (291)
suPAR	Adult: 151 patients	SIRS patients with versus without bacterial infection; TREM-1, CRP, PCT, MIF also assessed (193)
TREM-1	S1: adult: 631 patients	S1: emergency department patients; HMGB-1 and CD64 also assessed (126)
	S2: adult: 114 patients	S2: sepsis versus SIRS; PCT also assessed (207)
	S3: pediatric: 52 patients	S3: SIRS versus late onset neonatal sepsis; IL-6 also assessed (341)
	S4: adult: 95 patients	S4: sepsis versus SIRS; CRP also assessed (30)

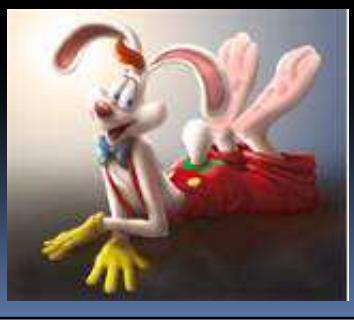
Reference numbers are given in parentheses.





Bactériémie aux Urgences

Est il utile et facile de repérer aux urgences, parmi les patients infectés,
ceux qui sont bactériémiques ?



Academic Emergency Medicine
Official Journal of the Society for Academic Emergency Medicine

Facile ?

ORIGINAL RESEARCH CONTRIBUTION

Disagreement Between Emergency Physician and Inpatient Physician Diagnosis of Infection in Older Adults Admitted From the Emergency Department

Jeffrey M. Caterino, MD, MPH, and Kurt B. Stevenson, MD, MPH

Abstract

Objectives: Older adults with infection are at increased risk of misdiagnosis while they are patients in the emergency department (ED) due to the common presence of nonspecific signs and symptoms. The primary objective was to determine the proportion of admitted older adult patients thought by the emergency physician (EP) to be infected, as compared with the diagnostic impression of inpatient physicians. The secondary objective was to determine the agreement between EP and inpatient physician diagnosis of specific infection types.

Methods: The authors conducted a prospective, observational, convenience sampling of a cohort of ED patients ≥65 years old admitted to the hospital with diagnoses of acute infection. EPs noted at least one suspected source of infection. Inpatient diagnosis of infection was determined by chart review of the inpatient chart. Outcomes included the presence of any infection and of specific infectious sources diagnosed within 48 hours of admission. EP and inpatient diagnoses were compared using proportions

Table 2
Characteristics of the Study Population

Variable	Number of Subjects	Percentage of Total Study Subjects
Age, yr		
65–74	55	53.4
75–84	34	33.0
≥85	14	13.6
Sex		
Female	54	52.4
Male	49	47.6
Extended care facility residence	19	18.4
Nonwhite race	20	19.4
Hispanic ethnicity	2	2.1
Infection severity in the ED		
Sepsis	35	33.3
Severe sepsis	7	6.7
Septic shock	3	2.9
Initial ED vital signs		
Hypotension (systolic blood pressure <90 mm Hg)	16	15.3
Fever (temperature ≥38.0°C)	28	26.7
Abnormal white blood cell count in ED ($<5 \times 10^9$ or $\geq 10 \times 10^9$/L)	76	72.4
In-hospital mortality	8	7.8

N = 103.

Results: The study included 103 patients diagnosed with a suspected infection by the EP. Nineteen patients (18.4%, 95% confidence interval [CI] = 11.5% to 27.3%) were not diagnosed with any infection by the inpatient physician. For specific infection sources, ED diagnosis of bloodstream infection often did not agree with the inpatient diagnosis. Sensitivity was 40.0% and specificity 78.4%, with an LR+ of 1.85 and LR− of 0.76. The phi coefficient was 0.15. EPs overdiagnosed pulmonary infection, with 72.1% specificity and an LR+ of 3.24. EP diagnosis had good accuracy for skin and soft tissue infection (sensitivity = 78.6% and specificity = 96.6%), with adequate LRs (LR+ of 23.3 and LR− of 0.22). Urinary tract infection (UTI) was underdiagnosed in the ED (sensitivity = 58.3%), but it is unclear if this is due to true ED underdiagnosis or due to overdiagnosis of UTI in the inpatient setting.

Conclusions: In older patients admitted from the ED, the provisional ED diagnosis and the inpatient diagnosis of an acute infection often disagree. In this sample, 18% of older ED patients diagnosed with infection during an ED stay were not diagnosed as infected by the inpatient physician. Regarding infection types, EPs were poor at diagnosing bacteremia and overdiagnosed pulmonary infections. EP diagnosis of skin and soft tissue infection generally agreed with the inpatient physician. There was also disagreement regarding presence of UTI, but the true nature of this difference is unclear from the data obtained in this study.

ACADEMIC EMERGENCY MEDICINE 2012; 19:908–915 © 2012 by the Society for Academic Emergency Medicine

Table 4
Test Characteristics for a Positive ED Diagnosis of Specific Infection Type as Compared to Inpatient Diagnosis

Source of infection	Sensitivity, % (95% CI)	Specificity, % (95% CI)	False-negative Rate, % (1 – sensitivity)	False-positive Rate, % (1 – specificity)	Positive Likelihood Ratio (95% CI)	LR− (95% CI)	Phi	Maximum phi
Bloodstream	40 (16–68)	78 (68–86)	60	22	1.85 (0.88–3.87)	0.76 (0.60–0.78)	0.15	0.73
Pulmonary	90 (77–97)	72 (59–82)	10	28	3.24 (2.14–4.92)	0.13 (0.09–0.72)	0.62	0.78
Skin and soft tissue	79 (49–95)	96 (90–99)	21	3	23.31 (7.41–73.29)	0.22 (0.08–0.60)	0.75	1.00
Urinary tract	58 (37–78)	95 (88–99)	42	5	11.52 (4.18–31.72)	0.44 (0.27–0.71)	0.59	0.83

Occult *Staphylococcus aureus* Bacteremia in Adult Emergency Department Patients: Rare but Important

Chia-Ming Fu,[1] Wen-Pin Tseng,[1] Wen-Chu Chiang,[1,2] Mei-Shu Lai,[2] Wei-Chu Chie,[2] Hao-Chang Chou,[1] Po-Ren Hsueh,[3] Matthew Huei-Ming Ma,[1] Cheng-Chung Fang,[1] Shyr-Chyr Chen,[1] Wen-Jone Chen,[1] and Shey-Ying Chen[1,2]

[1]Department of Emergency Medicine, National Taiwan University Hospital, [2]Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, and [3]Department of Laboratory Medicine, National Taiwan University Hospital, Taipei, Taiwan

Background. We sought to elaborate the epidemiology and outcomes of adult patients with occult *Staphylococcus aureus* bacteremia who were inadvertently discharged from the emergency department (ED) before positive blood culture results were obtained.

Retrospective Study
ED of National Taiwan University Hospital.
2500-bed, primary, secondary, tertiary care
The ED average of 100 000 visits annually.

All adults between from 2001 to 2010 whith positive blood cultures (true bacteraemia) reported after discharge from the ED.

759 patients sur 1 000 000 passages soit 2 00 000 patients infectés:

Soit 0,3 % patients infectés sortis avec Hémocs qui vont se positiver

Blood Culture Result	True Bacteremia, n = 759 (%)	Contamination, n = 497 (%)
Polymicrobial	39 (5.1)	1 (0.2)
Total isolate no.	805	498
Microbiology		
Gram-negative bacteria		
Escherichia coli	296 (36.8)	...
Klebsiella species[a]	75 (9.3)	...
Other *Enterobacteriaceae*[b]	50 (6.2)	...
Salmonella species[c]	30 (3.7)	...
Pseudomonas aeruginosa	11 (1.4)	...
Acinetobacter species	10 (1.2)	...
Other gram-negative bacteria[d]	36 (4.5)	...
Gram-positive bacteria		
Viridans streptococci	71 (9.8)	...
Staphylococcus aureus	65 (8.1)	...
β-hemolytic streptococci[e]	49 (6.1)	...
Enterococcus species[f]	21 (2.6)	...
Streptococcus bovis	10 (1.2)	...
Streptococcus pneumoniae	7 (0.9)	...
Coagulase-negative *Staphylococcus*	7 (0.9)	254 (51.0)
Propionibacterium acnes	...	115 (23.1)
Bacillus species	...	72 (14.5)
Corynebacterium species	...	31 (6.2)
Micrococcus species	2 (0.2)	19 (3.8)
Other gram-positive bacteria	2 (0.2)[g]	7 (1.4)
Anaerobic bacteria		
Peptostreptococcus species	20 (2.5)	...
Bacteroides species	17 (2.1)	...
Clostridium species	10 (1.2)	...
Other anaerobes[h]	16 (2.0)	...

Bactériémie aux Urgences: Role de la séméiologie classique ?

Clinical Review & Education

Special Communication | CARING FOR THE CRITICALLY ILL PATIENT

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

Mervyn Singer, MD, FRCP; Clifford S. Deutschman, MD, MS; Christopher Warren Seymour, MD, MSc; Manu Shankar-Hari, MBBS, MSc, PhD; Djillali Annane, MD, PhD; Michael Bauer, MD; Rinaldo Bellomo, MD; Gordon R. Bernard, MD; Jean-Daniel Chiche, MD, PhD; Craig M. Coopersmith, MD; Richard S. Hotchkiss, MD; Mitchell M. Levy, MD; John C. Marshall, MD; Greg S. Martin, MD, MSc; Steven M. Opal, MD; Gordon D. Rubenfeld, MD, MS; Tom van der Poll, MD, PhD; Jean-Louis Vincent, MD, PhD; Derek C. Angus, MD, MPH

IMPORTANCE Definitions of sepsis and septic shock were last revised in 2001. Considerable advances have since been made into the pathobiology (changes in organ function, morphology, cell biology, biochemistry, immunology, and circulation), management, and epidemiology of sepsis, suggesting the need for reexamination.

OBJECTIVE To evaluate and, as needed, update definitions for sepsis and septic shock.

PROCESS A task force (n = 19) with expertise in sepsis pathobiology, clinical trials, and epidemiology was convened by the Society of Critical Care Medicine and the European Society of Intensive Care Medicine. Definitions and clinical criteria were generated through meetings, Delphi processes, analysis of electronic health record databases, and voting, followed by circulation to international professional societies, requesting peer review and endorsement (by 31 societies listed in the Acknowledgment).

KEY FINDINGS FROM EVIDENCE SYNTHESIS Limitations of previous definitions included an excessive focus on inflammation, the misleading model that sepsis follows a continuum through severe sepsis to shock, and inadequate specificity and sensitivity of the systemic inflammatory response syndrome (SIRS) criteria. Multiple definitions and terminologies are

Diagnostic Criteria for Sepsis

Infection, documented or suspected, and some of the following:

Fever > 38.3°C or Hypothermia < 36°C

HR > 90/min

Tachypnea Altered mental status

Significant edema or fluid balance > 20 mL/kg over 24 hr

SBP < 90 mm Hg (or decrease > 40 mm Hg) MAP < 70

Hypoxemia Pao2/Fio2 < 300

Oliguria < 0.5 mL/kg/hr for 2 hrs despite fluid resuscitation

Ileus : absent bowel sounds

Chills ? Mottling ?

Lindvig *et al. Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine* 2014, **22**:39
http://www.sjtrem.com/content/22/1/39

SCANDINAVIAN JOURNAL OF trauma, resuscitation & emergency medicine

ORIGINAL RESEARCH Open Access

How do bacteraemic patients present to the emergency department and what is the diagnostic validity of the clinical parameters; temperature, C-reactive protein and systemic inflammatory response syndrome?

Katrine Prier Lindvig[1*], Daniel Pilsgaard Henriksen[1], Stig Lønberg Nielsen[2], Thøger Gorm Jensen[3], Hans Jørn Kolmos[3], Court Pedersen[2], Pernille Just Vinholt[4] and Annmarie Touborg Lassen[1]

Objective: Although blood cultures are often ordered based on the presence of fever, it is a clinical challenge to identify patients eligible for blood cultures. Our aim was to evaluate the diagnostic value of temperature, C-reactive protein (CRP), and Systemic Inflammatory Response Syndrome (SIRS) to identify bacteraemic patients in the Medical Emergency Department (MED).

Methods: A population-based cohort study including all adult patients at the MED at Odense University Hospital between August 1st 2009 - August 31st 2011.

Results: 11,988 patients were admitted to the MED within the study period. Blood cultures were performed on 5,499 (45.9%) patients within 2 days of arrival, of which 418 (7.6%) patients were diagnosed with bacteraemia. This corresponded to 3.5% of all patients. 34.1% of the bacteraemic patients had a normal rectal temperature (36.0°–38.0°C) recorded at arrival, 32.6% had a CRP < 100 mg/L and 28.0% did not fulfil the SIRS criteria.
For a temperature cut-point of >38.0°C sensitivity was 0.64 (95% CI 0.59–0.69) and specificity was 0.81 (0.80–0.82) to identify bacteraemic patients.

Conclusion: One third of the acute medical bacteraemic patients had a normal temperature at arrival to the MED. A normal temperature combined with a CRP < 100 mg/L and no SIRS criteria, ruled out bacteraemia.

Table 3 Diagnostic test for CRP, temperature and SIRS

	Non-bacteremic Patients *n (%)	Bacteremic Patients n (%)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	+ LR (95% CI)	- LR (95% CI)
Temperature > 38.0°C	1879 (88.5)	245 (11.5)	64.3 (59.3–69.1)	80.8 (80.0–81.6)	11.5 (10.2–13.0)	98.3 (98.0–98.6)	3.4 (3.1–3.6)	0.4 (0.4–0.5)
CRP ≥ 100 mg/dL	2064 (88.2)	277 (11.8)	67.4 (62.6–71.9)	79.0 (78.2–79.8)	11.8 (10.6–13.2)	98.3 (98.0–98.6)	3.2 (3.0–3.5)	0.4 (0.3–0.5)
SIRS	3546 (92.2)	301 (7.8)	72.0 (67.4–76.3)	69.4 (68.5–70.2)	7.8 (6.9–8.7)	98.6 (98.3–98.8)	2.4 (2.2–2.5)	0.4 (0.3–0.5)
Combination test	7140 (94.7)	397 (5.3)	95.0 (92.4–96.9)	38.3 (37.4–39.2)	5.3 (4.8–5.8)	99.5 (99.3–99.7)	1.5 (1.5–1.6)	0.1 (0.1–0.2)

PLOS ONE

Mise au point retro puis validation prospective d un score prédictif de bactériémie aux Urgences

RESEARCH ARTICLE

Identifying Patients with Bacteremia in Community-Hospital Emergency Rooms: A Retrospective Cohort Study

Taro Takeshima[1,2]*, Yosuke Yamamoto[1,3], Yoshinori Noguchi[4], Nobuyuki Maki[5], Koichiro Gibo[6], Yukio Tsugihashi[7], Asako Doi[8], Shingo Fukuma[1,3], Shin Yamazaki[9], Eiji Kajii[2], Shunichi Fukuhara[1,10]

PLOS ONE | Identifying Patients with Bacteremia in Community-Hospital Emergency Rooms

Score maxi 12

Table 3. Multivariate analysis (n = 1288) and scoring.

	OR	95% CI	p	β	score
History					
Age ≥ 65 years old	1.64	(1.07–2.52)	0.02	0.49	1
Chills	4.61	(3.03–7.01)	< 0.01	1.53	2
Vomiting	1.68	(1.02–2.76)	0.04	0.52	1
Signs					
Altered mental status	1.62	(1.10–2.37)	0.01	0.48	1
Body temperature ≥ 38°C	2.34	(1.56–3.50)	< 0.01	0.85	1
Systolic blood pressure < 90 mmHg	2.28	(1.34–3.90)	< 0.01	0.83	1
Focal abdominal sign	2.64	(1.51–4.61)	< 0.01	0.97	1
Laboratory data					
White blood cells ≥ 15,000/μL	2.06	(1.38–3.08)	< 0.01	0.72	1
Platelets < 150,000/μL	1.88	(1.31–2.68)	< 0.01	0.63	1
BUN ≥ 20 mg/dL	1.68	(1.12–2.50)	0.01	0.52	1
CRP ≥ 10 mg/dL	2.77	(1.94–3.95)	< 0.01	1.02	1

PLOS ONE | Identifying Patients with Bacteremia in Community-Hospital Emergency Rooms

SCORE > 5 : 50 % des patients sont bactériémiques

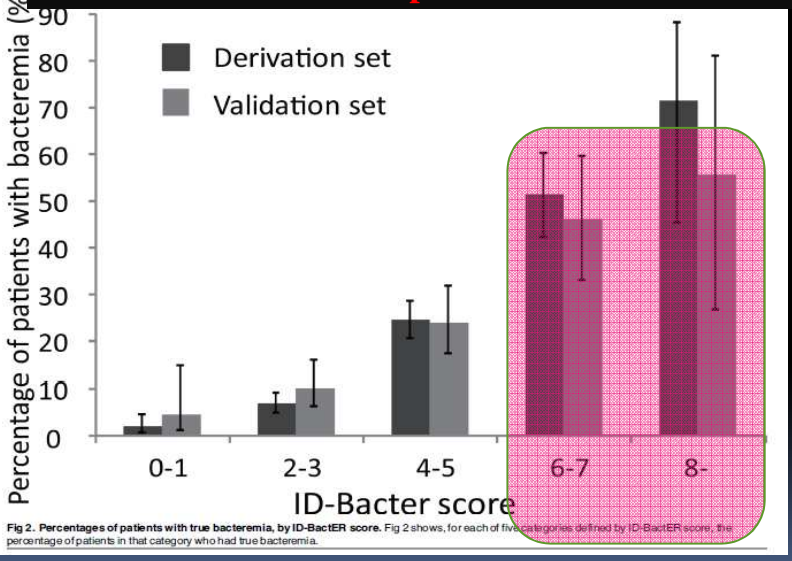


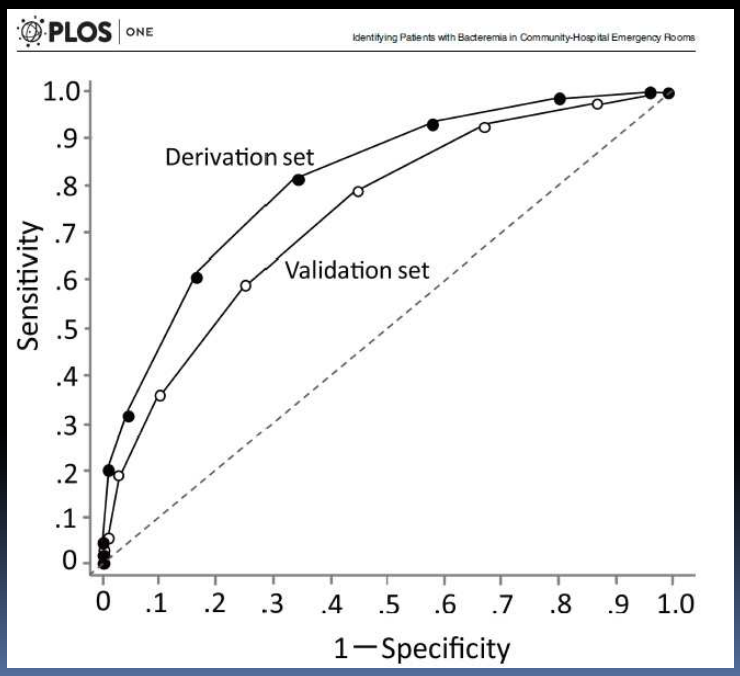
Fig 2. Percentages of patients with true bacteremia, by ID-BactER score. Fig 2 shows, for each of five categories defined by ID-BactER score, the percentage of patients in that category who had true bacteremia.

Results

There were 241 cases of bacteremia in the derivation data. Eleven candidate predictors were used in the ID-BactER score: age, chills, vomiting, mental status, temperature, systolic blood pressure, abdominal sign, white blood-cell count, platelets, blood urea nitrogen, and C-reactive protein. The AUCs was 0.80 (derivation) and 0.74 (validation). For ID-BactER scores ≥ 2, the sensitivities for derivation and validation data were 98% and 97%, and specificities were 20% and 14%, respectively.

Conclusions

The ID-BactER score can be computed from information that is readily available in the ERs of community hospitals. Future studies should focus on developing a score with a higher specificity while maintaining the desired sensitivity.



DONC repérer les patients bactèrièmiques aux urgences est facile lorsqu un Maximun de signes (score clinico biologique èlevè) est présent mais cela entraine une sensibilité faible

Alors pourquoi pas demander plus d hémocs ?

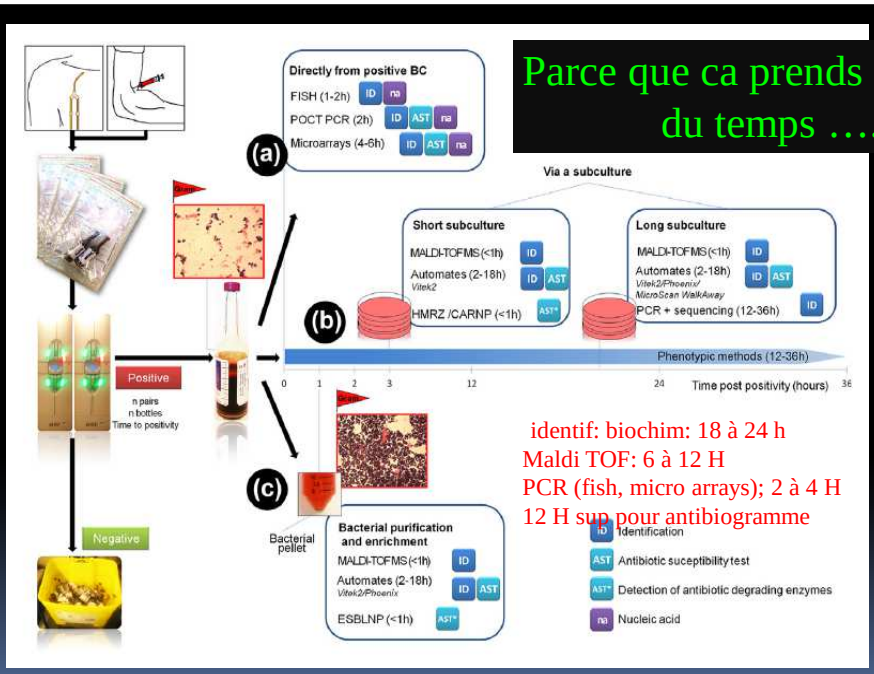
Parce que ca prends du temps ….

TABLE I. Main automated blood culture incubation systems currently commercially available

System (Manufacturer)	Main blood-culture media and characteristics	Positivity detection system
BD BACTEC (BD Diagnostics, Franklin Lakes, NJ, USA)	Standard aerobic and anaerobic broth media Media containing resin particles Media specifically designed for small blood volume inoculation Media containing a lysing agent to increase the recovery of organisms phagocytosed Media optimized for the growth of mycobacteria Specific algorithms for fastidious organisms (e.g. *Haemophilus* spp. and *Neisseria* spp.)	Fluorescent sensor of CO_2 production
BacT/ALERT 3D (bioMérieux, Durham, NC, USA)	Plastic bottles Standard aerobic and anaerobic broth media Media containing activated charcoal particles[a] or resin Media specifically designed for small blood volume inoculation Media supplemented with Middlebrook 7H9 for microbacteria growth Enriched media	Colorimetric sensor of CO_2 production
VersaTREK, (TREK Diagnostic Systems, ThermoFisher Scientific, Waltham, MA, USA)	Standard aerobic and anaerobic broth media for samples from 0.1 to 10 mL, optimized to minimize the impact of antibiotics	Monitoring of redox variations

[a]The presence of charcoal particles prevent the use of the pellet for direct identification from positive blood culture using MALDI-TOF MS.

Parce que ca prends du temps ….



identif: biochim: 18 à 24 h
Maldi TOF: 6 à 12 H
PCR (fish, micro arrays); 2 à 4 H
12 H sup pour antibiogramme

Blood culture-based diagnosis of bacteraemia: state of the art

O. Opota[1], A. Croxatto[1], G. Prod'hom[1] and G. Greub[1,2]
1) *Institute of Microbiology and* 2) *Infectious Diseases Service, University of Lausanne and University Hospital Centre, Lausanne, Switzerland*

Mise au point ….

Abstract

Blood culture remains the best approach to identify the incriminating microorganisms when a bloodstream infection is suspected, and to guarantee that the antimicrobial treatment is adequate. Major improvements have been made in the last years to increase the sensitivity and specificity and to reduce the time to identification of microorganisms recovered from blood cultures. Among other factors, the introduction in clinical microbiology laboratories of the matrix-assisted laser desorption ionization time-of-flight mass spectrometry technology revolutionized the identification of microorganisms whereas the introduction of nucleic-acid-based methods, such as DNA hybridization or rapid PCR-based test, significantly reduce the time to results. Together with traditional antimicrobial susceptibility testing, new rapid methods for the detection of resistance mechanisms respond to major epidemiological concerns such as methicillin-resistant *Staphylococcus aureus*, extended-spectrum β-lactamase or carbapenemases. This review presents and discusses the recent developments in microbial diagnosis of bloodstream infections based on blood cultures.

Microbial diagnosis of bloodstream infection: towards molecular diagnosis directly from blood

O. Opota[1], K. Jaton[1] and G. Greub[1,2]
1) *Institute of Microbiology and* 2) *Infectious Diseases Service, University of Lausanne and University Hospital Center, Lausanne, Switzerland*

Mise au point ….

Abstract

When a bloodstream infection (BSI) is suspected, most of the laboratory results—biochemical and haematologic—are available within the first hours after hospital admission of the patient. This is not the case for diagnostic microbiology, which generally takes a longer time because blood culture, which is to date the reference standard for the documentation of the BSI microbial agents, relies on bacterial or fungal growth. The microbial diagnosis of BSI directly from blood has been proposed to speed the determination of the etiological agent but was limited by the very low number of circulating microbes during these paucibacterial infections. Thanks to recent advances in molecular biology, including the improvement of nucleic acid extraction and amplification, several PCR-based methods for the diagnosis of BSI directly from whole blood have emerged. In the present review, we discuss the advantages and limitations of these new molecular approaches, which at best complement the culture-based diagnosis of BSI.

Mise au point ….

PLOS ONE

RESEARCH ARTICLE

16S Ribosomal Ribonucleic Acid Gene Polymerase Chain Reaction in the Diagnosis of Bloodstream Infections: A Systematic Review and Meta-Analysis

Guoming Su[1☯], Zhuqing Fu[2☯], Liren Hu[3], Yueying Wang[1], Zuguo Zhao[2], Weiqing Yang[1]*

1 Guangdong Provincial Key Laboratory of Medical Molecular Diagnostics, Guangdong Medical College, Dongguan, China, 2 Department of Microbiology and Immunology, Guangdong Medical College, Zhanjiang, China, 3 Department of Epidemiology and Health Statistics, School of Public Health, Guangdong Medical College, Zhanjiang, China

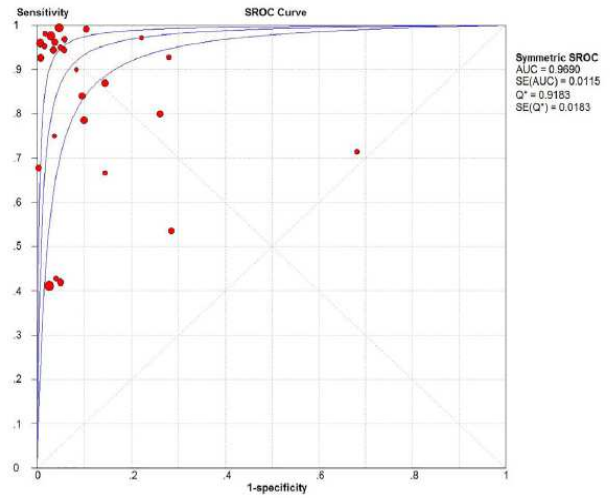


Fig 6. Summary receiver operating characteristic curve of 16S rRNA gene PCR diagnostic value in bloodstream infections.

doi:10.1371/journal.pone.0127195.g006

Parce que ca coute cher ….

Published in final edited form as:
Infect Control Hosp Epidemiol. 2014 August ; 35(8): 1021–1028. doi:10.1086/677161.

Cost Analysis of Strategies to Reduce Blood Culture Contamination in the Emergency Department: Sterile Collection Kits and Phlebotomy Teams

Wesley H. Self, MD, MPH[a], **Thomas R. Talbot, MD, MPH**[b], **Barbara R. Paul, MD**[c], **Sean P. Collins, MD, MSCI**[a], and **Michael J. Ward, MD, MBA**[a]

[a] Department of Emergency Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee, USA

[b] Departments of Medicine and Preventive Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee, USA

[c] Community Health Systems Professional Services Corporation, Franklin, Tennessee, USA

Parce que ca coute cher ….

Results—Compared to usual care, annual net savings using the sterile kit and phlebotomy team strategies were $483,219 and $288,980, respectively. Both strategies remained less costly than usual care across a broad range of sensitivity analyses.

Conclusions—EDs with high blood culture contamination rates should strongly consider evidence-based strategies to reduce contamination. In addition to improving quality, implementing a sterile collection kit or phlebotomy team strategy is likely to result in net cost savings.

Est-ce que c est utile ?

SURVIVING SEPSIS CAMPAIGN BUNDLES

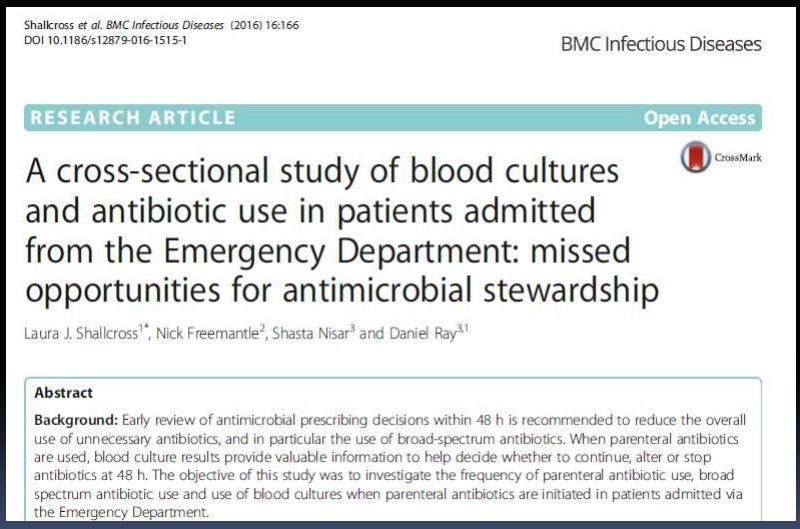
TO BE COMPLETED WITHIN 3 HOURS:

1) Measure lactate level
2) **Obtain blood cultures prior to antibiotics administration**
3) Administer broad spectrum antibiotics
4) 30 mL/kg crystalloid if hypotension or lactate 4mmol/

WITHIN 6 HOURS:

5) Vasopressors : hypotension in spite of initial fluid resuscitation maintain MAP > 65 mm Hg
6) If vasopressors or initial lactate 4 mmol/L:
- Measure central CVP aqnd ScvO2
7) Control lactate

Utile ? : bon usage des antibiotiques



Shallcross et al. BMC Infectious Diseases (2016) 16:166
DOI 10.1186/s12879-016-1515-1

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

A cross-sectional study of blood cultures and antibiotic use in patients admitted from the Emergency Department: missed opportunities for antimicrobial stewardship

Laura J. Shallcross[1*], Nick Freemantle[2], Shasta Nisar[3] and Daniel Ray[3,1]

Abstract

Background: Early review of antimicrobial prescribing decisions within 48 h is recommended to reduce the overall use of unnecessary antibiotics, and in particular the use of broad-spectrum antibiotics. When parenteral antibiotics are used, blood culture results provide valuable information to help decide whether to continue, alter or stop antibiotics at 48 h. The objective of this study was to investigate the frequency of parenteral antibiotic use, broad spectrum antibiotic use and use of blood cultures when parenteral antibiotics are initiated in patients admitted via the Emergency Department.

Utile ?

De toute facon les patients avec un tableau de

pneumonie,
pyelo néphrite,
angio cholite
péritonite,
méningite,
diarrhée invasive
Infection Peau et tissus mous

vont etre antibiothérapé ….

Utile ?

OUI car
Choix Atbiothérapie patients bactériémiques:
Bacéricide
Association aminosides mono/forte dose

Journal of Microbiology, Immunology and Infection (2014) 47, 469—477

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.e-jmii.com

ORIGINAL ARTICLE

Derivation of a clinical prediction rule for bloodstream infection mortality of patients visiting the emergency department based on predisposition, infection, response, and organ dysfunction concept

Chun-Fu Yeh [a], Kuan-Fu Chen [b,*], Jung-Jr Ye [a], Ching-Tai Huang [a,**]

[a] Division of Infectious Diseases, Department of Internal Medicine, Chang Gung Memorial Hospital at Linkou, Chang Gung University College of Medicine, Taoyuan, Taiwan
[b] Department of Emergency Medicine, Chang-Gung University and Chang-Gung Memorial Hospital, Keelung, Taiwan

Received 25 February 2013; received in revised form 1 June 2013; accepted 28 June 2013
Available online 19 August 2013

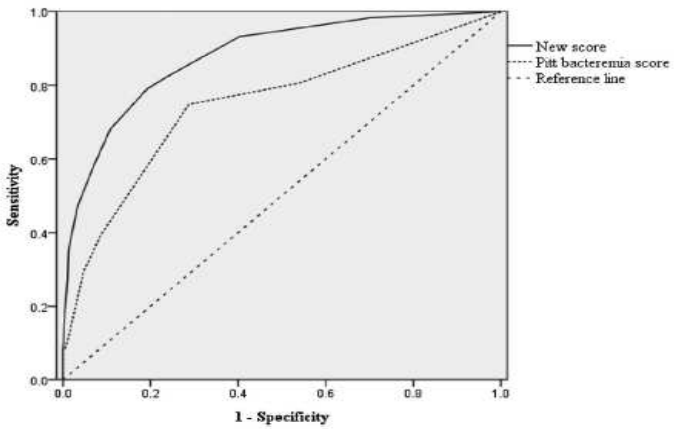


Figure 2. The receiver operating characteristic curves (ROC) comparing new score and Pitt bacteremia score to predict 28-day mortality of patients with bacteremia. The area under ROC (AUROC) for the new score is 0.881, with a better performance than Pitt bacteremia score (AUROC: 0.750, $p < 0.001$).

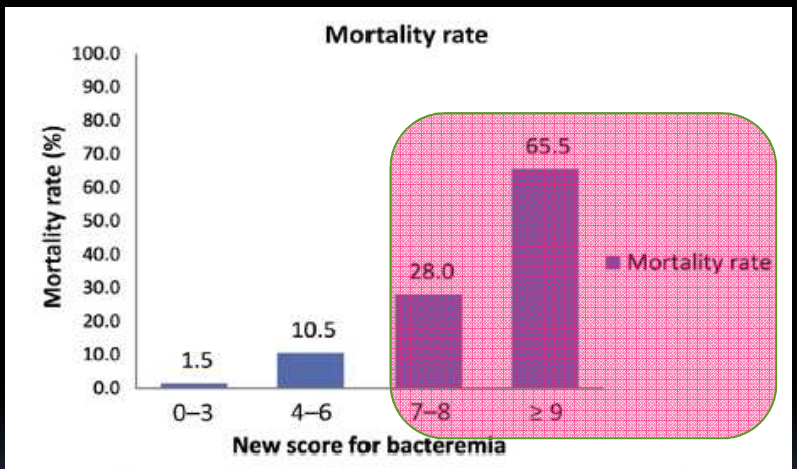


Figure 3. The 28-day mortality rate according to the new score for bacteremia in 992 bacteremic patients. Seventy-one patients with missing data are not included.

+2 points were assigned for malignancy, +4 for pneumonia, +2 for an unknown infectious focus, +2 for S. *aureus* bacteremia, +3 for body temperature <36°C, +3 for band form >5%, +2 for RDW >15%, +2 for pulse oximeter oxygen saturation <90%, and +2 for creatinine >2 mg/dL. The new score was calculated based on the summation of the points of the above nine variables.

Interessant mais score clinico biologique dépendant d un résultat d hémoculture: H 24

Sepsis biomarkers ?

REVIEW

Virulence 5:1, 154–160; January 1, 2014; © 2014 Landes Bioscience

Rapid diagnosis of sepsis

Frank Bloos and Konrad Reinhart*

Department of Anesthesiology and Intensive Care Medicine; Jena University Hospital; Jena, Germany

Keywords: sepsis, diagnosis, biomarker, cytokines, procalcitonin, PCR

Abbreviations: CRP, C-reactive protein; ICU, intensive care unit; IL, interleukin; LBP, lipopolysaccharide binding protein; MD2, myeloid differentiation factor 2; PCR, polymerase chain reaction; PCT, procalcitonin; sTREM-1, soluble triggering receptor expressed on myeloid cells 1; suPAR, soluble urokinase plasminogen activator receptor; TNF, tumor necrosis factor

Sepsis biomarkers ?

Table 1. Diagnostic value and limitations of biomarkers to separate infectious from non-infectious causes of inflammation

Biomarker	Source	Sens.	Spec.	AUC	LR^+	LR^-	Limitations
C-reactive protein[21]	Metaanalysis (n = 1386)	0.75	0.67	–	2.43	0.42	Slow kinetic, independent of infection severity, increased in many inflammatory diseases
Procalcitonin[35]	Metaanalysis (n = 3244)	0.77	0.79	0.89	4.0	0.29	Increased in various non-infectious causes of SIRS (i.e., cardiac arrest, severe trauma)
Interleukin-6[57]	Cohort study (n = 327)	0.82	0.75	0.86	–	–	Limited data, conflicting results
sTREM-1[78]	Metaanalysis (n = 1795)	0.79	0.80	0.87	4.0	0.26	Present in inflammatory disease without infection
LBP[57]	Cohort study (n = 327)	0.57	0.85	0.73	–	–	Non-specific marker of inflammation
suPAR[98]	Cohort study (n = 273)	–	–	0.62	–	–	Limited data; low diagnostic value for sepsis

Data give sensitivity (sens.), specificity (spec.), area under the curve (AUC) from receiver operating characteristics, positive (LR^+) and negative (LR^-) likelihood ratios of a biomarker for differentiation of infectious vs. non-infectious causes of inflammation. LBP, lipopolysaccharide binding protein; suPAR, soluble urokinase plasminogen activator receptor; sTREM 1, soluble triggering receptor expressed on myeloid cells 1.

Sepsis biomarkers ?

In the area of sepsis research, the use of biomarkers are as exciting as they are frustrating; close to 200 biomarker candidates in nearly 4,000 studies have been evaluated to date .

Pierrakos C, Vincent JL. Sepsis biomarkers: a review. *Crit Care 14: R15, 2010.*

Sepsis biomarkers ?

OPEN ACCESS Freely available online PLOS ONE

Pentraxin 3 (PTX3) Is Associated with Severe Sepsis and Fatal Disease in Emergency Room Patients with Suspected Infection: A Prospective Cohort Study

Raija Uusitalo-Seppälä[1]*, Reetta Huttunen[2,3], Janne Aittoniemi[4], Pertti Koskinen[5,6], Aila Leino[5,6], Tero Vahlberg[7], Esa M. Rintala[8]

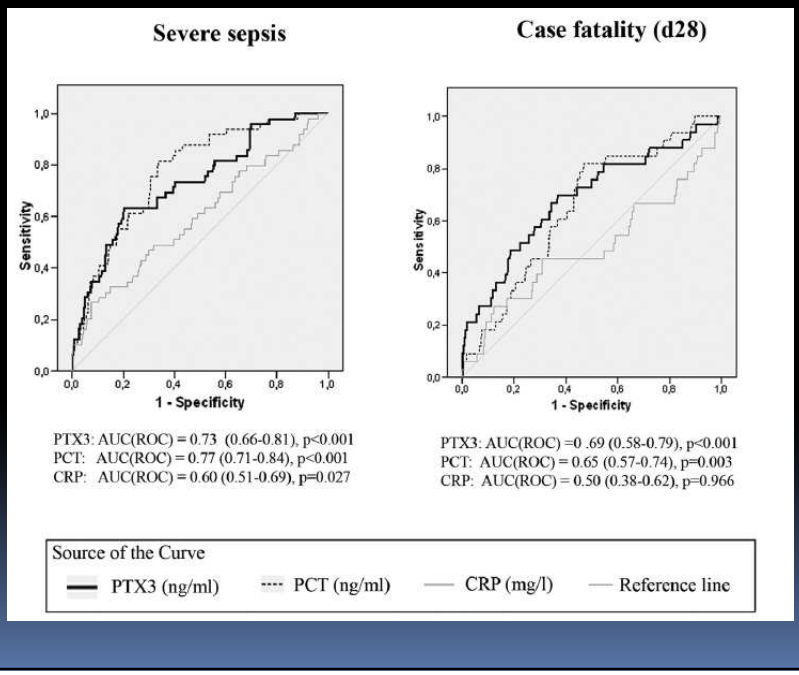
1 Department of Infectious Diseases, Satakunta Central Hospital, Pori, Finland, 2 Department of Internal Medicine, Tampere University Hospital, Tampere, Finland, 3 University of Tampere Medical School, University of Tampere, Finland, 4 Fimlab Laboratories, Tampere, Finland, 5 Department of Clinical Chemistry, Turku University, Turku, Finland, 6 TYKSLAB, Turku Univeristy Hospital, Hospital District of Southwest Finland, Turku, Finland, 7 Department of Biostatistics, Turku University, Turku, Finland, 8 Department of Hospital Hygiene and Infection Control, Turku University Hospital, Turku, Finland

Abstract

Background: Early diagnostic and prognostic stratification of patients with suspected infection is a difficult clinical challenge. We studied plasma pentraxin 3 (PTX3) upon admission to the emergency department in patients with suspected infection.

Methods: The study comprised 537 emergency room patients with suspected infection: 59 with no systemic inflammatory response syndrome (SIRS) and without bacterial infection (group 1), 67 with bacterial infection without SIRS (group 2), 54 with SIRS without bacterial infection (group 3), 308 with sepsis (SIRS and bacterial infection) without organ failure (group 4) and 49 with severe sepsis (group 5). Plasma PTX3 was measured on admission using a commercial solid-phase enzyme-linked immunosorbent assay (ELISA).

Predictive of mortality in ED but not specific of bacteriemic patients



Sepsis biomarkers

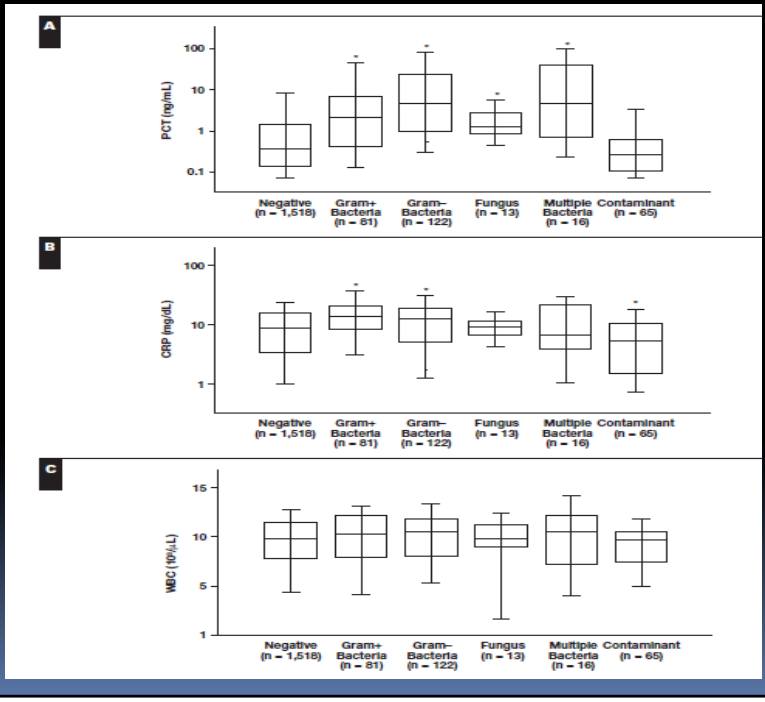
Clinical Value of Procalcitonin for Patients With Suspected Bloodstream Infection

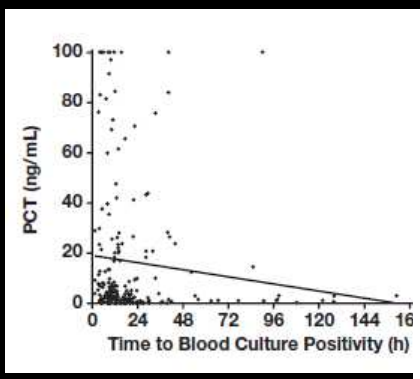
Takuya Hattori, MSc, Hideki Nishiyama, Hideki Kato, Shinobu Ikegami, Madoka Nagayama, Saori Asami, Miyuki Usami, Mayuko Suzuki, Itsuka Murakami, Makoto Minoshima, MSc, Hiroe Yamagishi, and Norihiro Yuasa, MD

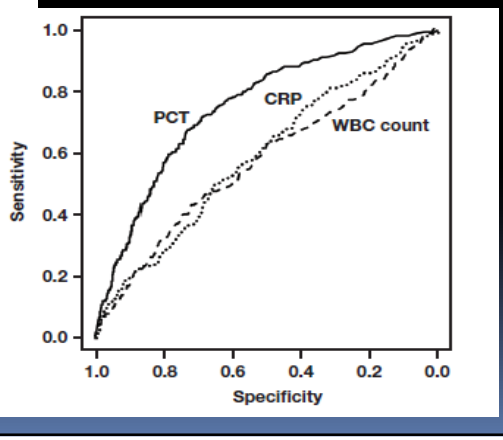
From the Department of Clinical Laboratory, Japanese Red Cross Nagoya Daiichi Hospital, Nagoya, Japan.

Key Words: Procalcitonin; Blood culture; Bloodstream infection; Renal function; C-reactive protein

DOI: 10.1309/AJCP4GV7ZFDTANGC







Tout ça pour ….

Table 3
Diagnostic Value for Positive Blood Culture of PCT, CRP, and WBC Count

Variable	PCT	CRP	WBC Count
Optimal cutoff value	0.9 ng/mL	12.5 mg/dL	12,000/μL (12.0 ×10^9/L)
Sensitivity (%)	71.9	66.1	67.4
Specificity (%)	69.1	50.4	46.3
Positive predictive value (%)	24.5	17.6	16.9
Negative predictive value (%)	94.6	90.3	90
Area under the ROC curve (95% confidence interval)	0.753 (0.720-0.786)	0.601 (0.562-0.641)	0.559 (0.517-0.601)

CRP, C-reactive protein; PCT, procalcitonin; ROC, receiver operating characteristic.

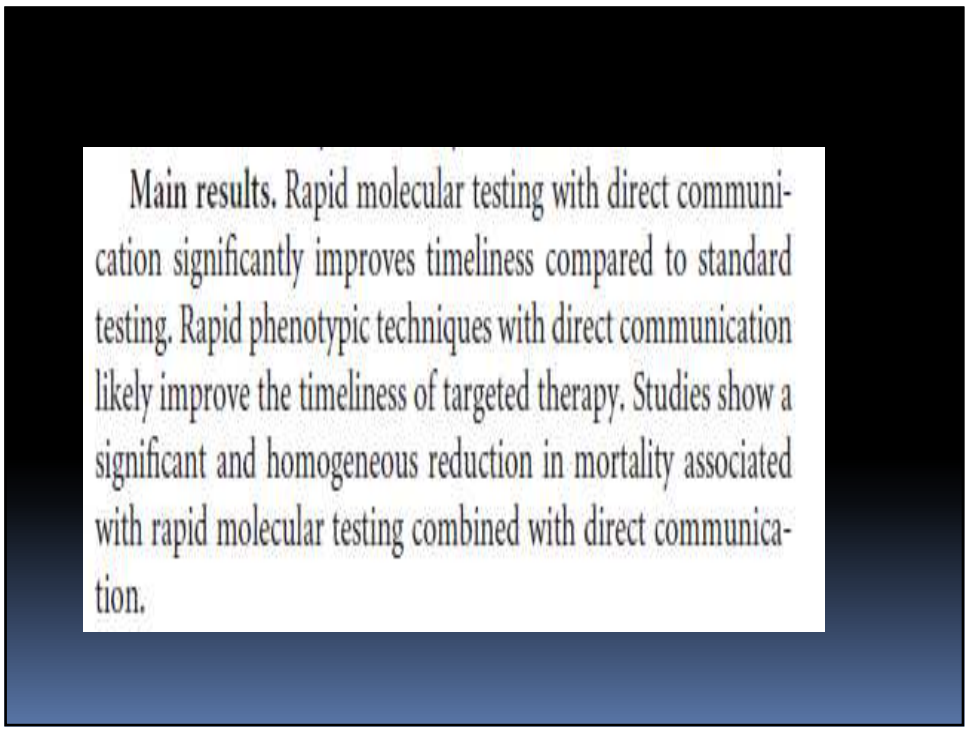
AMERICAN SOCIETY FOR MICROBIOLOGY | Clinical Microbiology Reviews

CLINICAL MICROBIOLOGY BEST PRACTICES

Effectiveness of Practices To Increase Timeliness of Providing Targeted Therapy for Inpatients with Bloodstream Infections: a Laboratory Medicine Best Practices Systematic Review and Meta-analysis

Stephanie S. Buehler,[a] Bereneice Madison,[a] Susan R. Snyder,[a] James H. Derzon,[a] Nancy E. Cornish,[b] Michael A. Saubolle,[c] Alice S. Weissfeld,[d] Melvin P. Weinstein,[e] Edward B. Liebow,[a] Donna M. Wolk[f]

Battelle Center for Analytics and Public Health, Atlanta, Georgia, USA[a]; Centers for Disease Control and Prevention, Center for Surveillance, Epidemiology and Laboratory Services (CSELS), Atlanta, Georgia, USA[b]; Banner Good Samaritan Medical Center, Banner Health, Phoenix, Arizona, USA, and University of Arizona College of Medicine, Phoenix, and University of Arizona College of Medicine, Tucson, Arizona, USA[c]; Microbiology Specialists Incorporated, Houston, Texas, USA[d]; Rutgers Robert Wood Johnson Medical School, New Brunswick, New Jersey, USA[e]; Geisinger Health System, Danville, Pennsylvania, USA[f]



Main results. Rapid molecular testing with direct communication significantly improves timeliness compared to standard testing. Rapid phenotypic techniques with direct communication likely improve the timeliness of targeted therapy. Studies show a significant and homogeneous reduction in mortality associated with rapid molecular testing combined with direct communication.

Emportez ces 3 doutes en garde:

1 **Les bactériémies chez les patients aux urgences sont fréquentes:**

4 à 8 % des patients ont des hémocs prélevées avec 85 % vrais négatifs

10 % vrais positifs

5 % contaminants

0,3 % des patients positifs étaient sortis ….

2 Les hémocs sont notre gold standard ….. pour l instant

% faux négatifs: bactéries viables lors du prélèvement avec flacon stérile

Long dèlais pour le clinicien

Cout si nombreux contaminants + vrais neg:

0 hémocs si apyrexie, no SIRS,

CRP /PCT/ other biomarker bas

3 La sensibilité des signes/scores clinico biologiques est faible

leur spécificité est bonne ID bacter, Pitt

4 Avenir: nouveaux biomarkers précoces,

voir doctor/test (bacti Diag …..)

Hémocultures : irremplaçables ?

REVIEW

Blood culture-based diagnosis of bacteraemia: state of the art

O. Opota[1], A. Croxatto[1], G. Prod'hom[1] and G. Greub[1,2]

1) *Institute of Microbiology and* 2) *Infectious Diseases Service, University of Lausanne and University Hospital Centre, Lausanne, Switzerland*

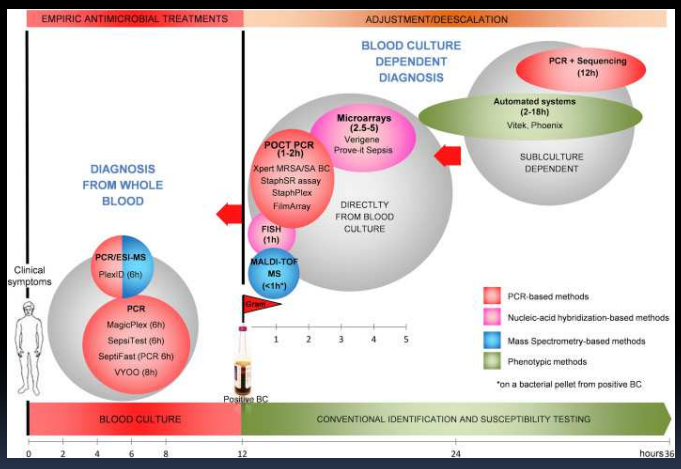
Abstract

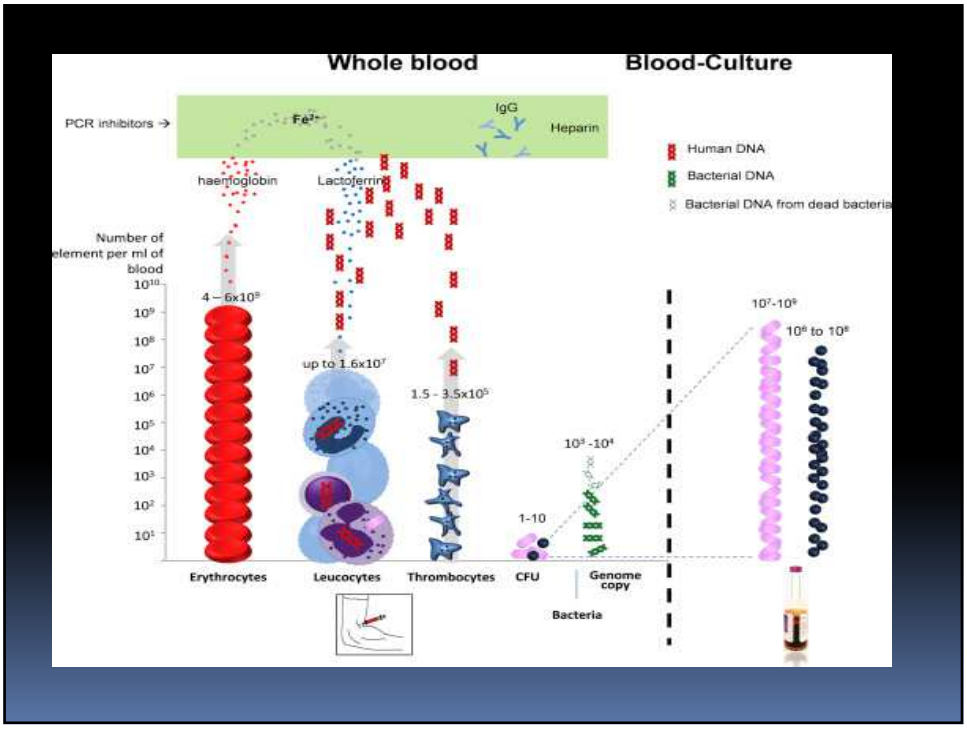
Blood culture remains the best approach to identify the incriminating microorganisms when a bloodstream infection is suspected, and to guarantee that the antimicrobial treatment is adequate. Major improvements have been made in the last years to increase the sensitivity and specificity and to reduce the time to identification of microorganisms recovered from blood cultures. Among other factors, the introduction in clinical microbiology laboratories of the matrix-assisted laser desorption ionization time-of-flight mass spectrometry technology revolutionized the identification of microorganisms whereas the introduction of nucleic-acid-based methods, such as DNA hybridization or rapid PCR-based test, significantly reduce the time to results. Together with traditional antimicrobial susceptibility testing, new rapid methods for the detection of resistance mechanisms respond to major epidemiological concerns such as methicillin-resistant *Staphylococcus aureus*, extended-spectrum β-lactamase or carbapenemases. This review presents and discusses the recent developments in microbial diagnosis of bloodstream infections based on blood cultures.

WBC count > 12,000/ µL or < 4000
or normal with > 10% immature forms

PCR or PCT > normal value (2 SD)
Hyperglycemia > 7.7 mmol/L without diabetes

Creatinine increase > 44.2 µmol/L
INR > 1.5 or aPTT > 60 s
platelelet < 100,000/ µL
Hyperbilirubinemia > 70 µmol/L
Hyperlactatemia > 1 mmol/L30




Whole blood
Blood-Culture
PCR inhibitors →
Fe²⁺
IgG
Heparin
haemoglobin
Lactoferrin
Human DNA
Bacterial DNA
Bacterial DNA from dead bacteria
Number of element per ml of blood
4 – 6x10⁹
up to 1.6x10⁷
1.5 - 3.5x10⁵
10³ -10⁴
1-10
10⁷-10⁹
10⁸ to 10⁸
Erythrocytes
Leucocytes
Thrombocytes
CFU
Genome copy
Bacteria