ADVANCES IN BIOMARKER TESTING FOR SEPSIS AND BACTERIAL INFECTIONS

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DIRECTOR OF CRITICAL SERVICES

SWEDISH COVENANT HOSPTIAL

DISCLOSURES:

Speaking engagements and consulting:

- Thermo Fisher Scientific, Middletown, VA
- Roche Diagnostics, Indianapolis, IN
- bioMerieux, Durham, NC

OBJECTIVES

- Define ‘infection’
- Describe the biology and kinetics of procalcitonin and other biomarkers used in the evaluation of sepsis
- Discuss the ability to use biomarker levels for mortality prediction in severe sepsis and septic shock patients
- Illustrate biomarker clinical utility when used to tailor individualized patient treatment in LRTI and Sepsis

WHAT IS AN INFECTION?

Infection exists when the body thinks it does

- We co-exist with 5,000,000,000 bacteria
- They are essential for our survival
- If kept in check this situation is mutually beneficial
- When the body reacts to a non-self organism for the purpose of containing or eliminating it, then there is a state of infection

TREATING INFECTION – THEN AND NOW

- Diagnosis of infection was based mostly on gut feeling. Corroboration with objective evidence was poor 60 years ago and remains poor today
- Antibiotics are prescribed not titrated
  - Most antibiotic regimens are based on duration not on individual response
- Severity of infection involves
  - Immunocompetency of patient
  - Duration of infection prior to presentation
  - Size of bacterial burden
  - Site of infection
  - Nutritional and functional status
  - etc

TREATING INFECTION – THEN AND NOW

- The duration of antibiotic therapy should be dictated by response to treatment
- White cell count and macromarkers are not sensitive enough nor specific enough to provide this

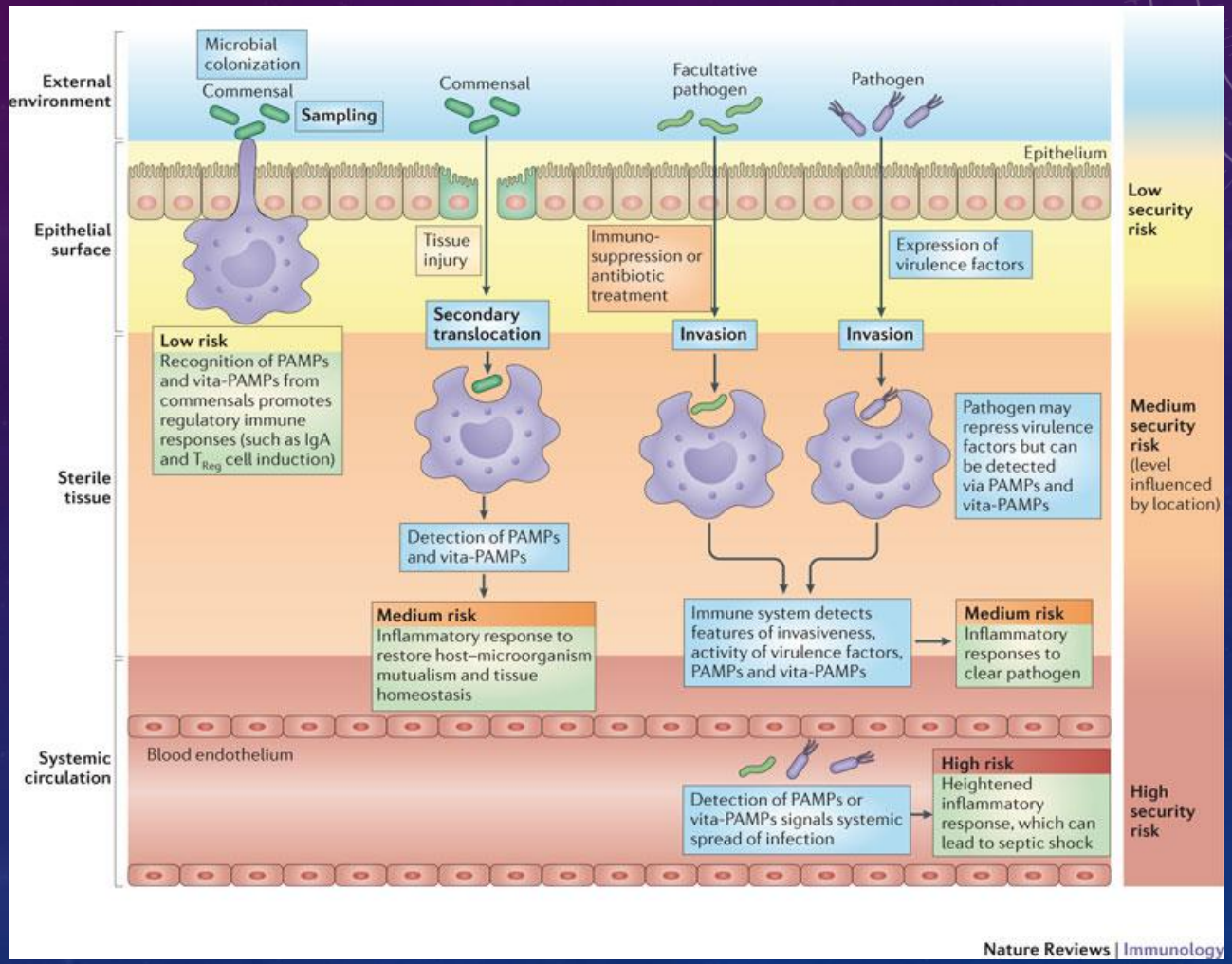
  2/3 of pts in the ICU have SIRS criteria

  1/4 of pts in a typical ICU have sepsis

TREATING INFECTION – THEN AND NOW

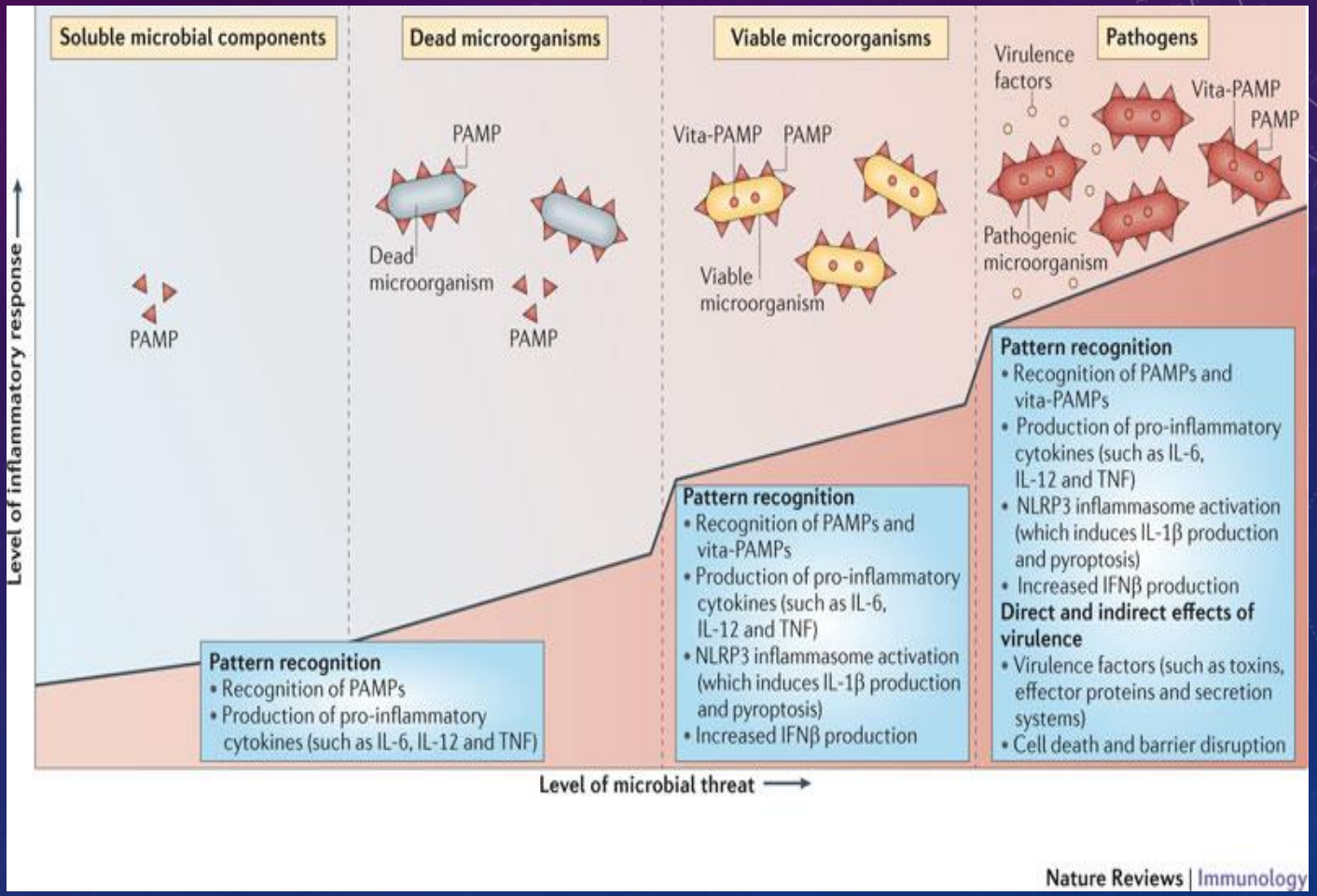
- The innate immune system cannot always differentiate sepsis from damage, since the latter is often part of the process
- Therefore the signal for infectious inflammation and sterile inflammation is often non specific

ROLE OF BACTERIA IN HEALTH AND DISEASE



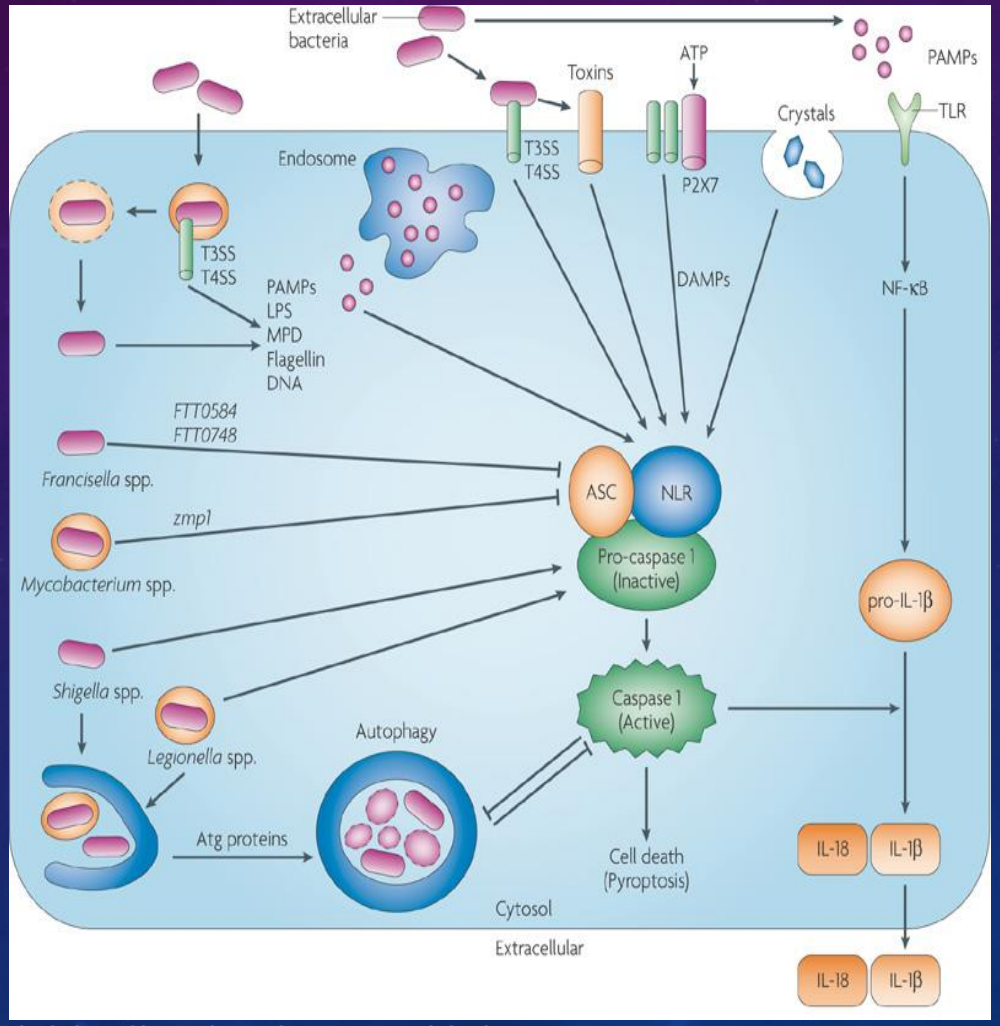
Blander & Sand **Beyond pattern recognition: five immune checkpoints for scaling the microbial threat**
Nature Reviews Immunology **12**, 215-225 (March 2012)

DOSE RESPONSE TO BACTERIAL PRESENCE



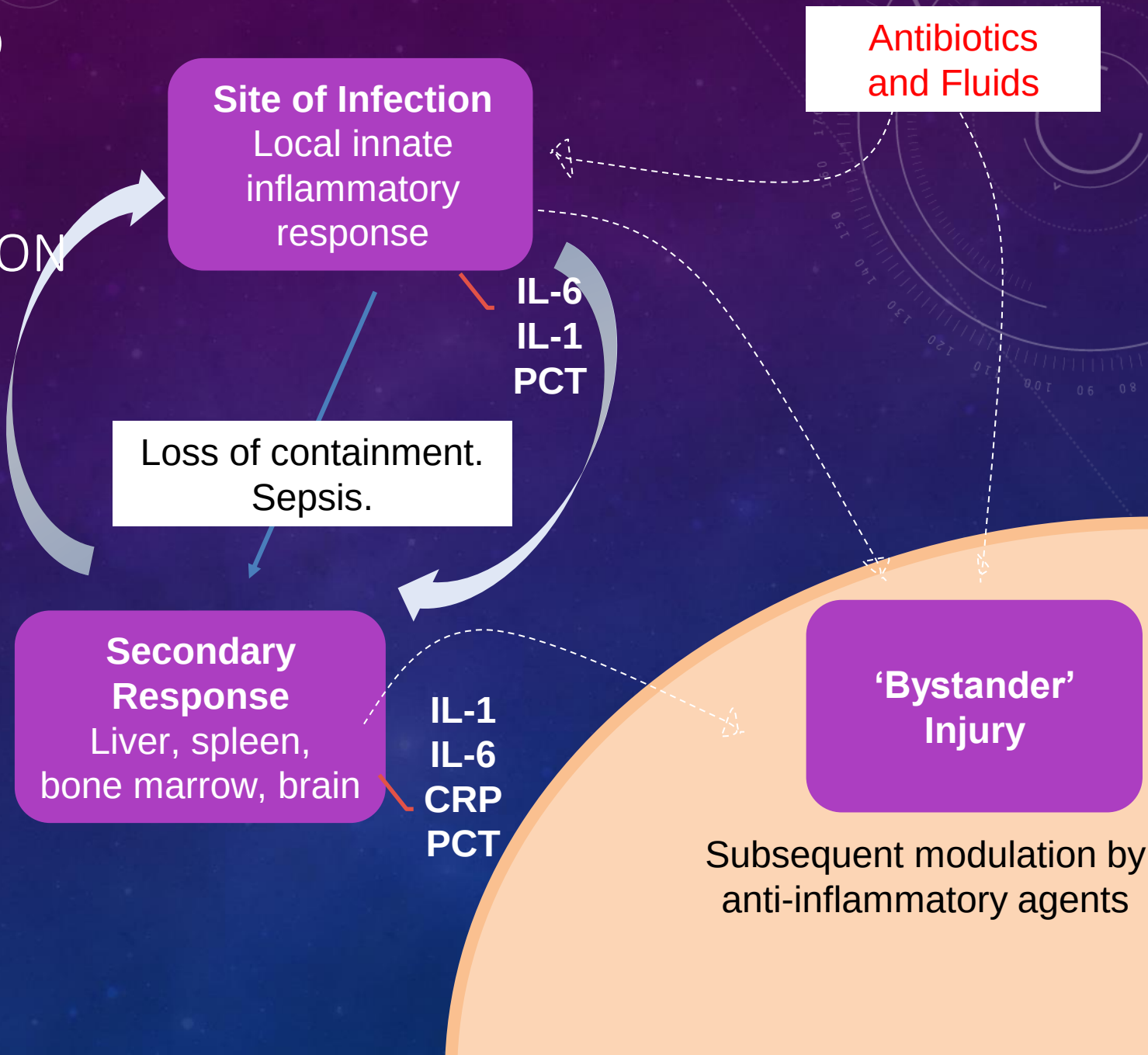
Blander & Sand **Beyond pattern recognition: five immune checkpoints for scaling the microbial threat**
Nature Reviews Immunology **12**, 215-225 (March 2012)

HOST RESPONSE TO INFECTION VS. INFLAMMATION

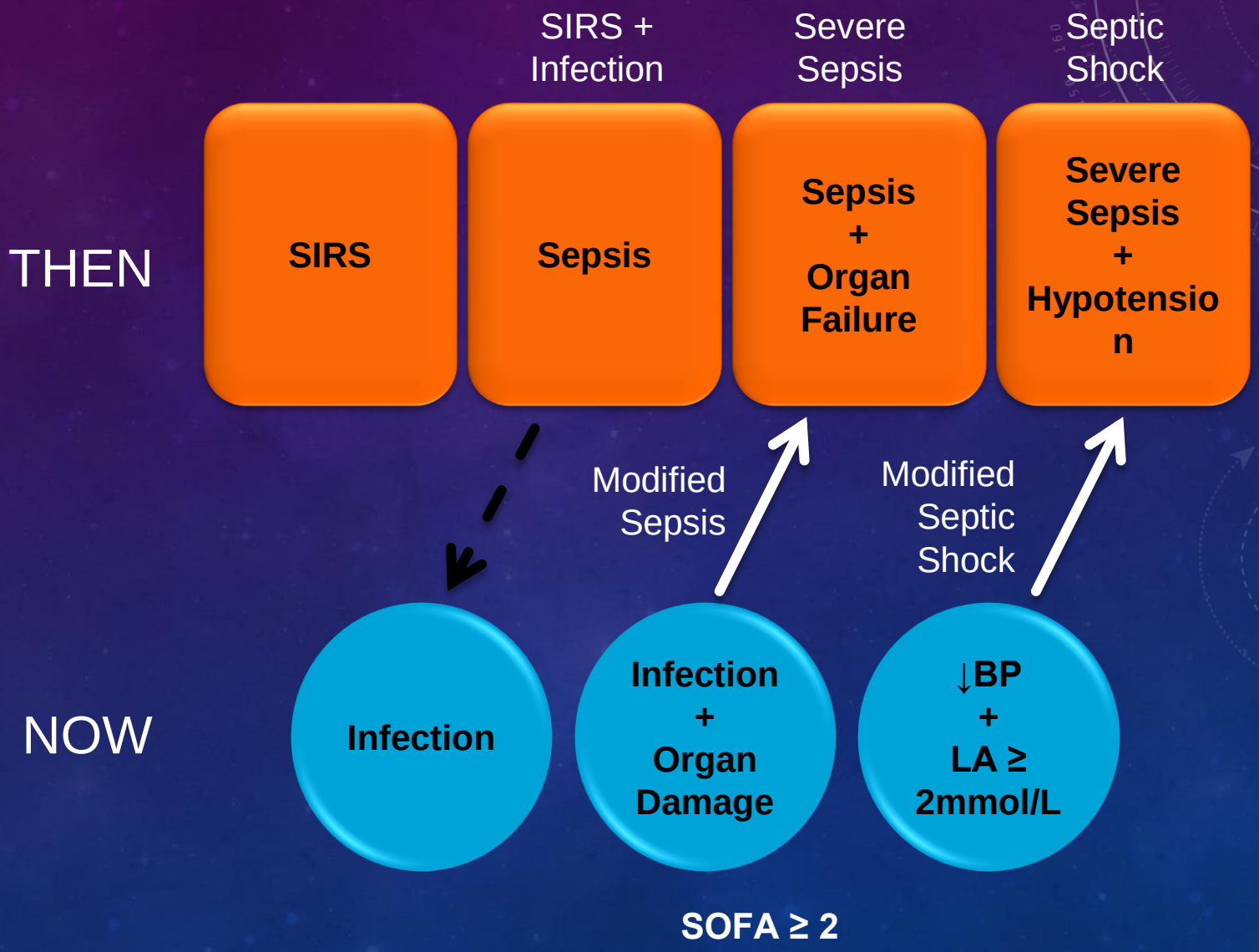


Diacovich & Gorvel. **Bacterial manipulation of innate immunity to promote infection**
Nature Reviews Microbiology **8**, 117-128 (February 2010)

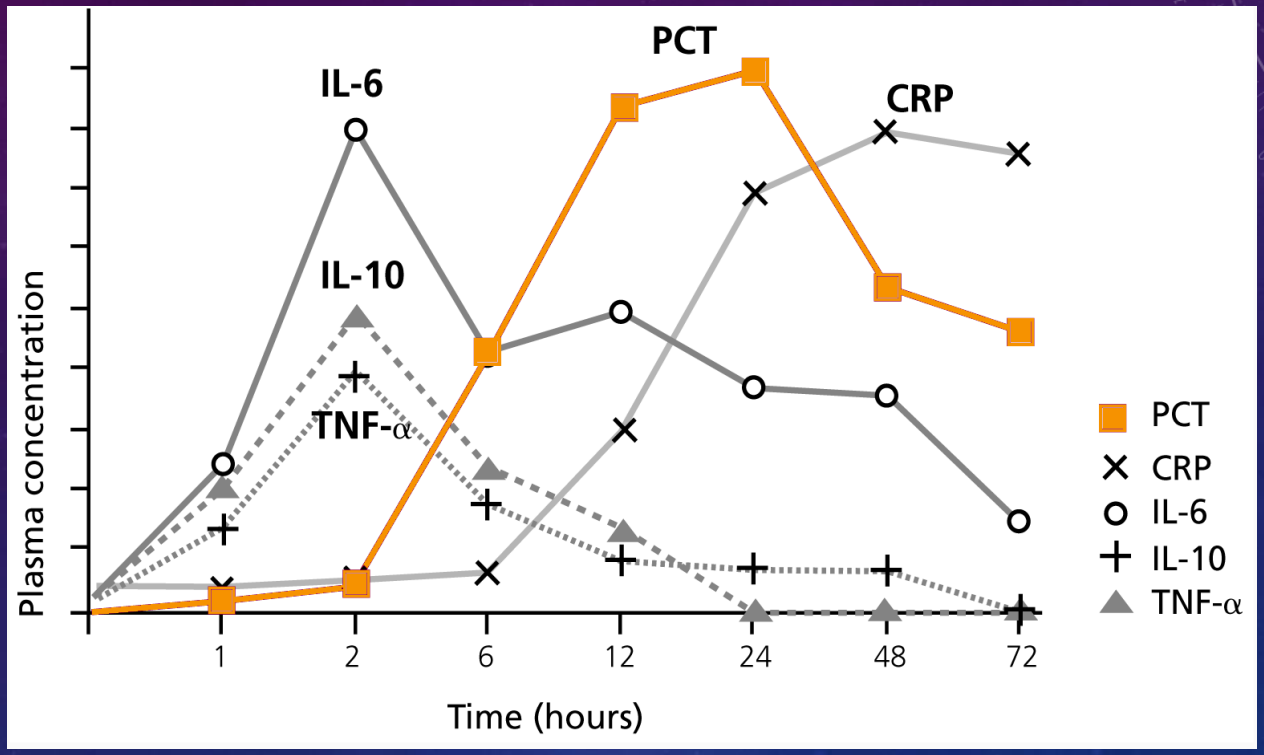
LOCAL AND SYSTEMIC RESPONSE TO INFECTION



DEFINING SEPSIS: THEN & NOW



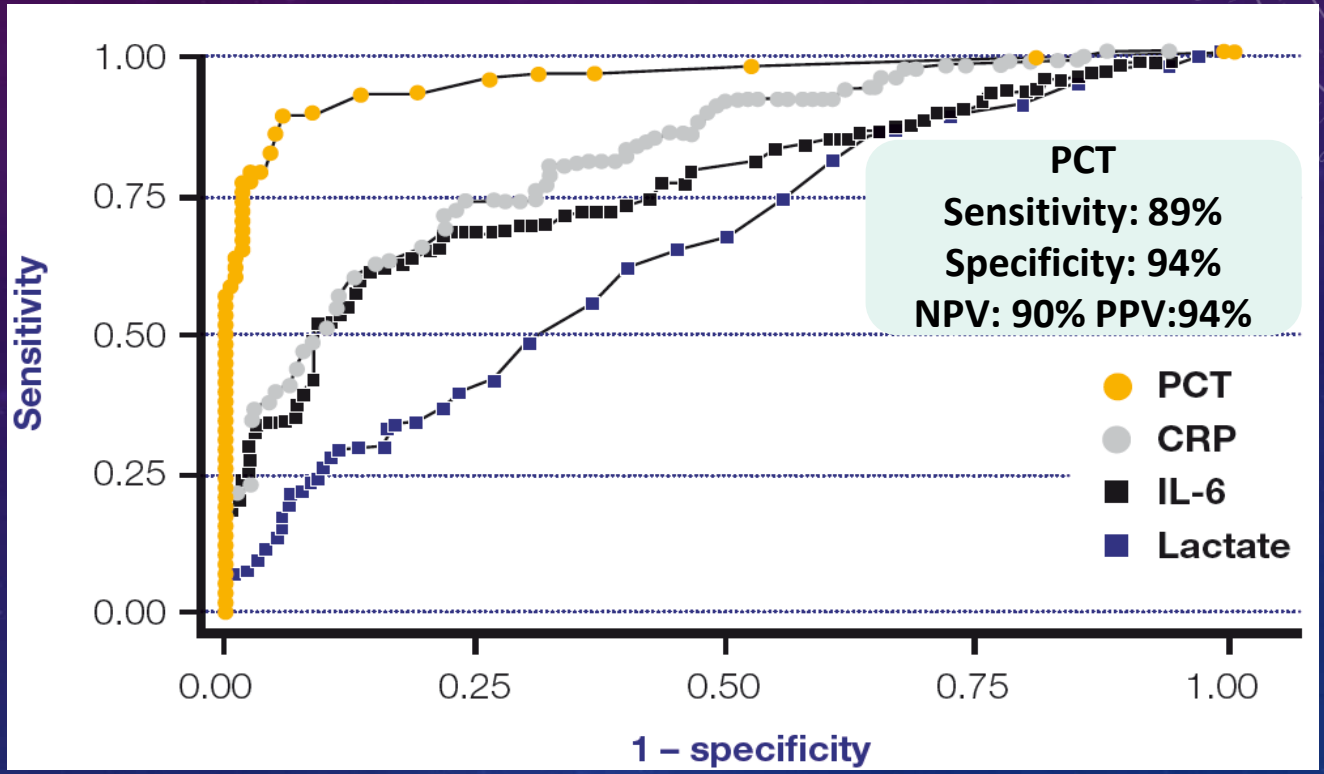
PCT KINETICS PROVIDE IMPORTANT INFORMATION ON PROGNOSIS OF SEPSIS PATIENTS



- Clinical symptoms alone are often insufficient for early and accurate diagnosis
- PCT levels can be observed within 3-6 hours after an infectious challenge with a peak up to 1000 ng/ml after 6-12 hrs. Half-life ~24hrs
- Specific to bacterial origin of infection and reflects the severity of the infection

Brunkhorst FM et al., Intens. Care Med (1998) 24: 888-892

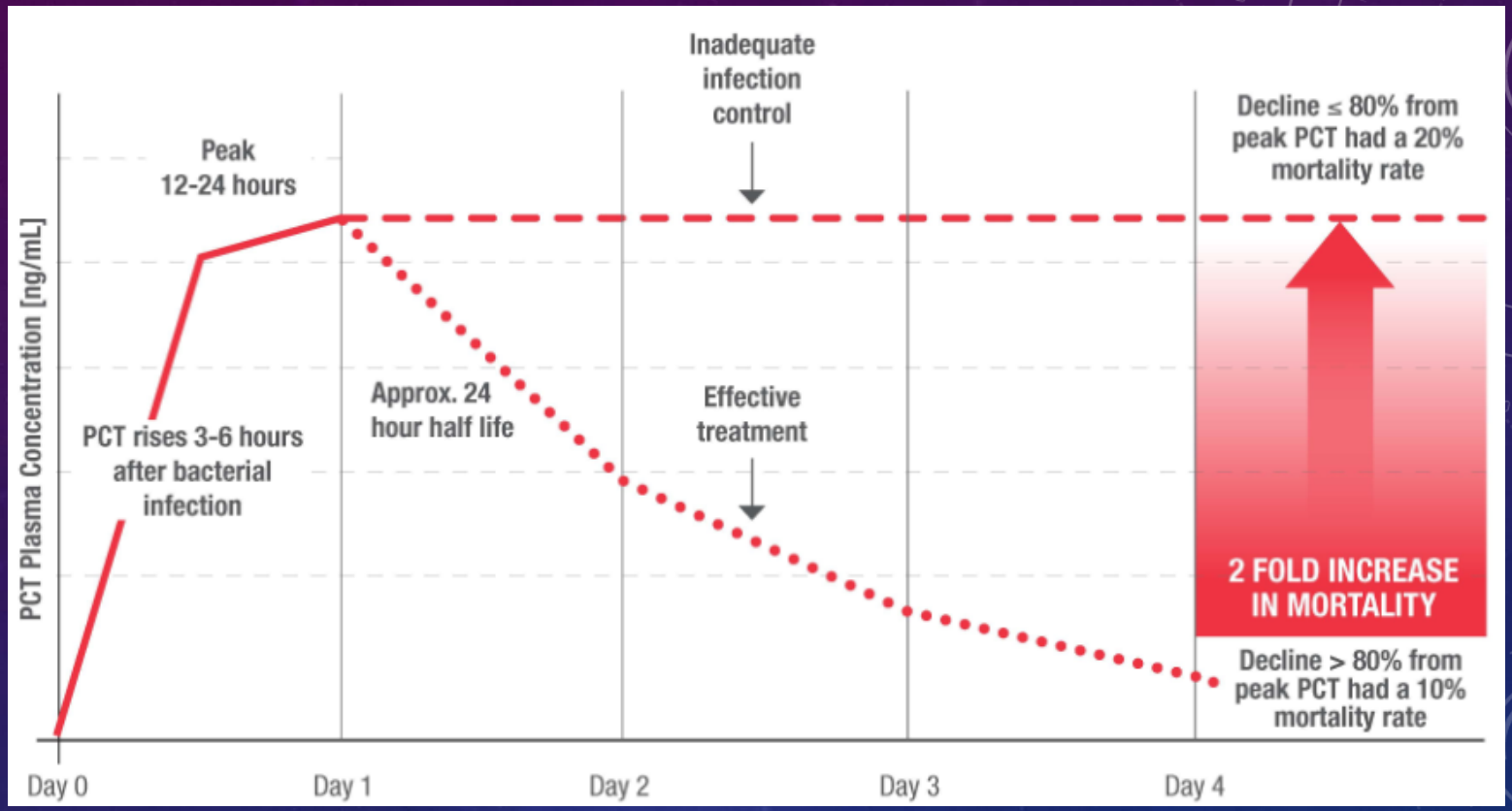
ADDING PCT RESULTS TO CLINICAL ASSESSMENT IMPROVES THE ACCURACY OF THE EARLY CLINICAL DIAGNOSIS OF SEPSIS



- PCT levels accurately differentiate sepsis from noninfectious inflammation
- PCT has been demonstrated to be the best marker for differentiating patients with sepsis from those with systemic inflammatory reaction not related to infectious cause

Simon L. et al. Clin Infect Dis. 2004; 39:206-217.

KINETICS OF PROCALCITONIN



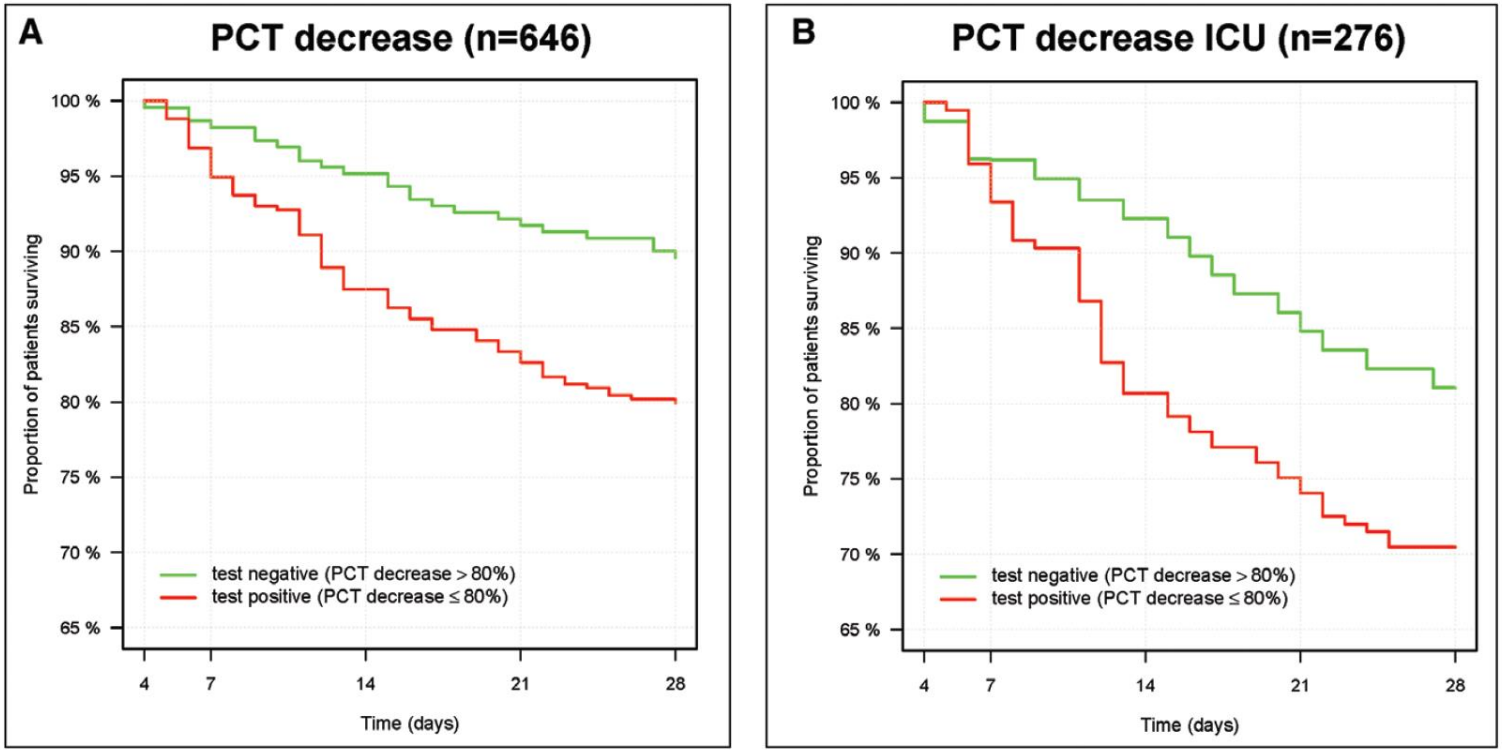
- Rapid and sustained response to bacterially induced systemic inflammation
- Half-life: 24 hours
- If the pathogen is not contained, infection spreads and the body up-regulates proinflammatory mediators

Harbarth et al. AJRCCM 2001
Jensen JU, Crit Care Med 2006;34:2596-602
Schuetz P, Gluck EH et al., Crit Care Med, 2013, 17:R115

OPEN

Serial Procalcitonin Predicts Survival in Severe Sepsis Patients: Results From the Multicenter Procalcitonin MOnitoring SEpsis (MOSES) Study

Philipp Schuetz, MD, MPH[1]; Robert Birkhahn, MD[2]; Robert Sherwin, MD[3]; Alan E. Jones, MD[4]; Adam Singer, MD[5]; Jeffrey A. Kline, MD[6]; Michael S. Runyon, MD, MPH[6]; Wesley H. Self, MD[7]; D. Mark Courtney, MD[8]; Richard M. Nowak, MD[9]; David F. Gaieski, MD[10]; Stefan Ebmeyer, MD[11]; Sascha Johannes, PhD[11]; Jan C. Wiemer, PhD[11]; Andrej Schwabe, PhD[11]; Nathan I. Shapiro, MD, MPH[12]



B·R·A·H·M·S PROCALCITONIN INTENDED USE

- Procalcitonin is intended for use in conjunction with other laboratory findings and clinical assessments to aid in the risk assessment of critically ill patients on the first day of ICU admission for progression to severe sepsis and septic shock
- Aiding assessment of mortality risk
- Recent FDA clearance includes using PCT to aid in antibiotic therapy decisions in the ICU, ED and patient wards

INSIGHT FOR LRTI THERAPY DECISIONS

PCT Plasma Concentration	
>0.50 ng/mL	Antibiotics Strongly Encouraged
>0.25 – 0.50 ng/mL	Antibiotics Encouraged
0.10 – 0.25 ng/mL	Antibiotics Discouraged
< 0.10 ng/mL	Antibiotics Strongly Discouraged

INSIGHT FOR SAFELY DISCONTINUING ANTIBIOTICS

CHANGE IN PCT CONCENTRATION	CURRENT PCT CONCENTRATION
Decline from peak PCT >80% and Clinical Improvement	Discontinue Antibiotics Sepsis ≤ 0.50 ng/mL
	LRTI ≤ 0.25 ng/mL

Important Considerations:
PCT Assay Sensitivity and Low-end Performance

Normal Range for B·R·A·H·M·S PCT: 0.05 ng/mL

USE OF PCT AT MY HOSPITAL

- Early adaptor
- In use for 8 years
- Over 200 levels drawn per month

USE OF PCT AT MY HOSPITAL

- Antibiotics are discouraged by pharmacy if the PCT is negative X 2 at onset of infection or during the treatment

CASE 1

- Patient presents with nausea, vomiting and abdominal pain
- Liver function tests are found to be abnormal with an obstruction type pattern
- WBC is elevated but without a left shift
- Lipase is normal
- Pre test probability strongest for ascending cholangitis

CASE 1: BIOMARKER EVALUATION

- Patient is resuscitated initially
- With 3 L of Normal Saline
- Antibiotics are started
- Cultures are obtained

Date	Lactate	PCT
0	6.5	0.20
0.25	4.0	
0.5	1.5	
1	1.8	10.7
2		10.7
3		5.7
4		2.3
5		1.4

Case 1: Biomarker Evaluation

- Patient is resuscitated initially with 3 L of Normal Saline
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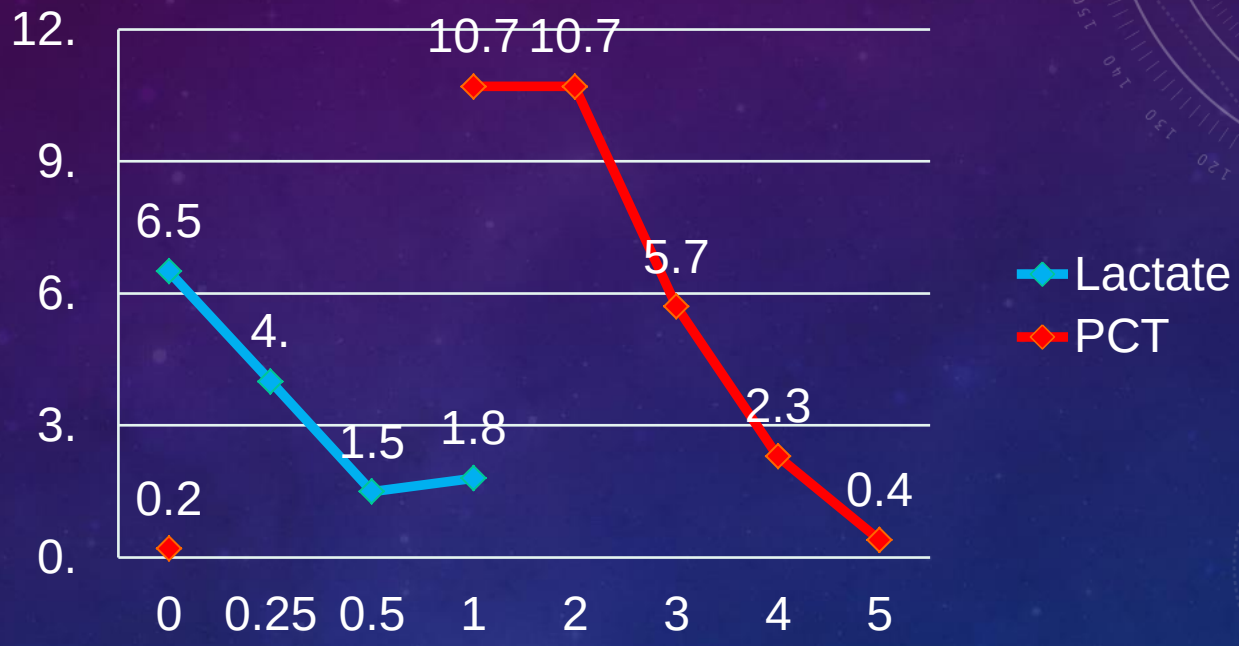
Case 1: Biomarker Evaluation



Date	0	0.25	0.5	1	2	3	4	5
Lactate	6.5	4.0	1.5	1.8				
PCT	0.2			10.7	10.7	5.7	2.3	1.4

CASE 1: CLINICAL FOLLOW UP

- The patient's blood pressure stabilized after 3 L of normal saline. He never required blood pressure support with vasopressors
- The lactate reduction indicated adequacy of resuscitation
- The PCT often rises for 24 to 36 hours after the onset of treatment since it often requires that long for antibiotics to achieve cidal tissue levels

CASE 2: SCENARIO I

- Presentation: Female with shortness of breath with modest hypoxia and bilateral patchy infiltrates on chest film.
  - WBCs are elevated with a modest shift to the left
  - Watery yellow tinged sputum production
  - No subjective fever

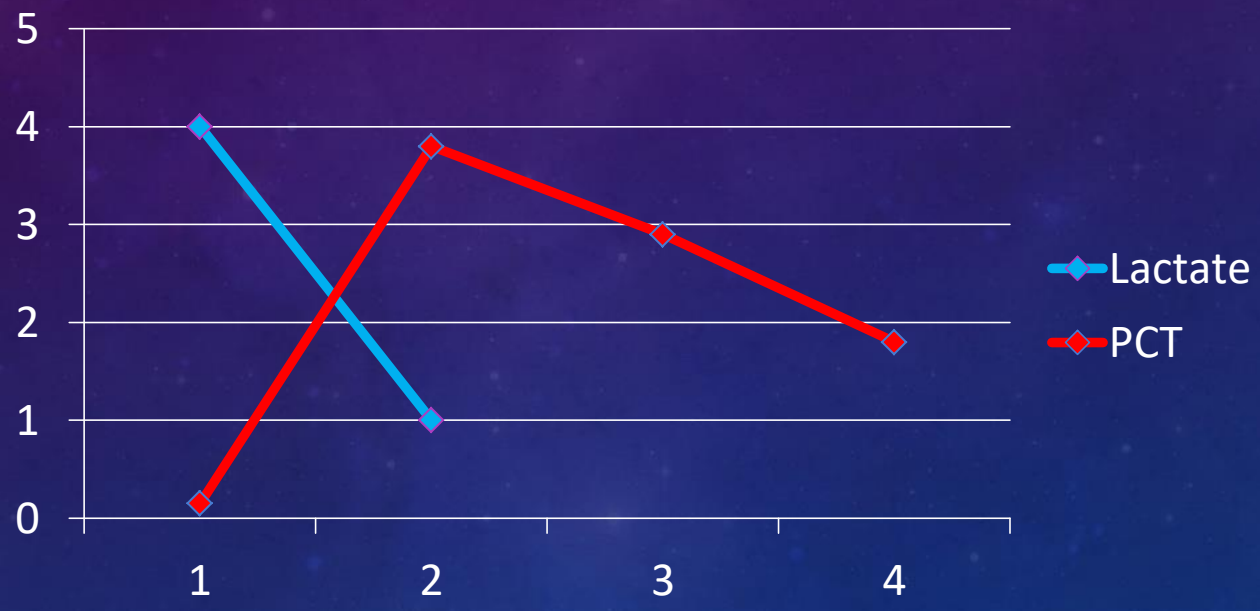
CASE 2: SCENARIO I

What would this pattern indicate?

Day	1	2	3
Lactate	3.5	4.2	1.2
PCT	<0.1	<0.1	

CASE 2: SCENARIO II

This time the LA and PCT are both elevated suggesting that the patient has pneumonia. Sputum was positive for gram+ cocci in chains.



Day	1	2	3	4
Lactate	4.0	1.0		
PCT	0.15	3.8	2.9	1.8

CASE 3

- This patient presents with a 2 day history of diarrhea and fever to 102
- Patient had recently undergone a revision of a prior hip surgery and received 48 hours of prophylactic antibiotics

CASE 3: LAB DATA

WBC = 11.2

Bands = 14%

Temp = 101.2

HR = 107

Physical Exam - abdomen distended and tender diffusely
Bowel sounds were hyperactive

Abdominal X-ray diffuse dilation of large bowel

CASE 3: BIOMARKER EVALUATION

Day	1	2	3	4	5	6	7	8	9	10
LA	1.2	1.5	1.5				4	9	>9	Expired
PCT	15.8	89	64	31	22	16	27	199	>299	

CASE 4

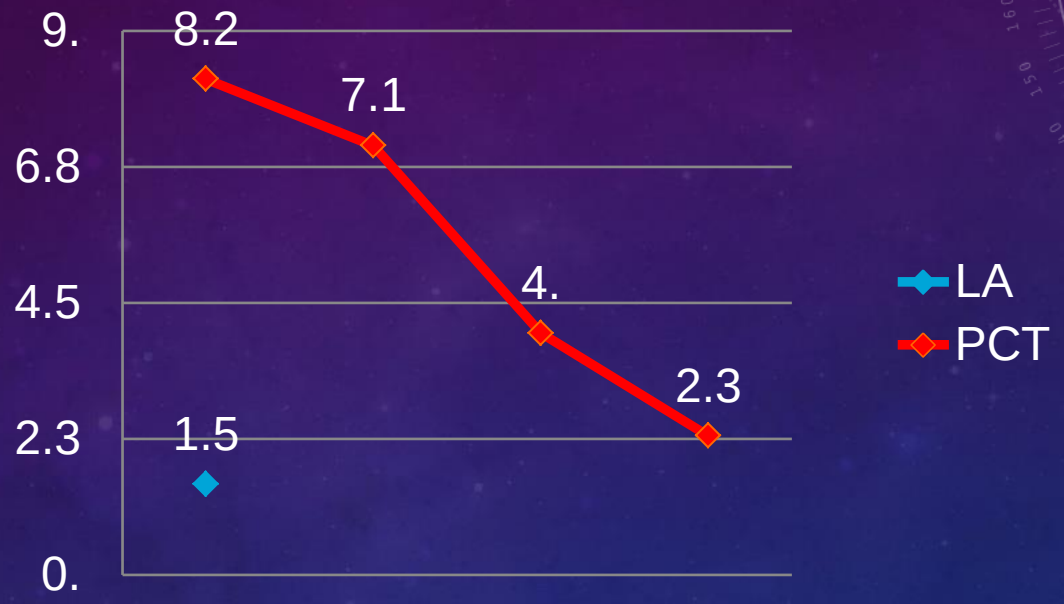
- Patient presents with frequency and dysuria
- UA demonstrates + LE, +nitrites, 24 WBC per HPF, many bacteria

CASE 4: BIOMARKER EVALUATION

Day	1	2	3	4
Lactate	4.6	1.5	1.5	0.8
PCT	6.2	5.6	6.4	6.8

CASE 4: PART 2

- Ultrasound demonstrated a perinephric abscess
- The abscess was drained by interventional radiology
- Patient was placed on additional antibiotics



Day	1	2	3	4
Lactate	1.5			
PCT	8.2	7.1	4.0	2.3

CURRENT US GUIDANCE

IDSA 2016: Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia

- For patients with HAP/VAP, *we suggest using **PCT** levels **plus clinical criteria** to guide the discontinuation of antibiotic therapy, rather than clinical criteria alone* (weak recommendation, low-quality evidence)

IDSA 2016: Implementing an Antibiotic Stewardship Program

- *In adults in ICUs with suspected infection, we suggest the use of **serial PCT** measurements as an ASP intervention to decrease antibiotic use (weak recommendation, moderate quality evidence)*

SCCM 2017: Surviving Sepsis Campaign Guidelines

- *We suggest that measurement of **procalcitonin** levels can be used to support shortening the duration of antimicrobial therapy in sepsis patients* (weak recommendation, low quality of evidence)

- *We suggest that **procalcitonin** levels can be used to support the discontinuation of empiric antibiotics in patients who initially appeared to have sepsis, but subsequently have limited clinical evidence of infection* (weak recommendation, low quality of evidence)

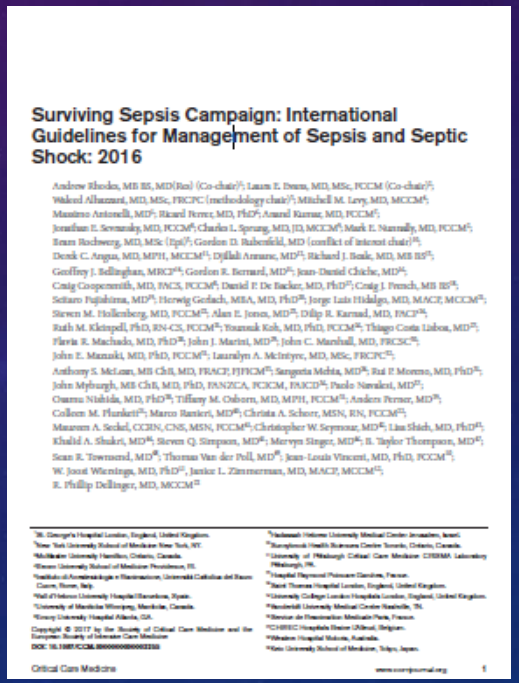
SURVIVING SEPSIS GUIDELINES 2016

D. Antimicrobial Therapy

*14. We suggest that measurement of **procalcitonin** levels can be used to support shortening the duration of antimicrobial therapy in sepsis patients*

*15. We suggest that **procalcitonin** levels can be used to support the discontinuation of empiric antibiotics in patients who initially appeared to have sepsis, but subsequently have limited clinical evidence of infection*

(weak recommendation, low quality of evidence)


Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016

Andrew Rhodes, MB BS, MD (Res) (Co-chair)[1]; Laura E. Evans, MD, MSc, FCCM (Co-chair)[2]; Waleed Alhazzani, MD, MSc, FRCPC (methodology chair)[3]; Mitchell M. Levy, MD, MCCM[4]; Massimo Antonelli, MD[5]; Ricard Ferrer, MD, PhD[6]; Anand Kumar, MD, FCCM[7]; Jonathan E. Sevransky, MD, FCCM[8]; Charles L. Sprung, MD, JD, MCCM[9]; Mark E. Nunnally, MD, FCCM[10]; Bram Rochwerg, MD, MSc (Epi)[11]; Gordon D. Rubenfeld, MD (conflict of interest chair)[12]; Derek C. Angus, MD, MPH, MCCM[13]; Djillali Annane, MD[14]; Richard J. Beale, MD, MB BS[15]; Geoffrey J. Bellingham, MRCP[16]; Gordon R. Bernard, MD[17]; Jean-Daniel Chiche, MD[18]; Craig Coopersmith, MD, FACS, FCCM[19]; Daniel P. De Backer, MD, PhD[20]; Craig J. French, MB BS[21]; Seitaro Fujishima, MD[22]; Herwig Gerlach, MBA, MD, PhD[23]; Jorge Luis Hidalgo, MD, MACP, MCCM[24]; Steven M. Hollenberg, MD, FCCM[25]; Alan E. Jones, MD[26]; Dilip R. Karnad, MD, FNCP[27]; Ruth M. Kleinpell, PhD, RN-CS, FCCM[28]; Younsuk Koh, MD, PhD, FCCM[29]; Thiago Costa Lisboa, MD[30]; Flavia R. Machado, MD, PhD[31]; John J. Marini, MD[32]; John C. Marshall, MD, FRCSC[33]; John E. Mazuski, MD, PhD, FCCM[34]; Lauralyn A. McIntyre, MD, MSc, FRCPC[35]; Anthony S. McLean, MB ChB, MD, FRACP, FJFICM[36]; Sangeeta Mehta, MD[37]; Rui P. Moreno, MD, PhD[38]; John Myburgh, MB ChB, MD, PhD, FANZCA, FCICM, FACCP[39]; Paolo Nanwani, MD[40]; Osamu Nishida, MD, PhD[41]; Tiffany M. Osborn, MD, MPH, FCCM[42]; Anders Perner, MD[43]; Colleen M. Plunkett[44]; Marco Ranieri, MD[45]; Christa A. Schorr, MSN, RN, FCCM[46]; Maureen A. Seckel, CCRN, CNS, MSN, FCCM[47]; Christopher W. Seymour, MD[48]; Lisa Shieh, MD, PhD[49]; Khalid A. Shukri, MD[50]; Steven Q. Simpson, MD[51]; Mervyn Singer, MD[52]; B. Taylor Thompson, MD[53]; Sean R. Townsend, MD[54]; Thomas Van der Poll, MD[55]; Jean-Louis Vincent, MD, PhD, FCCM[56]; W. Joost Wiersinga, MD, PhD[57]; Janice L. Zimmerman, MD, MACP, MCCM[58]; R. Phillip Dellinger, MD, MCCM[59]

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Critical Care Medicine www.ccmjournal.org 1

Adapted from: Rhodes A et al..

Intensive Care Med. 2017. *43*(3):304-377.

IDSA GUIDELINE 2016: PCT AND STEWARDSHIP

XVIII. In Adults in ICU With Suspected Infection, Should ASPs Advocate Procalcitonin (PCT) Testing as an Intervention to Decrease Antibiotic Use?

Recommendation

In adults in ICUs with suspected infection, ***we suggest the use of serial PCT measurements as an ASP intervention to decrease antibiotic use*** *(weak recommendation, moderate quality evidence).*


Clinical Infectious Diseases Advance Access published April 13, 2016

IDSA FEATURES

Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America

EXECUTIVE SUMMARY

Comment: "…. If implemented, each ASP must develop processes and guidelines to assist clinicians in interpreting and responding appropriately to results, and must determine if this intervention is the best use of its time and resources."

Adapted from: Barlam TF et al., Clinical Infectious Diseases 2016. [Epub ahead of print]

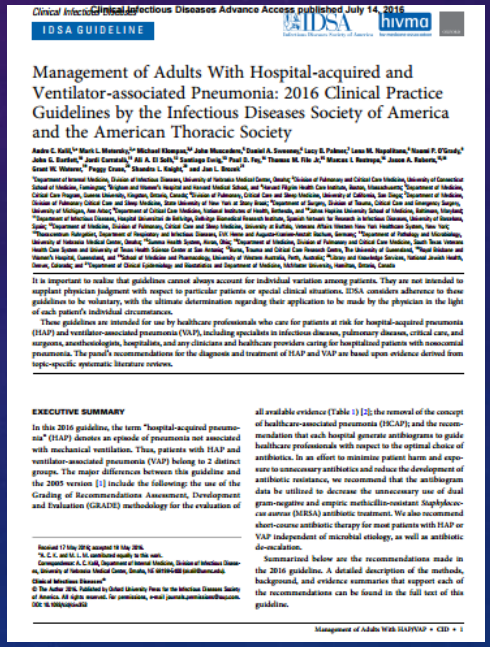
IDSA GUIDELINES 2016: PCT IN HCAP AND VAP

XXIV. Should Discontinuation of Antibiotic Therapy Be Based Upon PCT Levels Plus Clinical Criteria or Clinical Criteria Alone in Patients With HAP/VAP?

Recommendation:

For patients with HAP/VAP, *we suggest using **PCT** levels **plus clinical criteria** to guide the discontinuation of antibiotic therapy, rather than clinical criteria alone*

(weak recommendation, low-quality evidence)


Clinical Infectious Diseases Advance Access published July 14, 2016

IDSA GUIDELINE

Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society

EXECUTIVE SUMMARY

Adapted from: Kalil A et al., Clinical Infectious Diseases 2016. 1;63(5):e61-e111*]*

Table 1 Diagnostic Criteria for Sepsis
Infection, documented or suspected and some of the following:

General:
- Fever (>38.3C), hypothermia (<36C)
- HR >90bpm
- Tachypnea
- Altered Mental Status
- Significant Edema or fluid balance (>20 mk/kg over 24h)
- Hyperglycemia >140 mg/dL in absence of DM

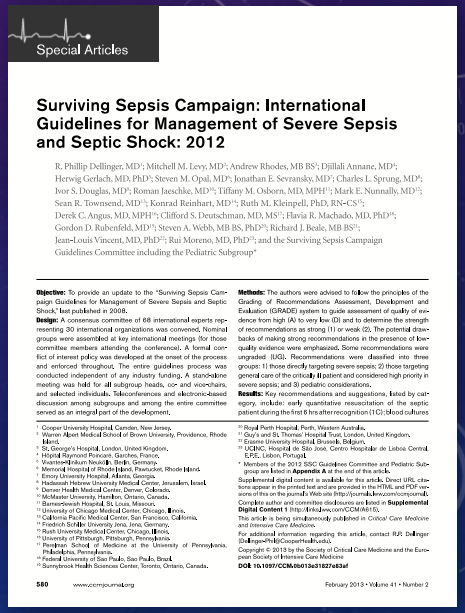
Inflammatory variables:
- Leukocytosis (WBC >12,000)
- Leukopenia (WBC <4000)
- Normal WBC >10% immature forms
- Plasma CRP above normal
- Plasma Procalcitonin above normal

Hemodynamic Variables
- Arterial hypotension

(SBP < 90mm Hg, MAP <70 mm Hg or a SBP decrease > 40 mm Hg in adults)

Organ Dysfunction variables:
- Arterial hypoxemia PaO2/Fio2 <300)
- Acute oliguria (UOP <0.5 mL/kg/hr fro at leas 2h despite adequate fluid resuscitation)
- Creatinine increase >0.5 mg/dL
- Coagulation abnormalities (INR >1.5 or PTT >60s)
- Ileus (absent bowel sounds)
- Thrombocytopenia (platelet count <100,000)
- Hyperbilirubinemia (plasma total bilirubin >4 mg/dL)

Tissue perfusion variables
- Hyperlactatemia (>1 mmol/L)
- Decreased capillary refill or mottling



Special Articles

Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012

R. Phillip Dellinger, MD[1]; Mitchell M. Levy, MD[2]; Andrew Rhodes, MB BS[3]; Djillali Annane, MD[4]; Herwig Gerlach, MD, PhD[5]; Steven M. Opal, MD[6]; Jonathan E. Sevransky, MD[7]; Charles L. Sprung, MD[8]; Ivor S. Douglas, MD[9]; Roman Jaeschke, MD[10]; Tiffany M. Osborn, MD, MPH[11]; Mark E. Nunnally, MD[12]; Sean R. Townsend, MD[13]; Konrad Reinhart, MD[14]; Ruth M. Kleinpell, PhD, RN-CS[15]; Derek C. Angus, MD, MPH[16]; Clifford S. Deutschman, MD, MS[17]; Flavia R. Machado, MD, PhD[18]; Gordon D. Rubenfeld, MD[19]; Steven A. Webb, MB BS, PhD[20]; Richard J. Beale, MB BS[21]; Jean-Louis Vincent, MD, PhD[22]; Rui Moreno, MD, PhD[23]; and the Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup*

Objective: To provide an update to the "Surviving Sepsis Campaign Guidelines for Management of Severe Sepsis and Septic Shock," last published in 2008.

Design: A consensus committee of 68 international experts representing 30 international organizations was convened. Nominal groups were assembled at key international meetings (for those committee members attending the conference). A formal conflict of interest policy was developed at the onset of the process and enforced throughout. The entire guidelines process was conducted independent of any industry funding. A stand-alone meeting was held for all subgroup heads, co- and vice-chairs, and selected individuals. Teleconferences and electronic-based discussion among subgroups and among the entire committee served as an integral part of the development.

Methods: The authors were advised to follow the principles of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to guide assessment of quality of evidence from high (A) to very low (D) and to determine the strength of recommendations as strong (1) or weak (2). The potential drawbacks of making strong recommendations in the presence of low-quality evidence were emphasized. Some recommendations were ungraded (UG). Recommendations were classified into three groups: 1) those directly targeting severe sepsis; 2) those targeting general care of the critically ill patient and considered high priority in severe sepsis; and 3) pediatric considerations.

Results: Key recommendations and suggestions, listed by category, include: early quantitative resuscitation of the septic patient during the first 6 hrs after recognition (1C); blood cultures

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* Members of the 2012 SSC Guidelines Committee and Pediatric Subgroup are listed in **Appendix A** at the end of this article.

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SUMMARY

- Procalcitonin is a specific and sensitive biomarker reflecting the host response to a systemic bacterial infection
- PCT and lactate are complementary markers
- PCT is used in ED, ICU, and hospital floors and is used to help determine both the severity of illness and the adequacy of source control
- The change in PCT over time reflects the patient's response to treatment and can aid in risk assessment for mortality in severe sepsis and septic shock patients

QUESTIONS?

SOFA score	0	1	2	3	4
Respiration PaO_2/FIO_2 (mm Hg) SaO_2/FIO_2	>400	<400 221–301	<300 142–220	<200 67–141	<100 <67
Coagulation Platelets $10^3/mm^3$	>150	<150	<100	<50	<20
Liver Bilirubin (mg/dL)	<1.2	1.2–1.9	2.0–5.9	6.0–11.9	>12.0
Cardiovascular[b] Hypotension	No hypotension	MAP <70	Dopamine <=5 or dobutamine (any)	Dopamine >5 or norepinephrine <=0.1	Dopamine >15 or norepinephrine >0.1
CNS Glasgow Coma Score	15	13–14	10–12	6–9	<6
Renal Creatinine (mg/dL) or urine output (mL/d)	<1.2	1.2–1.9	2.0–3.4	3.5–4.9 or <500	>5.0 or <200

SOFA AND QSOFA

SOFA

SOFA score	0	1	2	3	4
Respiration PaO_2/FIO_2 (mm Hg) SaO_2/FIO_2	>400	<400 221–301	<300 142–220	<200 67–141	<100 <67
Coagulation Platelets $10^3/mm^3$	>150	<150	<100	<50	<20
Liver Bilirubin (mg/dL)	<1.2	1.2–1.9	2.0–5.9	6.0–11.9	>12.0
Cardiovascular[b] Hypotension	No hypotension	MAP <70	Dopamine <5 or dobutamine (any)	Dopamine >5 or norepinephrine <0.1	Dopamine >15 or norepinephrine >0.1
CNS Glasgow Coma Score	15	13–14	10–12	6–9	<6
Renal Creatinine (mg/dL) or urine output (mL/d)	<1.2	1.2–1.9	2.0–3.4	3.5–4.9 or <500	>5.0 or <200

qSOFA

- Altered in mental status
- Decrease in systolic blood pressure of less than 100 mmHg
- Respiratory rate greater than 22 breaths/min