BIOMARKERS IN SEPSIS:
DO THEY REALLY GUIDE US?

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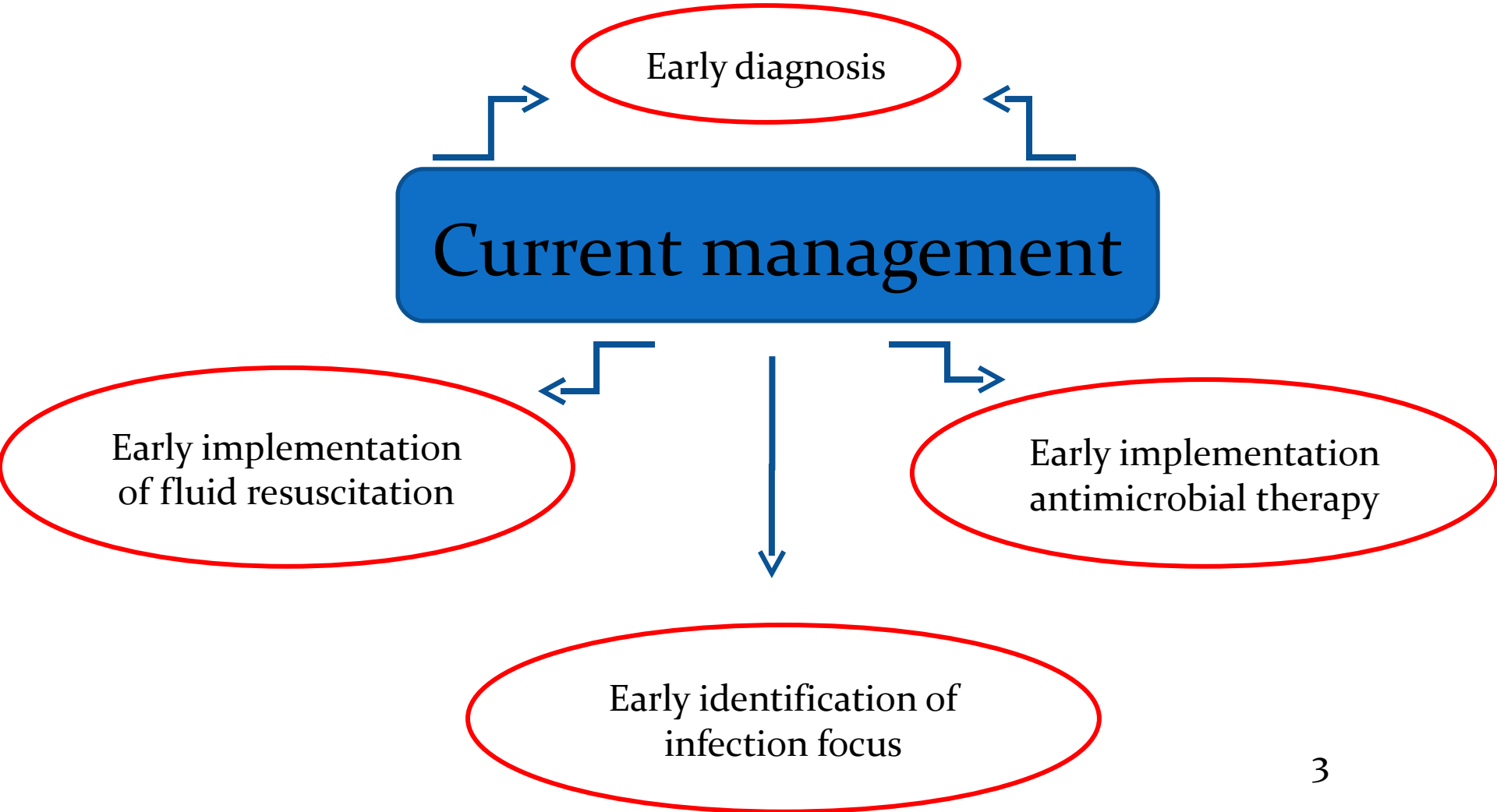
- NO CONFLICT OF INTEREST

We do not fully understand the pathogenesis of sepsis

There is no specific treatment of sepsis.



- The routine screening of SIRS with clinical parameters and identification of the source of infection
- Identifying biomarkers that
  - Can detect sepsis in an early and reversible phase
  - Can closely monitor the progression of the disease
  - Can estimate prognosis

BIOMARKER

The National Institutes of Health defines ideal biomarker characteristic

- objectively measured
- an indicator of
  - normal biological processes,
  - pathological processes, and/or
  - pharmacological responses to a therapeutic intervention
- readily obtainable from body fluids or tissue samples,
- give results in short period.
- The sensitivity, specificity, and predictive values

Several biomarkers are currently used in clinical practice, but do they have these characteristics ???

There has been a growing interest in identifying novel biomarkers.

Markers of Acute Inflammatory Response

CRP*:

- $^{235}_{92}$ levels within first 48 h of therapy ✱ correlate with an effective response to the initial antimicrobial therapy in septic patients.
- It's specificity in indicating the presence of an infection has been challenged
  - High levels of CRP among patients with burn injury without septic complications.
- Poor predictor of mortality compared with other biomarkers

*Role of biomarkers in sepsis care. Shock. 2013 Nov;40(5):358-65.

Potential Marker of Infection

Procalcitonin (PCT):

- 116-amino-acid peptide precursor of the hormone calcitonin,
- Reliable diagnostic and prognostic marker of sepsis,

Elevations of both CRP and PCT were added to the updated definition of sepsis in 2003

- Levels are significantly high in bacteremia and moderately elevated in fungemia.*

*Shock. 2009;31(6):586-91.

J Clin Endocrinol Metab. 2004;89(4):1512-25.

Potential Marker of Infection

Procalcitonin (PCT):

- Circulating levels
  - Superior diagnostic accuracy compared with other established biomarkers and indicators of sepsis*
  - Unaffected by the administration of anti-inflammatory therapy (glucocorticoids)**
  - In pediatric patients differentiating viral and bacterial infection (better than CRP, WBCcount, IL-6 levels)

*Infect. 2010;60(6):409-16.
**J Leukoc Biol. 2002;72(4):643-9.

Potential Marker of Infection

Procalcitonin (PCT):

- More sensitive marker in predicting late mortality at 30 days compared with CRP*
- Monitoring biomarker for antibiotic stewardship.
  - A recent meta-analysis of randomized controlled trials PCT-based algorithm may reduce antibiotic exposure in adult septic patients without compromising clinical outcomes. **
- Dynamic changes of PCT have predictive value for hospital stay.
  - A decrease in PCT level by 25% over a 5-day period ✱ useful indicator of survival in septic shock patients ***

* Shock. 2008 Mar;29(3):322-7.
**Crit Care Med. 2010 Nov;38(11):2229-41.
*** Shock. 2011;36(6):570-4.

Potential Marker of Infection

Procalcitonin (PCT):

- Significant heterogeneity among studies and selection criteria*
- Meta-analyses have not confirmed the superior diagnostic performance of PCT over other sepsis biomarkers. *
- Nonspecific elevations of PCT levels can occur in situations of massive stress, such as after severe trauma and surgery or in patients after cardiac shock**

*Systematic review and meta-analysis.Lancet Infect Dis. 2007 Mar;7(3):210-7.
**Clin Microbiol Rev. 2012; 25(4): 609–634.

Potential Marker of Infection

Procalcitonin (PCT):

- Most clinical studies correlate PCT levels on admission to the ICU with the subsequent diagnosis of sepsis or overall mortality.
- Levels may vary early during the development of sepsis and the test's predictive power is probably only significant later in the patient's course*
- Low levels helpful in ruling out the risk of sepsis because of a high negative predictive value, initially elevated levels in critically ill patients may be misleading **
- Must be used in conjunction with other laboratory findings for a correct diagnosis*

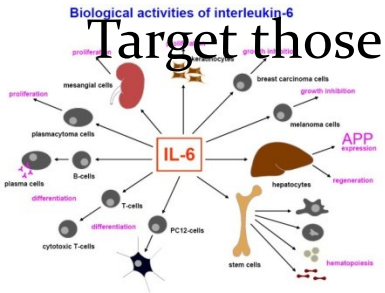
*BMC Infect Dis. 2011;11:224
*Clin Microbiol Infect. 2002;8:93–100
**Randomized trial. Crit Care Med. 2011 Sep;39(9):2048-58 (PASS study)

Markers of Acute Inflammatory Response

IL-6:

- Serum levels correlate with the severity of septic shock*
- Higher in nonsurvivors vs survivors.*
- High serum levels of IL-6 (>1,000 pg/mL) have been shown to predict sepsis-related death in adult patients**
- Even more powerfully predict survival in a mouse model of acute septic peritonitis

Target those mice that could benefit most from treatment.

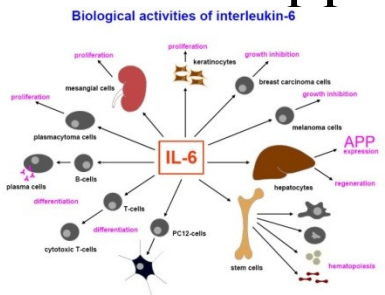


*Lancet. 2004 Jan 17;363(9404):203-9.
**J Intensive Care Med. 2011 Mar-Apr;26(2):73-87.

Markers of Acute Inflammatory Response

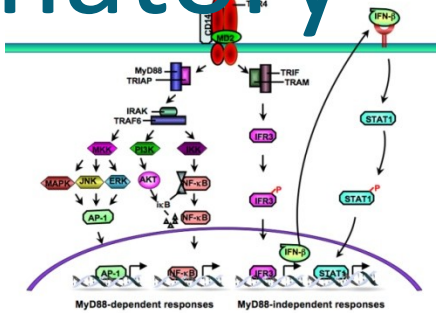
IL-6:

- Elevated in noninfectious conditions such as trauma, surgery, and stroke*
- Its' major role as a biomarker of sepsis appears to be prognostic, not diagnostic. *
- It may be able to identify patients with increased risk of developing severe sepsis, and who therefore need supportive therapy.**



*Intensive Care Med. 2011 ;26(2):73-87.
**Biomarkers of sepsis. Crit Rev Clin Lab Sci. 2013 Jan-Feb;50(1):23-36.

Markers of Acute Inflammatory Response



Lipopolysaccharide-binding protein:

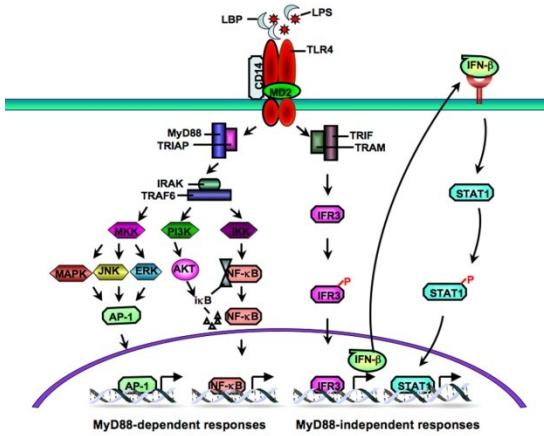
- Polypeptide synthesized in the liver and released bloodstream after glycosylation.
- Serum LBP levels increase several folds in sepsis
- In critically ill neonates and children, LBP was a better marker of sepsis than IL-6 and procalcitonin (PCT)*
- In the adult population, both IL-6 and LBP appeared to be superior to PCT as diagnostic markers of sepsis**

*Intensive Care Med. 2004 ;30(7):1454-60.
** Crit Care. 2006;10(2):R53.

Markers of Acute Inflammatory Response

Lipopolysaccharide-binding protein:

- On the other hand, in a recent prospective study, LBP only moderately discriminated sepsis from SIRS and inferior to IL-6 and PCT *
- Contraversies exist as diagnostic marker



* Crit Care Med. 2008;36(7):2014-22.

Markers of Impaired Metabolism

- The most commonly used parameters are the
  - Mixed venous O2saturation (SvO_2)
  - Central venous O2 saturation ($ScvO_2$), and
  - Serum lactate levels
  - Lactate clearence

Markers of Impaired Metabolism

Mixed venous O2saturation (SvO2) and Central venous O2 saturation (ScvO2), :

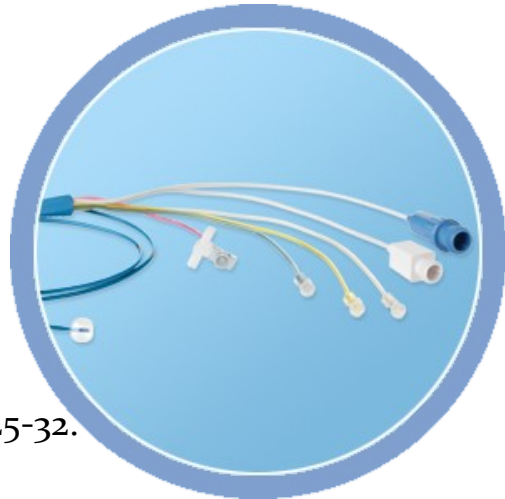
- Detect imbalance between oxygen delivery and consumption.
- A low levels indicates low oxygen delivery to tissues. Optimization of ScvO2 is considered one of the main resuscitation targets of the early goal-directed therapy (Surviving Sepsis Campaign 2012 guidelines*).
- Inability to achieve ScvO2 > 70% within the first 6 h associated with significantly increased mortality in patients with sepsis.**
- Patients reaching values of ScvO2 > 70% were twice more likely to survive***

*Surviving sepsis campaign: international guidelines. Crit Care Med. 2013 Feb;41(2):580-637.
**Multicenter study. Ann Emerg Med. 2010 Jan;55(1):40-46.
***A meta-analysis. Aust Crit Care. 2011 Nov;24(4):229-43

Markers of Impaired Metabolism

ScvO2 and SvO2 :

- Central venous oxygen saturation can replace mixed venous saturation???*
- Time, expertise, and specialized equipment



*Am J Respir Crit Care Med. 2011 Sep 1;184(5):514-20.
**Results of a national survey. Crit Care Med. 2007 Nov;35(11):2525-32.
**Crit Care Med. 2005 Aug;33(8):1888-9.

Markers of Impaired Metabolism

Serum lactate levels and lactate clearance

- Tissue hypoxia and anaerobic metabolism.
- Correlation between serum lactate levels and outcome/survival*
- Duration and degree of hyperlactatemia are important predictors of morbidity and mortality.*
- Admission lactate levels > 2 mmol/L was a significant independent risk factor for mortality in ICU patients**
- Sustained hyperlactatemia predictive of in-hospital mortality**
- Early lactate clearance was associated with improved outcomes

*Randomized controlled trial. Am J Respir Crit Care Med. 2010 Sep 15;182(6):752-61
*A systematic review. Scand J Trauma Resusc Emerg Med. 2011 Dec 28;19:74.
*Ann Emerg Med. 2005 May;45(5):524-8.
**Crit Care. 2009;13(3):R90

Markers Of Innate Immune Response

CD64

- Relatively stable after blood collection
- It's expression is measured by flow cytometry.
- Overexpression in blood monocytes and neutrophils in septic patients associated with leukocyte dysfunction

- In a recent meta-analysis *
  - expression on PMNs appeared to be a useful diagnostic parameter of bacterial infections (sens 79% - spec 91%)

*A systematic review and meta-analysis. J Infect. 2010;60(5):313-9.

Markers Of Innate Immune Response

CD64

- CD64 index of ≤ 1.19 predictive of - blood culture *
- CD64 index of ≥ 1.19 predictive of clinical and/or culture diagnosis of infection (sens 94.6% and spec 88.7%)*
- CD64 indices changes in response to antibiotic therapy*
- CD64 were increased in patients with sepsis compared to levels in healthy controls; distinguished between survivors and nonsurvivors at 28 days**

*J Clin Microbiol. 2009 Dec;47(12):3914-9.
**Sepsis biomarkers: a review. Crit Care. 2010;14(1):R15.

Markers Of Innate Immune Response

Triggering receptor expressed on myeloid cell 1 (TREM-1)

- Expressed on the surface of PMNL
- Involved in the signaling of the inflammatory response during infection.
- Correlates with severity of sepsis

Markers Of Innate Immune Response

sTREM-1 (soluble counterpart of TREM-1)

- Can differentiate SIRS, sepsis, severe sepsis, and septic shock (better then PCT and CRP)*
- Higher plasma levels in nonsurvivors vs survivors at the time of admission and before early goal-directed therapy**
- Plasma levels remained significantly higher until death in nonsurvivors vs survivors and predicting mortality better than PCT and CRP**

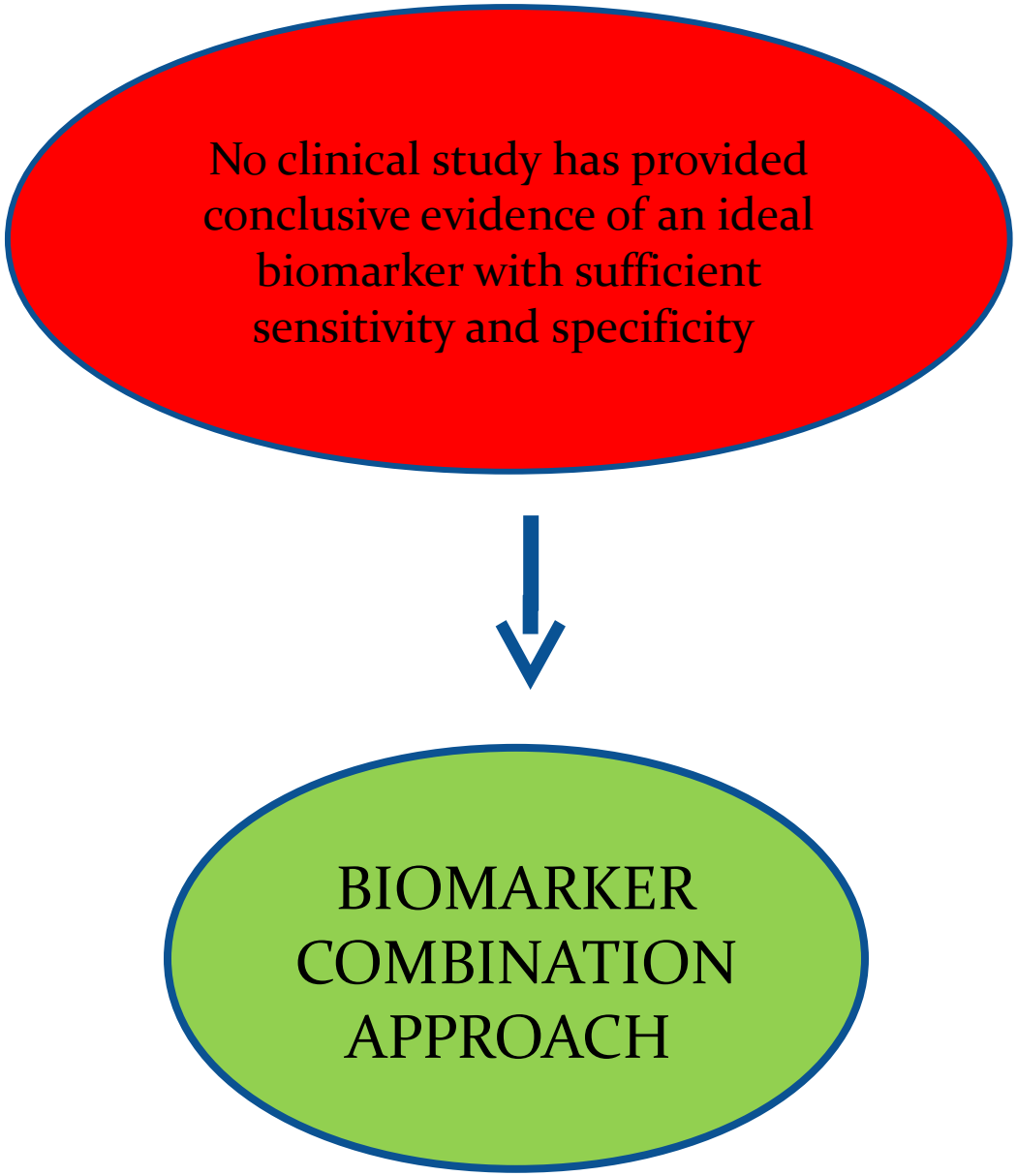
*Ann Intern Med. 2004 Jul 6;141(1):9-15.
**Shock. 2012 Jun;37(6):574-8.

Markers Of Innate Immune Response

sTREM-1

- Not specific for infection
- Recent meta-analysis including 11 studies showed that plasma sTREM-1 not sufficient in differentiating sepsis from SIRS*
- The clinical application of sTREM-1 as a diagnostic and prognostic marker still requires larger studies for further elucidation**

*Crit Care. 2012 Nov 29;16(6):R229.
**Am J Med Sci. 2013 Mar;345(3):178-84.


No clinical study has provided conclusive evidence of an ideal biomarker with sufficient sensitivity and specificity
BIOMARKER COMBINATION APPROACH

Biomarker Combination Approach

Prospective study*

- Bioscore using three biomarkers

CD64 index | PCT | sTREM-1

- Bioscore demonstrated a higher performance in diagnosing sepsis in the critically ill patients.
- The probability of sepsis
  - 3.8% for a bioscore of 0 (all three markers --)
  - $\frac{1}{28}$100% for a bioscore of 3 (all three markers above threshold)

*Am J Respir Crit Care Med. 2012;186(1):65-71.

Biomarker Combination Approach

The combination of several biomarkers

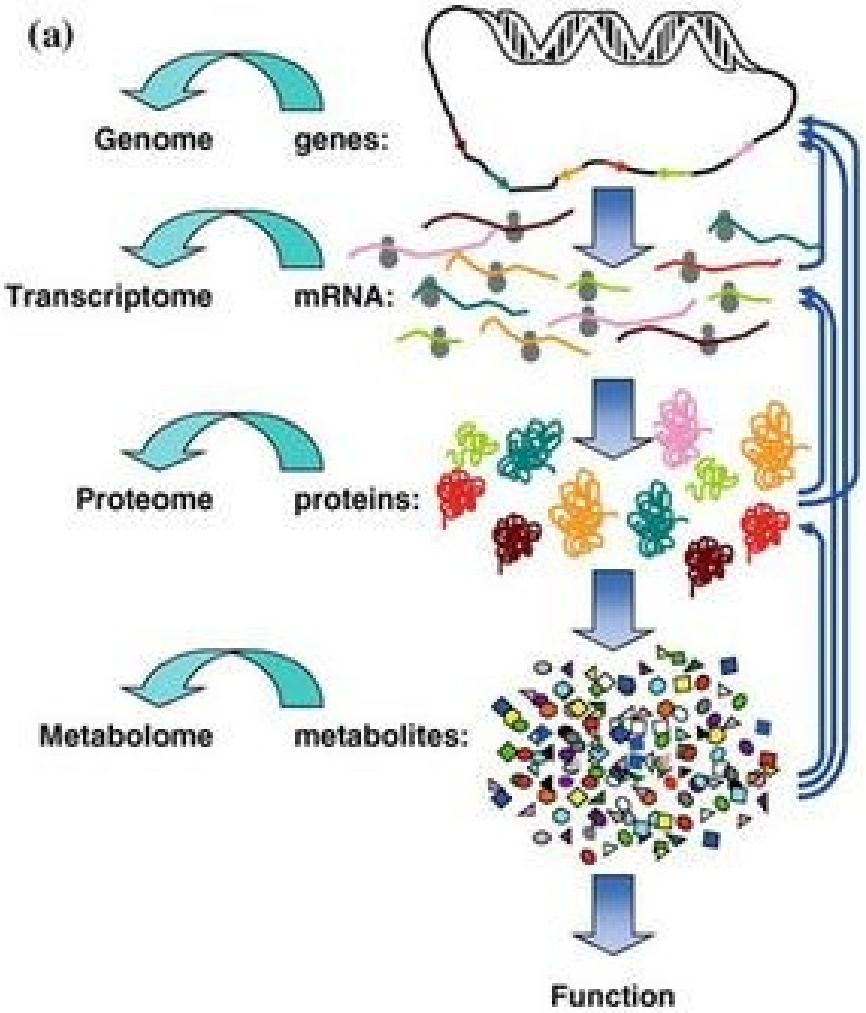
- Holds some promise to increase sensitivity and specificity

- Clinical utility and cost-effectiveness ???

Discovery Of Novel Candidates with The "Omic" Approach

High-throughput

Transcriptomics,



bolomics

Discovery Of Novel Candidates With The "Omic" Approach

- Example of biomarker discovery through genome-wide analysis of gene expression is the identification of IL-8 as a stratification biomarker in pediatric septic shock*
- Serum levels of the IL-8 protein >220 pg/mL
  - Predicting mortality at 28 days; sensitivity and specificity 75% negative predictive value of 95%.
  - A validation study further confirmed the predictive value of IL-8 for mortality
  - Prospective studies did not confirm the ability of IL-8 to serve as a stratification biomarker in sepsis**

*Am J Respir Crit Care Med. 2008;178(3):276-82.
**Crit Care Med. 2010;38(6):1436-41.

Discovery Of Novel Candidates with The "Omic" Approach

- Quantitative PCR (qPCR) and Liquid chromatography-tandem mass spectrometry (LC-MS/MS)
- Application of these technologies is not easily translatable into clinical routine analysis,
- Requires laboratory-based assays,
- Expensive and time-consuming.

CONCLUSIONS

- Many advances have been made in the identification
- Substantial discovery still remains to be made
- New high-throughput methodologies hold the promise
- Extensive clinical validation of these novel biomarkers

CONCLUSIONS

searching for reliable markers

WE HAVE A LONG WAY TO GO

Pathophysiologic Mechanisms of Sepsis

NOVEL TREATMENT STRATEGIES

DO THEY REALLY GUIDE US?

THANK YOU FOR YOUR ATTENTION