EXPLORE Healthcare Summit
Sepsis: Can We Finally Just Relax on the SOFA?
Mark Keuchel, D.O.

Background:

1. Sepsis is a wide-spectrum disease process that remains poorly understood
2. Early-goal directed therapy was the initial ground-breaking protocol that sought to improve morbidity and mortality in sepsis patients.
3. Subsequent studies have found that multiple parts of the early goal-directed protocol do not improve septic patients when held to rigid criteria. However, these studies have provided a guiding light to present-day therapies.

Where did it all begin?

Early Goal-Directed Therapy in the Treatment of Severe Sepsis and Septic Shock

- ***Idea Behind Study:*** The initial thought of goal-directed therapy came from a few ICU studies. The authors felt that previous studies enrolling patients for up to 72 hours showed no benefit because time to treatment was an important factor.
- ***Question:*** Does an early-goal directed therapy work prior to admission to an ICU?
- ***Bottom Line:*** An early goal-directed therapy compared with standard care at the time showed an improvement in mortality for septic shock.
- ***What They Believed:***
  - The authors believed that sepsis depleted oxygen supply and that balancing oxygen demand by maximizing preload, after load, and contractility would improved patient outcomes in septic shock.
  - They specifically state they believed vital signs, CVP, physical findings, and urinary output failed to recognize tissue hypoxia.
  - A goal-directed study to optimize ScvO2, arterial lactate, base deficit, and pH.
- ***What They Did:***
  - Three year study at one academic medical center
  - 236 patients completed the protocols
  - Inclusion: Two of four SIRS criteria, SBP <90mmHg after a 20mL/kg fluid bolus, and/or lactate level of 4 or greater
  - **Standard Therapy**
    - Inserted arterial and central venous catheters (not connected to ScvO2)
    - Inpatient admission ASAP
    - Blood and Urine cultures
    - Antibiotics ordered at physician discretion (not required in ED)
  - **Early Goal-Directed Therapy**
    - Inserted arterial and central venous catheters
    - Patients kept in ED for 6 hour duration
    - 500mL NS bolus q 30 minutes until CVP 8-12mmHg
    - MAP >65 - added vasopressors
    - MAP <90 - added venodilators
    - ScvO2 <70 - transfusion to a hematocrit of >30%
    - Normal hematocrit and low ScvO2? —> Dobutamine then intubation

- **Both Groups**
  - HR, BP, Temp, Urine output, CVP continuously monitored for 6 hours
  - Arterial and Venous blood gases
  - Lactic Acid
  - SAPS II, APACHE II, MODS scores for 72 hours
  - Patients followed for 60 days
- **What They Found:**
  - Improved mortality rate in septic shock patients (56.8% in standard vs 42.3% in EGDT) - no statistically significant difference in severe sepsis
  - Similar lactate concentrations and pH
  - No statistical difference in vasopressor use, mechanical ventilation, fluids administered, or ionotropes

Critical Point #1 - Emmanuel Rivers trial on early goal-directed therapy, although not the first, became the foundation for sepsis management and the basis on which further studies would be focused.

Greater New York Hospital Association - STOP Sepsis Collaborative

- ***Idea Behind:*** A joint venture of 57 hospitals in NYC to decrease mortality and provide unified guidelines for sepsis resuscitation
- ***What They Did:***
  - Developed evidence based guidelines for sepsis resuscitation
  - Published their guidelines
- ***Recommendations:***
  - Early screening in triage (even consider point of care lactate)
  - Early goal-directed therapy
  - Introduced a “non-invasive” pathway
  - CVP and ScvO2 were not goals
  - Time to antibiotics are important
  - Fluid response should be guided by bedside ultrasound (either echocardiography or IVC measurement)
  - Norepinephrine should be first-line vasopressor
- ***What They Found:***
  - They had an absolute risk reduction of 22% when following their guidelines

* At the same time, the National Quality Foundation was developing their guidelines *
  - Included are central lines for all patients, CVP and ScvO2 monitoring
  - These are typically adopted by CMS and The Joint Commission

Lactate in Sepsis

Lactate Clearance vs Central Venous Oxygenation Saturation as Goals of Early Sepsis Therapy: A Randomized Clinical Trial

- ***Idea Behind Study:*** Implementation of protocoled sepsis therapy has been hindered by invasive monitoring strategies. Furthermore, controversy existed in the medical community about measurement of tissue oxygen delivery
- ***Question:*** Are trending serial lactate measurements non-inferior to monitoring ScvO2 in severe sepsis and septic shock patients?
- ***Bottom Line:*** Targeting a goal of lactate clearance of 10% in 2 hours was non-inferior to monitoring ScvO2.
- ***What They Did:***
  - Prospective, Randomized, Parallel, Non-blinded, Non-inferior clinical trial
  - 3 Urban emergency departments
  - Patients defined as severe sepsis and septic shock
  - Primary outcome - absolute in-hospital mortality
  - **Both Groups -** structured quantitative resuscitation for 6 hours (EGDT)
  - **ScvO2 Group -** achieved CVP, MAP, and ScvO2 goals (>70%)
  - **Lactate Group -** achieve CVP, MAP, and Lactate goals (decrease by 10% in 2 hrs)
- ***What They Found:***
  - Of 300 total patients in the study, there was no difference in treatment (and in a subgroup analysis, a trend towards better outcomes in the lactate group)
    - In hospital mortality - lactate group 17%, ScvO2 group 23%
  - Only 10% required transfusions or ionotropes (significantly less than Rivers trial)
  - Overall mortality rate (20%) was significantly different than Rivers (37%)

Lactate Clearance As A Target of Therapy In Sepsis: A Flawed Paradigm

- ***Idea Behind Review:*** Lactate measurement and clearance are widely used as a marker of disease severity and resuscitation efforts
- ***What They Did:*** Review lactate articles and apply pathophysiological evaluation to determine relevancy of lactate measurements
- ***What They Found:*** Lactate was more a marker of physiologic stress and less a marker of oxygen depletion. Lactate was associated with more critically ill patients

Whole Blood Lactate Kinetics in Patients Undergoing Quantitative Resuscitation for Severe Sepsis and Septic Shock

- ***Question:*** Does lactate clearance predict mortality?
- ***Bottom Line:*** A lactate clearance of ≥ 10% was not a significant predictor of mortality
- ***What They Did:***
  - Compared lactate kinetics with survival in patients with septic shock
  - Looking for factors that appeared to perform well
  - Preplanned analysis of Jones cohort

- Calculated - relative lactate clearance, rate of lactate clearance, occurrence of early lactate normalization
- ***What They Found:***
  - 187 patients total
  - Overall survival was 76.5%
  - AUC to predict survival based on initial lactate was 0.64
  - AUC to predict survival based on lactate clearance was 0.58

** There are two main ways lactate is used in septic patients **

1) Risk stratifying patients based on initial lactate (screening occult sepsis)
   - Shapiro et al (2005) found AOC of lactate to predict mortality was 0.67
   - Even lactate as low as 2.5mmol/L had a sensitivity of 59% and specificity of 71%
   - Using Surviving Sepsis guideline of 4mmol/L - sensitivity drops to 36%
2) Guiding resuscitation of septic patients with serial lactates
   - Nguyen et al determined in 2004 study that lactate clearance of 10% was best predictor of mortality with a sensitivity of 44.7% and specificity of 84.4% and the overall accuracy of lactate was 67.7%
   - Lactate/Scvo2 was only used in Rivers and Jones trials to determine transfusions and dobutamine (which are both interventions rarely performed in today's management of septic patients)

Critical Point #2 - Although there is a correlation of increased lactate levels with morbidity and mortality, the literature does not support its use to guide clinical resuscitation

Central Venous Pressure (CVP)

Does Central Venous Pressure Predict Fluid Responsiveness? A Systemic Review of the Literature and the Tale of Seven Mares

- ***Idea Behind Study:*** CVP is routinely used as an endpoint for fluid resuscitation and this analysis was to identify articles relating CVP to volume status and response
- ***Question:*** Is CVP a marker for either circulating volume status or fluid responsiveness?
- ***Bottom Line:*** There is no association between CVP and circulating fluid volume and CVP does not predict fluid response
- ***What They Did:***
  - Included 24 studies (5 comparing CVP to volume status and 19 comparing CVP and fluid response)
  - Studies ranged from 1966 to 2007
- ***What They Found:***
  - The correlation coefficient of CVP and blood volume was 0.16 (0.00 being no relationship at all and +1.0 being a very strong relationship)

- The correlation coefficient of delta-CVP and fluid response was 0.11
- There were no studies that were able to predict CVP to either variable
- As early as 1971, studies were suggesting limited value of CVP

Does the Central Venous Pressure Predict Fluid Responsiveness? An Updated Meta-Analysis and a Plea for Some Common Sense

- ***Idea Behind Analysis:*** CVP continued to be recommended as a tool to guide fluid management in septic patients
- ***Aim:*** To perform an updated meta-analysis of recent studies regarding CVP in fluid responsiveness
- ***Bottom Line:*** There is no data to support the widespread practice of using central venous pressure to guide fluid therapy
- ***What They Did:***
  - Included 43 studies in the meta-analysis
  - Involved studies which included correlation coefficient or AUC between CVP and change in cardiac performance
- ***What They Found:***
  - AUC was 0.56
  - Summery correlation coefficient between baseline CVP and change in stroke volume was 0.18

Critical Point #3 - Central Venous Pressure (CVP) does not correlate with circulating blood volume or fluid responsiveness and should not be used to guide resuscitation of septic patients.

Red Blood Cell Transfusions

Is A Low Transfusion Threshold Safe In Critically Ill Patients With Cardiovascular Disease?

- ***Idea Behind Study:*** Critically ill patients often receive red blood cell transfusions but further studies are needed to understand the possible risks and benefits on treating anemia in patients with cardiovascular disease
- ***Question:*** To compare a restrictive red blood cell transfusion strategy with a more liberal strategy in volume resuscitated critically ill patients with cardiovascular disease
- ***Bottom Line:*** A restrictive red blood cell transfusion strategy generally appears to be safe in most critically ill patients with cardiovascular disease
- ***What They Did:***
  - Twenty-two academic and three community critical care units across Canada involving 357 patients
  - Randomized controlled trial
  - Restrictive arm - allogenic red blood cell transfusions at hemoglobin concentration of 7g/dL

    - Liberal arm - allogenic red blood cell transfusions at hemoglobin concentration of 10g/dL
- ***What They Found:***
    - Similar mortality rates in-hospital and at 30 and 60 days.
    - No statistically difference in all survival measures

Blood Transfusion Practices in Sepsis

- ***Idea Behind Review:*** There is a significant amount of confusion regarding transfusion strategies in patients with sepsis
- ***Aim:*** Review literature addressing transfusion practices
- ***Bottom Line:*** A restrictive transfusion strategy appears safe and changing guidelines support a more restrictive strategy
- ***Recommendations:*** There are several complications with transfusion including infection, transfusion related acute lung injury (TRALI), transfusion associated circuitry overload (TACO) and increased mortality. Several studies have a shown a restrictive strategy to have similar outcomes compared to a higher threshold.

Lower versus Higher Hemoglobin Threshold for Transfusion in Septic Shock - TRISS

- ***Idea Behind Study:*** Blood transfusion are frequently given to patients with septic shock but many patients are not actively bleeding
- ***Question:*** What are the effects on mortality of leuko-reduced blood transfusion at a lower versus a higher hemoglobin threshold among patients with septic shock who are in the intensive care unit?
- **Bottom Line:** A lower transfusion strategy appears safe and as compared to higher transfusion threshold in patients with septic shock
- ***What They Did:***
    - 32 ICUs involving 998 patients
    - Randomized trial
    - Lower hemoglobin threshold - <7g/dL
    - Higher hemoglobin threshold - <9g/dL
    - Reassess hemoglobin within 3 hours post transfusion
    - Intervention period was entire ICU stay to a maximum of 90 days
- ***What They Found:***
    - 1545 transfusion given in lower threshold group
    - 3088 transfusions given in higher threshold group
    - 176 (36.1%) patients in lower transfusion group never received a transfusion
    - 6 (1.2%) of patients in the higher transfusion group never received a transfusion
    - 43% (lower threshold) versus 45% (higher threshold) patients in the died by 90d
    - No difference in mortality at 90 days, life support measures, number of days alive or number of days out of the hospital

Critical Point #4 - A restrictive transfusion strategy (<7g/dL), in the absence of active bleeding or ischemia, is recommended in lieu of a more liberal strategy.

Vasopressors

Background

1) Initially norepinephrine was believed to cause more adverse outcomes and was avoided
2) A 2004 Cochran review could not determine if norepinephrine or dopamine was first-line vasopressors
3) Both were included in the initial Surviving Sepsis Guidelines

Comparison of Dopamine and Norepinephrine in the Treatment of Shock - SOAP II

- ***Idea Behind Study:*** Guidelines recommended either norepinephrine or dopamine as a first-line vasopressors in septic shock but other studies have shown more adverse outcomes in dopamine
- ***Question:*** Is norepinephrine the drug of choice over dopamine as first-line vasopressors to reduce rate of death among patients in shock?
- ***Bottom Line:*** Norepinephrine had similar rates of death but significantly lower rate of adverse events compared to dopamine and should be used as first-line agent in shock
- ***What They Did:***
  - 8 hospital involving 1679 patients
  - Primary endpoint - death at 28 days with second endpoint being adverse events
  - Randomly assigned to norepinephrine or dopamine groups
  - In patients with persistent hypotension, open-label norepinephrine was used
- ***What They Found:***
  - No difference in mortality (52.5% dopamine versus 48.5% norepinephrine)
  - More adverse events in dopamine (24.1%) versus norepinephrine (12.4%)
  - More patients in the dopamine group had persistent hypotension and required open-label norepinephrine (26% versus 20%).

Dopamine Versus Norepinephrine In Treatment of Septic Shock: A Meta-Analysis

- ***Idea Behind Review:*** Provide an updated meta-analysis of the current literature comparing norepinephrine versus dopamine for shock
- ***What They Did:***
  - Included 11 studies involving 2768 patients comparing norepinephrine to dopamine in shock
- ***Bottom Line:***
  - Dopamine was associated with an increased risk of death compared to norepinephrine ($p<0.01$)
  - Dopamine had increased risk of arrhythmias ($p=0.001$)
- ***Recommendation:*** Norepinephrine should be used as the first-line vasopressor in shock as it is associated with decreased adverse events when compared to dopamine

Critical Point #5 - Norepinephrine is the first-line vasopressors in septic shock

Antibiotic Administration

Duration of Hypotension Before Initiation of Effective Antimicrobial Therapy is the Critical Determinant of Survival in Human Septic Shock*

- ***Idea Behind Study:*** To determine the impact on mortality of delays in initiation of antibiotics in septic shock patients
- ***Question:*** Does time to antibiotics influence mortality in septic shock patients?
- ***Bottom Line:*** Effective antimicrobial administration within the first hour of documented hypotension was associated with increased survival to hospital discharge in septic shock patients
- ***What They Did:***
  - Retrospective Cohort Study between 1989 and 2004
  - 14 ICUs and 10 hospitals in USA and Canada involving 2731 patients
  - Primary outcome - survival to hospital discharge
- ***What They Found:***
  - Administration of antimicrobial within the first hour of documented hypotension was associated with survival rate of 79.9%.
  - Each hour of delay in antimicrobial administration over the ensuing 6 hours was associated with an average decrease in survival of 7.6%.
  - 50% of septic shock patients received antimicrobial therapy within the first 6 hours of documented hypotension

The Impact of Timing of Antibiotics on Outcomes in Severe Sepsis and Septic Shock: A Systematic Review and Meta-Analysis

- ***Idea Behind Study:*** Review the literature to determine an association between timing of antibiotic administration and mortality in severe sepsis and septic shock
- ***Question:*** Does time to administration of antibiotics improved outcomes?
- ***Bottom Line:*** There is no significant mortality benefit of administering antibiotics within 3 hours of emergency department triage or within 1 hour of shock recognition in severe sepsis or septic shock. Timing metrics are not supported by the available evidence.
- ***What They Did:***
  - Meta-analyze the available data on association between timing of antibiotics and mortality including 11 publications involving 16,178 patients
  - Included adult patients with severe sepsis and septic shock, reported time to antibiotics, and mortality
  - Antibiotic timing defined as
    - <3 hours versus >3 hours from triage
    - <1 hour versus >1 hour from shock/severe sepsis recognition
  - Performed sensitivity analysis of the effect of time to antibiotics from severe sepsis and septic shock recognition in hourly increment
- ***What They Found:***
  - In the <3 hour group (10,208 patients), they had 2574 die (25.2%)
  - In the >3 hour group (5,970 patients), they had 1,793 die (30.0%)
  - Pooled Odds Ratio was 1.16 (95% CI, 0.92-1.46; p=0.21)

Critical Point #6 - Administration of effect broad-spectrum antibiotics should not be delayed once recognition of severe sepsis and/or septic shock occur; however, the literature does not support time-to-antibiotics as a quality care metric

Intravenous Fluid Resuscitation

Comparison of Two Fluid-Management Strategies in Acute Lung Injury (FACCT Trial)

- ***Idea Behind Study:*** Optimal fluid management in patients with acute lung injury is unknown
- ***Question:*** Does diuresis or fluid restriction improve lung function and mortality?
- ***Bottom Line:*** There was no difference in 60-day mortality but conservative fluid management improved lung function and shorted the duration of mechanical ventilation
- ***What They Did:***
  - Randomized study
  - Primary end-point was 60-day mortality
  - Compared a conservative versus a liberal fluid strategy
- ***What They Found:***
  - Improved outcomes with conservative fluid strategy although mortality had no statistical difference
  - Average 7-day fluid balance was -136mL in conservative group while it was +6226mL in liberal strategy

Mortality After Fluid Bolus in African Children with Severe Infection - FEAST Trial

- ***Idea Behind Study:*** Fluid resuscitation literature is limited, especially in children
- ***Question:*** Does fluid bolus or albumin improved outcomes in children with severe infection compared to no bolus?
- ***Bottom Line:*** Fluid boluses significantly increased 48-hour mortality in critically ill children with impaired profusion
- ***What They Did:***
  - Primary endpoint was 48-hour mortality
  - Randomly assigned children with severe febrile illness to receive one of the following at the time of admission:
    - 20-40mL/kg of 5% albumin solution
    - 20-40mL/kg 0.9% saline solution
    - No fluid bolus
  - All received antimicrobial therapy, maintenance fluids, and supportive care
- ***What They Found:***
  - Data and safety monitoring committee recommended halting recruitment after 48-hour mortality was higher in fluid/albumin bolus groups versus no fluid bolus
    - Albumin mortality - 10.6%
    - 0.9% NS mortality - 10.5%
    - No bolus mortality - 7.3%
  - 4-week mortality was also higher in the fluid bolus versus no bolus groups

Restricting Volumes of Resuscitation Fluid in Adults with Septic Shock After Initial Management: the CLASSIC randomized, parallel group, multi center feasibility trial

- ***Idea Behind Study:*** There are many protocols for fluid resuscitation but minimal evidence for support
- ***Question:*** Does a protocol restricting resuscitation fluid versus a standard care protocol after initial resuscitation in ICU patients with septic shock improve outcomes?
- ***Bottom Line:*** There was a trend toward better patient-centered outcomes in all categories with fluid restriction strategy
- ***What They Did:***
  - Randomized 151 adults with septic shock in the ICU
  - Fluid restriction group received fluid boluses only if signs of severe hypo perfusion occurred
  - Standard care group fluid boluses were permitted as long as circulation improved
- ***What They Found:***
  - Resuscitation fluid volumes at day 5 and during ICU stay were lower in the fluid restriction group than standard care by 1.2 liters and 1.4 liters respectively
  - There were no statistical differences in fluid balances or serious adverse events

Critical Point #7 - Intravenous fluids should not be accepted as a benign therapy. Strict protocols mandating specific volume for all patients are not supported by the evidence.

A Randomized Trial of Protocol-Based Care for Early Septic Shock - ProCESS Trial

- ***Idea Behind Study:*** Protocol based resuscitation of septic patients had been adopted as the standard for treatment but many aspects of care remain in question
- ***Question:*** Are all aspects of the early goal-directed therapy required?
- ***Bottom Line:*** Protocol-based resuscitation of patients in whom septic shock was diagnosed did not improve outcomes
- ***What They Did:***
  - 31 hospitals involving 1341 patients
  - Patients placed into one of three groups
    - Early goal-directed therapy
    - Protocol based therapy without central lines, ionotropes, or transfusion
    - Usual Care
  - Primary endpoint was 60-day in-hospital mortality
  - Tested EDGT against usual care and EGDT against protocol base therapy
- ***What They Found:***
  - Primary endpoint - 60-day in-hospital mortality
    - EGDT - 92 (21%)
    - Protocol based therapy - 81 (18.2%)
    - Usual Care - 86 (18.9%)

Goal-Directed Resuscitation for Patients with Early Septic Shock - ARISE Trial

- ***Idea Behind Study:*** The effectiveness of early goal-directed therapy remains uncertain
- ***Question:*** Does aggressive EGDT versus usual care improved outcomes?
- ***Bottom Line:*** Early goal-directed therapy did not reduce all-cause mortality at 90 days
- ***What They Did:***
  - 51 hospitals involving 1600 patients
  - Primary outcome was 90 day all-cause mortality
- ***What They Found:***
  - Primary endpoint - 90 day mortality
    - EGDT - 147 (18.6%)
    - Usual Care - 150 (18.8%)
  - No significant difference in survival time, in-hospital mortality, duration of organ support, or length of hospital stay
  - Patients in EGDT received increased fluid volumes, vasopressor support, transfusions, and dobutamine

Trial of Early, Goal-Directed Resuscitation for Septic Shock - ProMISe Trial

- ***Idea Behind Study:*** International guidelines recommend early goal-directed therapy but its effectiveness remains uncertain and adoption of protocols remains limited
- ***Question:*** Does early goal-directed therapy protocol lead to improved outcomes?
- ***Bottom Line:*** In patients with septic shock, a strict early goal-directed therapy protocol did not lead to an improvement in outcome.
- ***What They Did:***
  - Randomized Trial with integrated cost-effectiveness analysis
  - 56 hospitals involving 1260 patients
  - Early Goal-Directed Therapy versus Usual Care
  - Primary outcome - all cause mortality at 90 days
- ***What They Found:***
  - Primary outcome - all cause mortality at 90 days
    - EGDT - 184 (29.5%)
    - Usual Care - 181 (29.2%)
  - Increased utilization of resources without improvement in outcome
    - EGDT had increased use of intravenous fluids, vasoactive drugs, transfusions, and longer stays in the intensive care unit

Early, Goal-Directed Therapy for Septic Shock - A Patient Level Meta-Analysis

- **Idea Behind Analysis:** Multiple trials have shown no benefits from the single-center EGDT trial. This meta-analysis was designed to prospectively to improve statistical power.
- **Bottom Line:** Early goal-directed therapy did not improve outcomes, even in the sickest cohort of patients, and increased hospitalization costs
- **What They Did:**

    - Synchronized entry criteria, intervention protocols, outcomes measures, and data collection across the trials
    - Primary outcome was 90-day mortality
    - Secondary outcomes of 1-year survival, organ support, and hospitalization costs
    - 3723 patients at 138 hospitals
- **What They Found:**
    - Similar mortality at 90 days EGDT (24.9%) and usual care (25.4%).
    - Subgroup analysis showed no benefit of EGDT for patients with worse shock

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

- ***Idea Behind Consensus:*** The definitions of sepsis and septic shock had not been revised since 2001 and considerable changes in sepsis understanding have occurred requiring an updated definition
- ***Objective:*** "To evaluate and, as needed, update definitions for sepsis and septic shock."
- ***Bottom Line:*** Updated definition should include only two categories (sepsis and septic shock) and should be defined as a rise in SOFA score by ≥2 points. Furthermore, a new bedside clinical term qSOFA can be used as a triage tool.
- ***What They Did:***
    - Convened a task force involving the Society of Critical Care Medicine and the European Society of Intensive Care Medicine
    - Reviewed articles and had thorough discussion with endorsements
- ***Recommendations:***
    - Sepsis is a life threatening organ dysfunction caused by a dysregulated host response to infection.
    - Defined as an increase in the SOFA score of 2 points or more
    - Septic Shock - vasopressor requirement to maintain MAP of 65mmHg or greater and serum lactate level greater than 2mmol/L in absence of hypovolemia
    - Rapidly identify patients with qSOFA score (H.A.T. mnemonic)
        - Hypotension - SBP < 100mgHg
        - Altered Mental Status
        - Tachypnea - respiratory rate of 22/min or greater

Prognostic Accuracy of Sepsis-3 Criteria for In-Hospital Mortality Among Patients with Suspected Infection Presenting to the Emergency Department

- **Idea Behind Study:** The definition of sepsis has changed to include the qSOFA score but prognostic value is uncertain
- **Bottom Line:** The use of qSOFA in emergency department patients with suspected infection had greater prognostic accuracy for in-hospital mortality than did SIRS.
- **What They Did:**
    - International prospective cohort study
    - 30 emergency departments including 879 patients
    - 4-week period consecutively enrolling patients with suspected infection
- **What They Found:**
    - Overall in-hospital mortality of 8%
    - qSOFA score <2 - 3% mortality

- qSOFA score ≥ 2 - 24%
- AUROC of 0.80 compared to 0.65 for SIRS
- Hazard ratio of qSOFA for death was 6.2 compared to 3.5 for severe sepsis

Critical Point #8 - qSOFA and SOFA scores are not screening tools for sepsis, they are predictors of mortality in patients with suspected infection.

Where Are We Now in Sepsis Care?

1. **Early Recognition** - SIRS vs qSOFA vs Clinical Gestalt?
2. **Fluid Administration** - an exact dose cannot be universally recognized for all patients. There are techniques such as passive leg raise and bedside cardiac echocardiography that can help assist the clinician about fluid responsiveness
3. **Antibiotics** - appropriately chosen to treat the most common pathogen for the affect organ system. Broad spectrum may have early benefit in undifferentiated patients but must be weaned quickly
4. **Vasopressors** - early use of vasopressors (especially norepinephrine) with MAPs <65mmHg as many septic patients are vasoplegic and not volume deplete

Predicting Fluid Responsiveness by Passive Leg Raising: A Systematic Review and Meta-Analysis of 23 Clinical Trials

- ***Idea Behind Review:*** To review the literature describing passive leg raising to increase venous return allowing for the prediction of fluid responsiveness
- ***Bottom Line:*** "Passive leg raising retains a high diagnostic performance in various clinical settings and patient groups."
- ***What They Did:***
  - Reviewed 23 studies with 1,013 patients
  - Included patients spontaneously breathing and on mechanical ventilation
- ***What They Found:***
  - Specificity of 92% and summery AUROC 0.95.
  - Mode of ventilation, type of fluid, measurement technique did not affect diagnostic performance

Safety of Peripheral Intravenous Administration of Vasoactive Medication

- ***Idea Behind Study:*** Central venous access is not a benign procedure and some patients only need a brief period of vasoactive medications
- ***Question:*** Is the administration of vasoactive medications through peripheral venous access safe?
- ***Bottom Line:*** Administration of norepinephrine, dopamine, or phenylephrine by peripheral intravenous access was feasible and safe
- ***What They Did:***
  - 20-month study at single center involving 734 patients

- Monitored used of norepinephrine, dopamine, and phenylephrine from a peripheral intravenous line
- ***What They Found:***
  - Extravasation of vasoactive medication occurred in 2% without any tissue injury
  - 13% of patients required insertion of central intravenous access

Critical Point #9 - Early goal-directed therapy, although shown beneficial in one small single-center study, is not supported by subsequent larger randomized trials and should be abandoned as the standard which guidelines as based

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