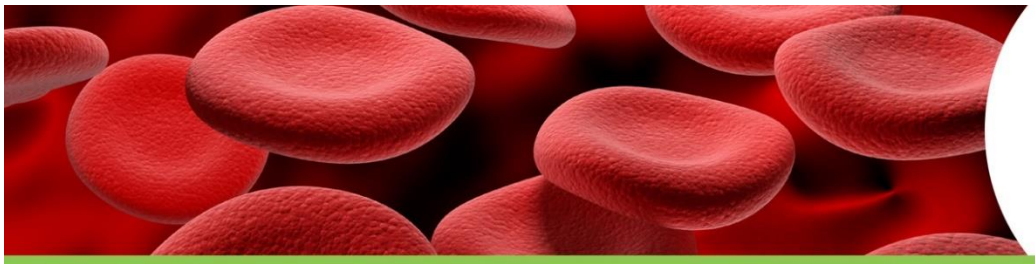

CHA SEPSIS

Pillars of Sepsis Research

2020 – Guidelines for the Management of Septic Shock and Sepsis-Associated Organ Dysfunction in Children

- Weiss, S. L., Peters, M. J., Alhazzani, W., Agus, M.S. Flori, H. R., Inwald, D. P., … & Tissieres, P. (2020). Guidelines for the Management of Septic Shock and Sepsis-Associated Organ Dysfunction in Children. *Pediatric Critical Care Medicine*, 21(2), e52-2106. https://doi.org/10.1097/PCC.0000000000002198
- First-ever guidelines for pediatric sepsis
- Provides 77 statements on the management and resuscitation of children with septic shock and other sepsis-associated organ dysfunction.

2017 – Early, Goal-Directed Therapy for Septic Shock – A Patient-Level Meta-Analysis

- Prism Investigators. (2017). Early, Goal-Directed Therapy for Septic Shock – A Patient-Level Meta-Analysis. *New England Journal of Medicine, 376*, 2223-2234. https://doi.org/10.1056/NEJMoa1701380
- Note: Prior to randomization > 92 percent of patients were identified early and provided the three-hour bundle (including 2L of fluid and antibiotics given within 70 minutes of presentation to emergency department).
- Conclusions: In this meta-analysis of individual patient data, early, goal-directed therapy did not result in better outcomes than usual care and was associated with higher hospitalization costs across a broad range of patient and hospital characteristics. Authors stated: "it remains possible that general advances in the provision of care for sepsis and septic shock, to the benefit of all patients, explain part or all of the difference in findings between the trial by Rivers et al. and the more recent trials."

2016 – The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

- Singer, M., Deutschman, C. S., Seymour, C. W., Shankar-Hari, M., Annane, D., Bauer, M., ... & Hotchkiss, R. S. (2016). The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA*, *315*(8), 801-810. https://doi.org/10.1001/jama.2016.0287
    - **A Users' Guide to the 2016 Surviving Sepsis Guidelines.** (2017). *Critical Care Medicine*. (2017). https://doi.org/10.1097/CCM.0000000000002257
    - Note: These definitions have not been adopted in the U.S. due to conflicts with Centers for Medicare and Medicaid's (CMS) SEP-1 core measure (and ICD-10s), which is based on original definitions for sepsis, severe sepsis and septic shock (Bone, 1992).

- **Recommendations:** Sepsis should be defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. For clinical operationalization, organ dysfunction can be represented by an increase in the Sequential (sepsis-related) Organ Failure Assessment (SOFA) score of two points or more, which is associated with an in-hospital mortality greater than 10 percent. Septic shock should be defined as a subset of sepsis in which particularly profound circulatory, cellular and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone. Patients with septic shock can be clinically identified by a vasopressor requirement to maintain a mean arterial pressure of 65 mm Hg or greater and serum lactate level greater than 2 mmol/L (> 18 mg/dL) in the absence of hypovolemia. This combination is associated with hospital mortality rates greater than 40 percent. In out-of-hospital, emergency department or general hospital ward settings, adult patients with suspected infection can be rapidly identified as being more likely to have poor outcomes typical of sepsis if they have at least two of the following clinical criteria that together constitute a new bedside clinical score termed quickSOFA (qSOFA): respiratory rate of 22/min or greater, altered mentation or systolic blood pressure of 100 mm Hg or less.

2017 – Time to Treatment and Mortality During Mandated Emergency Care for Sepsis

- Seymour, C. W., Gesten, F., Prescott, H. C., Friedrich, M. E., Iwashyna, T. J., Phillips, G. S., … & Levy, M. M. (2017). *New England Journal of Medicine, 376*, 2235-2244. https://doi.org/10.1056/NEJMoa1703058
    - **Note:** Eighty-two percent of patients had the three-hour bundle completed within three hours. Per interview with Tiffany Osborn (co-author), "for each hour sepsis treatment is delayed, the study found a patient's risk of death increases by four percent."

2001 – Early Goal-Directed Therapy in the Treatment of Severe Sepsis and Septic Shock

- Rivers, E., Nguyen, B., Havstad, S., Ressler, J., Muzzin, A., Knoblich, B., ... & Tomlanovich, M. (2001). Early goal-directed therapy in the treatment of severe sepsis and septic shock. *New England Journal of Medicine, 345*(19), 1368-1377. https://doi.org/10.1056/NEJMoa010307
- **Conclusions:** Early goal-directed therapy provides significant benefits with respect to outcome in patients with severe sepsis and septic shock.

1992 – Definitions for Sepsis and Organ Failure and Guidelines for the Use of Innovative Therapies in Sepsis

- Bone, R. C., Balk, R. A., Cerra, F. B., Dellinger, R. P., Fein, A. M., Knaus, W. A, … & Sibbald, W. J. (1992). Definitions for Sepsis and Organ Failure and Guidelines for the Use of Innovative Therapies in Sepsis. *CHEST, 101*, 1644-1655. https://doi.org/10.1378/chest.101.6.1644
- This study supports the importance of early identification and a three-hour bundle in impacting patient mortality. The definitions in this article were the basis for CMS SEP-1 core measure.

Other key articles:

- **Delay Within the 3-Hour Surviving Sepsis Campaign Guideline on Mortality for Patients with Severe Sepsis and Septic Shock**. (2018). *Critical Care Medicine*. https://doi.org/10.1097/CCM.0000000000002949
- **Increased Time to Initial Antimicrobial Administration is Associated with Progression to Septic Shock in Severe Sepsis Patients.** (2017). *Critical Care Medicine*. https://doi.org/10.1097/CCM.0000000000002262
- **Survival Benefit and Cost Savings from Compliance with a Simplified 3-Hour Sepsis Bundle in a Series of Prospective, Multisite, Observational Cohorts**. (2017). *Critical Care Medicine*. https://doi.org/10.1097/CCM.0000000000002184
- **Changing Definitions of Sepsis.** (2017). *Turkish Journal of Anaesthesiology and Reanimation*. https://doi.org/10.5152/TJAR.2017.93753
- Concerning the following three articles, it should be noted that prior to randomization, patients were identified early and more than 80 percent had received antibiotics and an average of 2,500 mL of fluid and a lactate was drawn. In essence, the three-hour bundle was administered prior to the randomization. There was no statistically significant difference in mortality between the groups.
    - **Protocolised Management in Sepsis (ProMISe):** A Multicentre Randomised Controlled Trial of the Clinical Effectiveness and Cost-Effectiveness of Early, Goal-Directed, Protocolised Resuscitation for Emerging Septic Shock. (2015). *Health Technology Assessment*. https://doi.org/10.3310/hta19970
    - **A Randomized Trial of Protocol-Based Care for Early Septic Shock (ProCESS)**. (2014). *New England Journal of Medicine*. https://doi.org/10.1056/NEJMoa1401602
    - **Goal-Directed Resuscitation for Patients with Early Septic Shock (ARISE)**. (2014). *New England Journal of Medicine.* https://doi.org/10.1056/NEJMoa1404380
- **Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock.** (2006). *Critical Care Medicine*. https://doi.org/10.1097/01.CCM.0000217961.75225.E9