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Biomarkers for Clinical Decision Making in the ICU

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- Three types of biomarkers: Type 0 marks disease course, Type 1 marks the effects of therapy, and Type 2 serve as surrogate endpoints
- Categories include routine bedside data (labs, temperature), profile analysis, and specialty assays (lactate, procalcitonin)
- Utility determined by production, concentration, excretion, filtration, timing, and metabolism of biomarkers
- Goal of many biomarkers may be to group data for favorable/unfavorable outcomes for earlier outcome prediction to guide treatment discussions with patients and families
- Clinical examination (HR, skin mottling) performs just about as well in predicting mortality as SAPS II, APACHE IV, SOFA (Himestra B, et al. 2020) although none of these are precise
- Fluid balance should be both a biomarker and a therapeutic goal
    - Resuscitation, Optimization, Stabilization, Evacuation (ROSE) -each phase has a biomarker/trigger (urine output, lactate, ultrasound) (Ogbu OC, et al. 2015)
    - Fluid overload increases Major Adverse Kidney Events (MAKE = death, renal replacement therapy dependence, decease in GFR by 50% or more from baseline), (Woodward CW, et al. 2019), and mortality, including in patients receiving ECMO (Fong KM, et al. 2019) and those with CKD (Zoccali, et al 2017).
- Other useful biomarkers include procalcitonin for termination of antibiotic therapy (Pepper DJ, 2019) and C-Reactive protein in pancreatitis.
- Syndromes can be used as biomarkers including development of Persistent Inflammation Immune Catabolism Syndrome (PICS) as increasing risk for recurrent infection, long-term survival, and long-term performance status (Gardener AK, et al. 2019)
- Biomarkers may be used in study design to include varying disease phenotypes to those with most potential benefit
- Specialty Assays like thromboelastography (TEGs) can be used to determine clotting competency for personalized blood therapies based on profile/pattern
    - CRASH 2 and 3- tranexamic acid dose not does not benefit those with fibrinolysis shutdown
        - DVT, mortality, and massive transfusion increased in pediatric patients with fibrinolysis shutdown (Lepper CM, 2019). No TXA
- Organism detection via bacterial DNA more sensitive than blood cultures alone, leading to earlier effective antimicrobial treatment
- Acute Kidney Injury (AKI)
    - Goal to capture subclinical injury, which is difficult using oliguria, SCr, impact of plasma volume expansion, POCUS to determine
    - Potential targets:
        - Klotho- antiaging membrane bound protein with deficiency resulting in accelerated aging
            - Increased AKI in patients with decreased Klotho. Combined with levels of fibroblast growth factor 23 (FGF 23) and SCr, these levels and ratios can predict MAKE 90 on arrival (Neyra JA, et al. 2019)
        - TIMP-2*IGFBP7, suPAR- rapid markers
            - Not all commercially available
    - There are AKI phenotypes with different outcomes and responses to therapy, including vasopressors (Bhatraju PK, et al. 2019).
- Artificial Intelligence (AI) and Machine Learning
    - Biomarker goal: One element→ panel of elements →AI/Machine learning (algorithm)
    - AI includes cluster analysis
    - Types of AI include supervised learning (ex. finds patients with sepsis), unsupervised learning (asks algorithm to group), reinforcement learning (determines optimal treatment pathway for specific patient).
- Conclusions
    - Biomarkers are more than lab tests; syndromes can also be used as biomarkers
    - Profiles are more valuable than single values to understand patient trajectory
    - Data to support machine learning is the future

Balanced Crystalloids in the Intensive Care Unit

Ryan M, Brown, MD

Review differences between balanced and non-balanced crystalloids in routine use

- Solutions are differentiated by chloride content
- The term 'buffered solution' comes from the pH buffers in these fluids such as lactate, acetate, and gluconate
    - Do serum levels of these buffers increase with infusion? In healthy patients, there was no associated increase in lactate concentration in patients receiving lactated ringer's solution. There was also no difference in acid/base.

Review evidence supporting balanced crystalloid use in sepsis and other common disorders

- SPLIT: Plasma-Lyte versus saline
    - Double-blind, cluster randomized, double crossover RCT in 4 ICUs
    - Mostly elective cardiac surgery, low APACHE II scores, only 84 patients with sepsis
    - Results: No significant difference in primary outcome of AKI
- SALT-ED: Balanced crystalloids (Lactated Ringer's/Plasma-Lyte) versus saline
    - Prospective, single-center, single-ICU, cluster randomized, multiple crossover trial in patients presenting to ED and admitted outside of an ICU
    - Results: No significant difference between groups on death, new RRT, or AKI
- SMART: Balanced crystalloids versus saline
    - Pragmatic, cluster-randomized, multiple crossover trial conducted in 5 ICUs at single-center
    - Results: The use of balanced crystalloids resulted in significantly lower rate of composite outcome of death, new RRT, or persistent renal dysfunction (NNT 94)
- Data for balanced crystalloids in sepsis (unpublished data from SMART study)
    - Sepsis subgroup (n = 1,640) from SMART study found difference in mortality: reduced in-hospital 30-day mortality compared to saline, NNT 20, AAR = 4.9%, p 0.01, adjusted OR 0.74
    - In sepsis, balanced crystalloids may reduce lactate levels and vasopressor requirements vs saline
- Data for balanced crystalloids in other populations:
    - Surgery: Balanced crystalloids reduced administration of vasopressors, sodium bicarbonate, and blood products among patients undergoing surgery compared to saline – is there a hemodynamic effect of these fluids that contributes to outcomes? (Waters JH, et al 2001; Pfortmueller CA, et al 2017)
    - DKA: Balanced crystalloids lead to faster resolution of DKA and discontinuation of insulin drip (unpublished data from SMART)
    - Pancreatitis: Lactated Ringer's reduced systemic inflammation compared to saline (Wu BU, et al 2011)
    - ED: (unpublished data from SMART): Biggest mortality benefit in patients with sepsis seen in those who received crystalloids in the ED, begging the question, is the most important fluid the first fluid that patients receive?
- Lactated Ringer's versus Normosol?
    - Not a lot of data, but possibly some improvement in acid-base in Normosol (chloride value is lower in Normosol)
    - BASE trial: single-center study at Vanderbilt, awaiting results
        - Primary outcome: bicarbonate level
        - 2000 patients admitted to medical ICU
        - Randomized to receive either Normosol or lactated ringer's in crossover study

Discuss crystalloid use in the hyperkalemia

- Use of crystalloids in hyperkalemia and/or ESRD?
    - Balanced crystalloids have small amount of potassium, however, multiple RCTs in patients with ESRD undergoing renal transplant demonstrated higher potassium and worsened acidosis in patients assigned to saline compared to balance crystalloids (O'Malley CMN, et al 2005; Khajavi MR, et al 2009; Modi MP, et al 2012; Portura E, et al 2015)
    - Subgroup analysis from SMART study in patients with K > 6.5 and AKI on admission found a reduced rate of severe hyperkalemia in those that received balanced fluids. This result was underpowered but may be clinically important.
    - In patients with hyperkalemia, consider sodium bicarbonate over saline
        - BICAR-ICU: significant reduction in composite outcome of mortality and less use of RRT in patients that presented with AKIN scores of 2-3 and received sodium bicarbonate vs saline

Discuss crystalloid use in cerebral edema

- TBI or cerebral edema
    - In SMART study, patients with TBI did not have lower mortality with balanced crystalloids
    - However, lactated ringer's is hypo-osmolar, thus saline may be safer infusion in this population
- Fluid administration with blood transfusions: theoretical risk of calcium in lactated ringer's precipitating with citrate in blood products, however no complications reported in observational studies
    - If nervous about using lactated ringer's, Plasma-Lyte and Normosol are approved by US blood bank for administration with blood products

Choice of Fluid Recommendations:

- Balanced crystalloids should be first line fluid for critically ill, especially those with sepsis
- Balanced crystalloids should be delivered in ED
- If hyperkalemia, (K < 6.5), still consider using balanced crystalloids
- Even if K > 6.5, balanced crystalloids are likely better than saline
    - If concerned, use an isotonic bicarbonate drip (150 mEq sodium bicarbonate in 1 Liter D5W)
- Consider bicarbonate drip if metabolic acidosis (ph < 7.2) and AKI present

Acute Pulmonary Embolism in 2020

Azeem Elahi, MD

Epidemiology and pathophysiology of PE

- VTE causes 1 death every 6 minutes in the US (274 deaths per day)
- Pathophysiology: Virchow's triad: circulatory stasis, hypercoagulable state, endothelial injury
    - Hypercoagulable states:
        - Inherited thrombophilia (factor V Leiden, relative risk (RR) of VTE is 7.0)
        - Oral contraceptive use RR is 4.0 (combined with FVL, RR increases to 35!)
    - Acquired thrombophilia:
        - History of prior thrombotic event: 18% risk of recurrence at 2 yrs, 30% at 8 years
        - RR of VTE recurrence = 7.9
        - Cyber (e-DVT): rise in younger patients diagnosed with VTE due to video games, consider including in H&P
- Most emboli thought to arise from lower extremity veins, however can arise in non-lower extremity veins
- Thrombi develop at sites of decreased flow, such as valve cusps or bifurcations

Hemodynamics: pulmonary vascular resistance

- PE-induced vasoconstriction leads to increased RV afterload, decreased RV contractility, LV preload, drop in CO and systemic BP, ultimately leading to obstructive shock and potentially death
- Respiratory failure: V/Q mismatch contributes to hypoxemia
- Clinical presentation: often known as great masquerader as the diagnosis is often missed
    - Common symptoms include: dyspnea, chest pain +/- elevated troponins (could be MI), pleuritic chest pain (could be pleurisy), cough (could be pneumonia), calf pain (could be pulled muscle), worsening hypoxia in ICU (could be aspiration), and hypotension in ICU (could be sepsis)

Review the diagnostic and treatment algorithm for PE

- Gold standard diagnosis is CT PE
- Can use 2-dimensional echo as adjunct to help with diagnosis:
    - Enlarged RV or flattened intraventricular septum (RV pushing into it septum and flattens LV)
    - McConnell's sign (akinetic wall)
- Risk stratification – important as mortality increases with severity, want to identify and treat quickly
    - High (massive) – 5% of patients: hemodynamic instability, cardiac arrest
    - Intermediate (sub-massive)
    - Low (non-massive)
- Treatment
    - Oxygenation
      Resuscitation: careful with fluid bolus in patients with overextended RV,
      Systemic anticoagulation: Low molecular weight heparin, unfractionated heparin, or DOAC
    - Systemic thrombolysis: leads to faster improvement and improvement in PA pressure and PA resistance compared to UFH alone in massive PE
    - Advanced therapies: catheter directed therapies
    - ECMO
- Consideration of PE response team: collaboration between interventional team, critical care team, and ED
- Treatment decision pathway – no RCT yet, PE response team may be helpful to have these discussions

Describe particular considerations for endotracheal intubation for PE

    - 6 Ps maximize success
        - Preparation: equipment, suction, monitor, IV access, RSI meds, vasopressors
            - Consider avoiding RSI drugs that cause hypotension
        - Preoxygenation: NRB, Optiflow, NIPPV, BMV
        - Positioning
        - Paralysis with induction
        - Placement
        - Post-intubation: pre-empt hypotension, keep plateau <30cmH20
    - Consider ECMO in patients with massive PE or severe submassive PE

Endocrine Emergencies: Adrenal to Thyrotoxic Crisis

Amanda E. Edwards, MMS, PA-C

Amanda reviewed the pathophysiology of adrenal insufficiency and secondary adrenal insufficiency. She walked through cases for the presentation, physical examination, diagnosis, and management of autoimmune adrenalitis presenting with adrenal crisis, bilateral adrenal hemorrhage, and thyroid storm with associated cardiomyopathy.

A review of relevant primary literature was discussed starting with the Annane trial (2002) that showed possible mortality benefits to steroid supplementation in septic shock patients. Next up was the CORTICUS trial (2008) which did not demonstrate any mortality difference between the groups, although critiqued that they enrolled patients later than Annane and colleagues. The HYPRESS trial (2016) studied continuous infusion hydrocortisone (HCT) in severe sepsis patients. They identified the same amount of progression into septic shock as well as the same mortality and time in ICU outcomes. These findings suggest that HCT has no role in severe sepsis but possibly in septic shock patients. Next, the ADRENAL trial (2018) studied septic shock patients on vasopressors for > 4 hours and mechanical ventilation (MV). There was no difference in 90-day mortality compared to placebo. Secondary endpoints were a more rapid shock resolution of 3 vs. 4 days compared to placebo, shorter ICU LOS of 10 vs. 12 days, shorter MV of 6 vs. 7 days and overall fewer blood transfusions. Lastly, the APROCCHSS trial (2018) studied HCT + fludrocortisone versus placebo and showed improved mortality of 43% vs. 49%. Also, an improvement in resolution of septic shock and more MV free days were seen in the steroid group. Mortality benefit remains controversial but both ADRENAL and APPROCHSS showed improvement in septic shock and a decreased time on mechanical ventilation. In summary, critical illness-related corticosteroid insufficiency (CIRCI) is complex and consider using random cortisol stimulation tests. The SSC and SCCM recommendations are a little muddy.

Shifting gears to thyroid crisis, it was presented that hyperthyroidism is prevalent in 1.2% of the US population. Thyroid storm is a systemic decompensation from thyrotoxicosis. It is a clinical diagnosis with high mortality of 8-25% and diagnosed with the Burch-Wartofsky Point Scale. Treatments include propylthiouracil or methimazole to stop thyroid hormone synthesis, propranolol or esmolol infusion to reduce peripheral action of thyroid hormone at the tissue level, or iodide (Lugol's Solution) to block new hormone release. Part of the treatment includes reversing systemic decompensation with HCT IV and treating the precipitating events (commonly sepsis). Lastly, definitive therapy is decided upon at a later time. In summary, patients give rich histories, don't forget about precipitating events, keep adrenal insufficiency on your differential, CIRCI is controversial, and thyroid storm is a clinical diagnosis with six mainstays of management.

COVID-19: The Latest Updates from the Firehose of Therapeutics Research*

Julie Ann Justo, PharmD, MS, BCPS-AQ ID

*Data current as of June 4th, 2020

- COVID-19 is thought to exist in 3 phases (Sidiqqi HK, et al. 2020)
  - Early (Stage I)- viral replication with mild symptoms
  - Pulmonary phase (Stage II)- viral replication is decreasing but host inflammatory increasing. Pulmonary symptoms increase. This is thought to be the ideal time for therapy.
  - Hyperinflammation (Stage III)- ARDS, SIRS/shock, cardiac failure due to host inflammatory response
- Numerous experimental therapies for COVID-19

Experimental Therapies for COVID-19

Agent(s)	Mechanism(s) of Action
Hydroxychloroquine, chloroquine	Increase of endosomal pH inhibits viral endocytosis and cell fusion; impaired ACE2 glycosylation blocks virus entry; immunomodulatory effects
Remdesivir, favipiravir, ribavirin	Inhibition of RNA-dependent RNA polymerase to inhibit viral replication
Lopinavir/ritonavir	Inhibition of 3-chymotrypsin-like (3CL) protease
Umifenovir (Arbidol)	S protein/ACE2 interaction inhibits membrane fusion of viral envelope
Leflunomide	Inhibition of viral replication and assembly
Thalidomide	Immunomodulatory effects (reduced inflammatory cell infiltration, reduced cytokines like interleukin-6 [IL-6] and tumor necrosis factor [TNF])
Convalescent plasma	Virus-specific antibodies promote immune response
Tocilizumab, sarilumab, siltuximab	Inhibition of IL-6 receptor or of IL-6 directly (siltuximab-specific)
Anakinra	Inhibition of interleukin-1 (IL-1) receptor
Baricitinib, ruxolitinib	Janus kinase (JAK) inhibition; AP2-associated protein kinase 1 inhibition (baricitinib-specific)
Corticosteroids	Suppress immune and inflammatory responses

1. Sanders JM, et al. JAMA. 2020 April;323:1824-36.
2. Zhong J, et al. Lancet Rheumatol. 2020 May 20. doi:10.1016/S2665-9913(2)30120-x.

- Hydroxychloroquine (HCQ) and chloroquine
  - HCQ better tolerated; *in vitro* potency demonstrated at therapeutic doses
  - Data are mixed with observational cohort (n = 36) with many limitations (Gautret P, et al. 2020) showing benefit but data from NYC (n = 1376) showing no difference in intubation or death in hydroxychloroquine vs. no HCQ (Geleris J, et al. 2020) and from NY state (n = 1428) indicating no significant difference in hospital mortality in patients treated with HCQ, HCQ and azithromycin, azithromycin alone, or standard of care (Rosenberg ES, et al. 2020).
  - A randomized controlled trial (n = 150) that was not blinded demonstrated no difference in negative conversion of PCR at 28 days, although patients in both groups received antiretroviral agents (Tang W, et al. 2020)
  - Prolonged QT_c a common complication of hydroxychloroquine in combination with azithromycin (Mercuro N, et al. 2020 and Chorin E, et al. 2020)
    - Increased risk of cardiac arrest with HCQ and azithromycin noted by Rosenburg
- Remdesivir (RDV)
  - Gilead study of RDV vs. placebo- 231 participants randomized 2:1 fashion in double-blind study, concomitant treatment was allowed (Wang Y, et al. 2020).
    - Receipt ≤ 10 days from symptom onset decreased time to clinical improvement (18 vs 23 days, p = NS)
  - ACTT-1 NIH study included 1059 patients evaluating RDV x 10 days vs placebo- no other agents allowed (Biegle JH, et al. 2020)
    - Time to improvement on ordinal scale primary outcome
      - Median recovery 11 days vs 15 days placebo; RR 1.32 (95% CI 1.12-1.55, p < 0.001)
    - No statistically significant difference in 14-day mortality or serious adverse events

        - GILEAD SIMPLE- 5 vs 10 days RDV Phase 3, open label trial in 397 patients with severe COVID-19 (Goldman JD, et al. 2020)
            - Clinical improvement on ordinal scale- 64% for 5-day and 54% for 10-day RDV
                - 10-day RDV significantly worse clinical status at baseline
                - 86% completed 5 days, 44% completed 10 days because of discharge or death
                - Serious ADEs and death no difference
            - Higher mortality noted in those intubated by day 5 in 5-day vs 10-day RDV course; the n is small but has lead to the recommendation for 5 days of RDV for patients except those receiving MV or ECMO, where the recommendation is 10 days.
- Convalescent plasma
    - Likely results in lower inflammatory markers (Duan K, et al. 2020) and is safe with < 1% serious adverse events in evaluation of safety data from 5000 patients (Joyner MJ, et al. 2020)
- Tocilizumab
    - Higher D-Dimer, Il-6, ferritin levels and lower lymphocyte counts in nonsurvivors vs. survivors (Zhou F, et al. 2020)
    - Timing of immune modulation is key; if too early may be harmful and if too late may not be helpful.
    - Decreased CRP and temperature with improved oxygen saturation noted in case series from China (Xu X, et al. 2020)
    - Pre-print observational cohort data of 154 patients who required mechanical ventilation (Somers EC, et al. 2020)
        - Propensity score inverse probability weighing and adjusted analysis
            - HR 0.55 (95% CI 0.33 – 0.9) for mortality, also improved likelihood of clinical improvement on ordinal scale with tocilizumab.
            - 28-day mortality 18% tocilizumab vs 36% standard of care, p = 0.01
        - Superinfections a tradeoff, occurring in 54% receiving tocilizumab vs 26%
- Corticosteroids- still controversial due to SARS and MERS data
    - Patients with ARDS in Wuhan had reduced risk of death with methylprednisolone (HR 0.38; 95% CI 0.2-0.72, p = 0.003) (Wu C, et al. 2020)
    - Early short course of steroids vs. standard of care in patients with moderate/severe COVID (n = 213) has lower incidence of composite endpoint including ICU transfer, mechanical ventilation, and death (34.9% vs 54.3%, p = 0.0005) (Fadel R, et al. 2020)

Management of the Pre-Shock Patient: What to Do with the Sick Heart Failure Patient

Stuart D. Russel, MD

Dr. Russell's presentation covered management of patients presenting with an acute heart failure exacerbation and bordering near cardiogenic shock. He presented a stepwise approach to these patients beginning with an assessment of their hemodynamic profile. Do they have adequate perfusion based on skin temperature (warm or cold)? Are they experiencing volume overload (dry or wet)? His focus then shifted to the sickest quadrant of this stratification: those poorly perfused with volume overload (cold and wet). If patients are hypotensive it is reasonable to stop their home antihypertensive medications, particularly beta-blockers with the caveat that providers must be mindful to resume these on discharge. It was previously a common practice for tachycardic patients to receive digoxin, however based on data from the DIG trial compared to placebo there was no difference in mortality for patients hospitalized with an acute heart failure exacerbation. Inotropic agents may alleviate symptoms but also have no mortality benefit and carry other adverse reactions including arrhythmias. Diuresis and medical management is often guided by right heart catherization which provides useful information on the patient's cardiac power (the rate at which the heart imparts hydraulic energy into the arterial system to maintain the circulation of the blood). Lastly, Dr. Russell covered the European guideline recommendations for monitoring spot urine sodium levels and titrating diuretics aggressively to achieve adequate diuresis. Inability to get these patients to their goal weight puts them at an increased risk for rehospitalization from another exacerbation.

Tales from the Battlefield: Cardiogenic Shock from a Cardiologist's Perspective

Stuart D. Russel, MD

Dr. Thohan began by presenting two cases of cardiogenic shock after myocardial infarction (MI), both of which received ECMO support. One patient died and the other did not. This set the stage to differentiate between the care that was provided to these two patients. A takeaway being that early recognition of cardiogenic shock after MI and early ECMO equals better outcomes.

The stages of cardiogenic shock were reviewed based on physical exam, biochemical markers, and hemodynamic parameters. It was shown that early revascularization (SHOCK trial, 1999) improves patient outcomes at 6 months. It is important to be mindful of the mechanical complications of MI (especially in a shock state after an MI). This is a surgical emergency. Taking a closer look at the SHOCK trial, patients with early revascularization showed survival benefit compared to patients with stabilization then revascularization. The question arises of whether you should perform a complete revascularization or just fix the occluded vessel. Outcomes of those with culprit lesion revascularization versus multi-vessel were better for mortality and all-cause. Essentially, avoid doing too much! Stabilize the patient and fix the culprit lesion only.

The frequency of cardiogenic shock complicating acute MI has stayed the same over the last 10 years despite changes and advances in treatments. Survivors are often discharged home with NYHA Functional Class 1 or 2 heart failure (in those followed out to 11 years).

Mechanical circulatory support is considered once chemical support is not enough. This completely or partly artificially supports pulmonary or cardiac circuits. Dr. Thohan reviewed the Tandem Heart Percutaneous Ventricular Assist Device (pVAD) and the Impella. He also discussed the increasing use of VA ECMO as a bridge to recovery or durable LVAS. Survival to discharge data were reviewed for these devices. Impella specifically was compared to IABP in a randomized trial. Overall, Impella improves measures of perfusion and power but with the same 30-day outcomes as IABP and 46% mortality. The
EUROSHOCK registry of Impella use shows individuals with an MI and cardiogenic shock plus an Impella implanted still had poor outcomes over time.

Dr. Thohan's interpretation: many times patients already have end organ dysfunction so time to recognition and time to deployment is delayed. In patients with cardiogenic shock complicating MI, the longer you wait, the increased risk of death. Tying it back to the two cases: both patients were on vasopressor support, both on a balloon pump, and both on ECMO. The differences: case 2 had a SWAN in place early, a shock team deployed as soon as they entered the ICU and VA ECMO initiated between hours 2-4 (case 1 was at hour 8).

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