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StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-.

Systemic Inflammatory Response Syndrome

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Last Update: November 16, 2020.

Introduction

Systemic inflammatory response syndrome (SIRS) is an exaggerated defense response of the body to a noxious stressor (infection, trauma, surgery, acute inflammation, ischemia or reperfusion, or malignancy to name a few) to localize and then eliminate the endogenous or exogenous source of the insult. It involves the release of acute-phase reactants which are direct mediators of widespread autonomic, endocrine, hematological and immunological alteration in the subject. Even though the purpose is defensive, the dysregulated cytokine storm has the potential to cause massive inflammatory cascade leading to reversible or irreversible end-organ dysfunction and even death.

SIRS with a suspected source of infection is termed **sepsis**. Confirmation of infection with positive cultures is therefore not mandatory, at least in the early stages. Sepsis with one or more end-organ failure is called **severe sepsis** and with hemodynamic instability in spite of intravascular volume repletion is called **septic shock**. Together they represent a physiologic continuum with progressively worsening balance between pro and anti-inflammatory responses of the body.

The American College of Chest Physicians/Society of Critical Care Medicine-sponsored sepsis definitions consensus conference also identified the entity of **Multiple organ dysfunction syndrome (MODS)** as the presence of altered organ function in acutely ill septic patients such that homeostasis is not maintainable without intervention.[1]

Objectively, SIRS is defined by the satisfaction of any two of the criteria below –

- Body temperature over 38 or under 36 degrees Celsius.
- Heart rate greater than 90 beats/minute
- Respiratory rate greater than 20 breaths/minute or partial pressure of CO₂ less than 32 mmHg
- Leucocyte count greater than 12000 or less than 4000 /microliters or over 10% immature forms or bands.

In the pediatric population, the definition is modified to a mandatory requirement of abnormal leukocyte count or temperature to establish the diagnosis, as abnormal heart rate and respiratory rates are more common in children.

To summarize, almost all septic patients have SIRS, but not all SIRS patients are septic. Kaukonen et al. explained exceptions to this theory by suggesting that there are subgroups of hospitalized patients particularly at extremes of age who do not meet criteria for SIRS on presentation but progress to severe infection and multiple organ dysfunction and death. Establishing laboratory indices to identify such subgroup of patients along with the clinical criteria that we currently rely upon has been therefore gaining prominence over the recent years.[2]

Several scores exist to assess the severity of organ system damage. The Acute Physiology and Chronic Health Evaluation (APACHE) score version II and III, Multiple organ dysfunction (MOD) score, sequential organ failure assessment (SOFA) and logistic organ dysfunction (LOD) score are to name a few.

HISTORY

With the advent of new concepts in pathophysiology and therapeutic interventions for sepsis in the early 90s, there was an increasing need to identify a homogenous group of potential subjects for clinical trials investigating new innovative therapeutic strategies. Borne out of the plethora of emerging studies, one opinion was unanimous. An early, time-sensitive approach to diagnosis and intervention is necessary to have a significant impact on patient survival and morbidity. Identifying the subjects at any setting with easy to use standardized parameters, therefore, held the key. The American College of Chest Physicians/Society of Critical Care Medicine-sponsored sepsis definitions consensus conference held in Chicago, Illinois in August 1991 aimed at establishing a standard group of clinical parameters to identify those subjects easily in any clinical setting. Thus was born the SIRS definition.[1]

It underwent further modification in the second chapter of the meeting in 2001 in Washington, DC. This conference proposed a conceptual framework of the staging of sepsis using the PIRO acronym (predisposition, insult or infection, response, and organ dysfunction).[3]

The goal of the initial definition was to be highly sensitive using easily available parameters across all healthcare settings. An unavoidable corollary of such a definition was, therefore, the lack of specificity. A few more relevant pitfalls of the SIRS definition, as has been pointed out in the literature, include the following:[4]

1. The universal prevalence of the parameters in an ICU setting
2. Lack of ability to distinguish between beneficial host response from pathologic host response that contributes to organ dysfunction
3. Distinguishing between infectious and non-infectious etiology purely based on the definition
4. Lack of weight to each criterion – e.g., fever and elevated respiratory rate have precisely the same significance as leukocytosis or tachycardia by the SIRS definition.
5. Inability to predict organ dysfunction.

Kaukonen et al. in their study of over 130000 septic patients established that one out of eight patients in their observational study of sepsis did not have two or more SIRS criteria.[2] Also, they also established that each criterion in the SIRS definition does not translate to an equivalent risk of organ dysfunction or death.

In the wake of this debate, in 2016, the European Society of Intensive Care Medicine and the Society of Critical Care Medicine (SCCM) created a task force that proposed Sepsis-3, a new definition for sepsis. The new definition excluded the establishment of SIRS criteria to define sepsis and made it more nonspecific as any life-threatening organ dysfunction caused by the dysregulated host response to infection.[5] The task force claimed that sequential organ failure assessment (SOFA) has a better predictive validity for sepsis than SIRS criteria. It has better prognostic accuracy and the ability to predict in-hospital mortality. To reduce the complexity of calculating the SOFA, they introduced q SOFA.

Q SOFA

3 component assessment system with:

- Systolic blood pressure below 100 mm Hg
- Highest respiratory rate exceeding 21
- Lowest Glasgow coma score under 15

Although the validity of q SOFA, is limited in an ICU setting, it has consistently outperformed SIRS criteria in the prediction of organ dysfunction in a non-ICU and ER setting. The use of vasopressors, mechanical ventilation, and aggressive therapeutic interventions in ICU limit the efficacy of q SOFA.[6]

Interestingly Hague et al. in their study of the utility of SIRS criteria in gastrointestinal surgery, patients also found it to be a useful criterion to identify postoperative complications.[7]

Etiology

At a molecular level, the etiopathogenesis of systemic inflammatory response syndrome broadly divides into

1. **DAMAGE ASSOCIATED MOLECULAR PATTERN (DAMP)**
2. **PATHOGEN ASSOCIATED MOLECULAR PATTERN (PAMP)**

Although the list is not all-inclusive some common etiologies from clinical perspective include

DAMAGE ASSOCIATED MOLECULAR PATTERN (DAMP)

- Burns
- Trauma
- Surgical procedure-related trauma
- Acute aspiration
- Acute pancreatitis
- Substance abuse and related intoxications
- Acute end-organ ischemia
- Acute exacerbation of autoimmune vasculitis
- Medication adverse reaction
- Intestinal ischemia and perforation
- Hematologic malignancy
- Erythema multiforme

PATHOGEN ASSOCIATED MOLECULAR PATTERN (PAMP)

- Bacterial infection
- Viral syndrome-like influenza
- Disseminated fungal infection in immunosuppressed
- Toxic shock syndrome derived from both exotoxins and endotoxins

PAMP can also be classified based on the location and extent of dissemination of infection, which ranges from localized organ-specific infection to disseminated bacteremia and sepsis.

Epidemiology

The problem with a highly sensitive and less specific definition of systemic inflammatory response syndrome is inaccurate capture of the true incidence. Not all patients with SIRS get to a healthcare facility or get hospitalized. Clinicians often manage acute viral syndromes in peak season in urgent care and emergency room setting with self-containment afterward. Only those who progress beyond, in the continuum of severity, are truly captured in the patient census. That also reflects a bias on the severity and all-cause mortality, as well as related outcome measures.

Churpeck et al. in their large scale study involving 269951 hospitalized patients found that 15% of patients met at least two diagnostic criteria for SIRS during admission while an overwhelming 47% met them at least once during the hospital stay. The mortality rate was significantly higher in patients with SIRS (4.3%) than in those without SIRS (1.2%).[8] Pittet et al. revealed an overall in-hospital incidence of 542 episodes per 1000 hospital days.[9]

Comstetdt et al. demonstrated that 62% of patients who presented to the emergency department with SIRS had a confirmed infection, while within the same cohort of patients, 38% of infected patients did not present with SIRS.[10]

Rangel and Fausto et al. in their prospective study of admissions in a tertiary care center showed that 68% of hospital admissions in their surveyed units met SIRS criteria. 26% developed sepsis, 18% developed severe sepsis, and 4% developed septic shock within 28 days of admission.[11]

As far as variation across sex and race is concerned, Choudhry et al. had observed a protective effect of estrogen in animal models with trauma, hemorrhage, and sepsis. Similarly, NeSmith et al. reported a lower incidence of SIRS in women and African Americans.[12][13]

For understandable reasons, extremes of age and concomitant medical comorbidities negatively impact the outcome of SIRS.

Pathophysiology

Inflammation triggered by an infectious or noninfectious stimuli sets forth a complex interplay of the humoral and cellular immune response, cytokines, and complement pathway — eventually, systemic inflammatory response syndrome results when the balance between proinflammatory and anti-inflammatory cascades tip over towards the former.

Roger Bone laid out a five-stage overlapping sepsis cascade that starts with SIRS and progresses to MODS, if not appropriately countered by compensatory anti-inflammatory response or alleviation of the primary inciting etiology. [14]

Stage 1 is a local reaction at the site of injury that aims at containing the injury and limit spread.

Immune effector cells at the site release cytokines that in turn stimulate the reticuloendothelial system promoting wound repair through local inflammation. There is local vasodilatation induced by nitric oxide and prostacyclin (rubor) and disruption of the endothelial tight junction to allow margination and transfer of leucocytes into tissue space. The leakage of cells and protein-rich fluid in extravascular space causes swelling (tumor) and increased heat (calor). Inflammatory mediators impact the local somatosensory nerves causing pain (dolor) and loss of function (functio laesa). That loss of function also allows the part of the body to repair instead of persistent use.

Stage 2 is an early compensatory anti-inflammatory response syndrome (CARS) in an attempt to maintain immunological balance. There is a stimulation of growth factors and recruitment of macrophages and platelets as the level of pro-inflammatory mediators decreases to maintain homeostasis.

Stage 3 is when the scale tips over towards proinflammatory SIRS resulting in progressive endothelial dysfunction, coagulopathy, and activation of the coagulation pathway. It results in end-organ micro thrombosis, and a progressive increase in capillary permeability, eventually resulting in loss of circulatory integrity.

Stage 4 is characterized by CARS taking over SIRS, resulting in a state of relative immunosuppression. The individual, therefore, becomes susceptible to secondary or nosocomial infections, thus perpetuating the sepsis cascade.

Stage 5 manifests in MODS with persistent dysregulation of both SIRS and CARS response.

At a cellular level, non-infectious noxious stimuli, an infectious agent or an endotoxin or exotoxin produced by an infection activates a multitude of cells including neutrophils, macrophages, mast cells, platelets, and endothelial cells.

The early response mediated by these inflammatory cells involves three major pathways

- Activation of IL-1 and TNF alfa.
- Activation of prostaglandin and Leukotriene pathway
- Activation of C3a – C5a complement pathway

Interleukin 1 (IL1) and tumor necrosis factor alfa (TNF-alpha) are the early mediators within the first hour. Their role is of paramount importance in tilting the scale towards a proinflammatory overdrive.

Their actions can broadly divide into three categories

1. Propagation of cytokine pathway
2. Alteration of coagulation causing microcirculatory abnormalities
3. Release of stress hormones

PROPAGATION OF CYTOKINE PATHWAY

The release of IL1 and TNF-alpha results in dissociation of nuclear factor-kB (NF-kB) from its inhibitor. NF-kB is thus able to induce the mass release of other proinflammatory cytokines including IL-6, IL-8, and Interferon-gamma. IL-6 induces the release of acute-phase reactants including procalcitonin and C reactive protein. Infectious triggers tend to produce a greater surge of TNF-alpha and thus IL-6 and IL-8. Another potent proinflammatory cytokine is High mobility group box 1 (HMGB1) protein which is involved in the delayed cytotoxic response of SIRS and sepsis. It has been established as an independent predictor of 1-year mortality in an observational study of traumatic brain injury patients.[15]

ALTERATION OF COAGULATION CAUSING MICROCIRCULATORY ABNORMALITIES

Like most other early responses in SIRS, alteration of the coagulation pathway also gets triggered by IL-1 and TNF-alpha. Fibrinolysis becomes impaired by the activation of plasminogen activator inhibitor-1. There is direct endothelial injury, thus resulting in the release of tissue factor, which triggers the coagulation cascade. Also, the anti-inflammatory mediators Activated protein C and antithrombin get inhibited. As a result, there is widespread microvascular thrombosis, an increase in capillary permeability, as well as fragility and impairment of tissue perfusion contributing to progressive organ dysfunction.

RELEASE OF STRESS HORMONES

Primarily the catecholamine, vasopressin, and activation of the renin-angiotensin-aldosterone axis result in an increased surge of endogenous steroids. Catecholamines are responsible for the tachycardia and tachypnea component of sepsis while glucocorticoids contribute to leucocyte count increase as well as their margination in the peripheral circulation.

CARS

The compensatory anti-inflammatory response is mediated by Interleukins IL-4 and IL-10 which tend to inhibit the production of TNF-alpha, IL-1, IL-6, and IL-8. The balance of SIRS and CARS decides where the termination point in the continuum of SIRS to MODS is. CARS has its own perils. If allowed to perpetuate, it subjects the surviving individual to a prolonged state of immunosuppression. The individual thus becomes susceptible to nosocomial infection, which can thus reinitiate the septic cascade.

History and Physical

Early clinical presentation irrespective of etiology, mirrors the pathological phenomena of rubor, calor, dolor, tumor, and functio laesa. A thorough history of location, character, radiation, and exacerbating – relieving factors of pain, duration, and time correlation of symptom are important. Where the etiology and primary source is not as obvious, history should focus on any alteration from usual activities, including new medications, food intake, exposure, travel, or recreational agents of abuse.

Identification of specific risk factors through history may help prioritize intensive treatment strategy, e.g., preexisting immunosuppression, diabetes mellitus, solid tumors and leukemia, dysproteinemias, cirrhosis of the liver, and extremes of age.

A complete physical examination is not only helpful in localizing the source but also to assess the true extent of involvement and complications related to end-organ involvement. It also helps in guiding the appropriate investigations and imaging studies.

The definition of systemic inflammatory response syndrome has its basis in vital signs other than the evaluation of leucocyte count. However, vital signs can be falsely altered by the stress of arrival to a healthcare facility in extremes of age or by concomitant use of medications (beta-blockers, calcium channel blockers). Hence periodic evaluation of vital signs and evidence of persistent instability becomes important to establish the diagnosis.

Evaluation

Over the years, a gradual paradigm shift has occurred from placing sepsis on the shoulders of clinicians to the incorporation of more objective parameters. While it is unquestionably a clinical diagnosis and cannot be defined by merely diagnostic assays without clinician's recognition of signs, prompt identification of uniform clinical criteria became increasingly important.

As newer inroads were made at the end of the 20th century in the complex pathophysiology, etiology and pharmacotherapy targets, the need for early diagnosis and intervention became obvious to make an impact on mortality and morbidity. The recognition of the continuum from early inflammation to multiorgan dysfunction added more incentive. Thus was born the necessity to diagnose systemic inflammatory response syndrome both in the backdrop of infection and in noninfectious stress where the body later becomes susceptible to a secondary infection.

The establishment of clinical criteria was where the initial endeavor lay. Thus were born APACHE score, SIRS score, SOFA and q SOFA score, LOD score. Each one of them evolved with an intent to find a simpler, easily applicable prompt scoring system that can be used in any clinical setting to predict

- Identification of sepsis
- Risk of organ dysfunction
- In-hospital mortality

If the etiology of SIRS is identified early, investigations are individualized to the organ in focus. In the absence of an apparent source, a time-sensitive search for infectious sources becomes a priority. Health care facilities across US and society guidelines endorse a routine collection of specimens from blood, sputum, urine and any other obvious wound for culture within the first hour of assessment and before initiation of antimicrobial therapy.

Depending on the severity of the presentation, routine investigations involve periodic evaluation of basic metabolic panel, and lactic acid level to assess the extent of end-organ injury and perfusion impairment.

With time, there has also been an emerging discussion in the community about the importance of distinguishing sepsis earlier in SIRS with the help of biomarkers, even before microbial cultures come positive.

Biomarkers also become important in identifying SIRS due to secondary infection in patients who were initially admitted with a noninfectious etiology, e.g., trauma or burns or for a planned surgical intervention. Mere clinical criteria are not enough to capture the change in etiopathogenesis midway through hospitalization.[16][17]

PROCALCITONIN (PCT)

A glycoprotein precursor of calcitonin, procalcitonin is produced by C cells of thymus and also from leucocytes, liver, kidney, adipose, and muscle tissue.[18] In healthy individuals, serum levels are usually below 0.1 mg/dl but can be significantly abnormal in bacterial, fungal, or parasitic infections. Levels can mildly elevate in viral infection or noninfectious acute inflammation, and can also rise in individuals with neuroendocrine tumors or post-surgical stress. [19] Serum concentrations rise within 2 to 4 hours of the inflammatory surge and fall rapidly after halting the primary insult. Half-life is about 25 to 30 hours. The peak serum concentration, therefore, seems to parallel the timeline of disease severity and outcome.[18][20][21][22]

Research has mostly focused on the utility of procalcitonin in differentiating infectious from a non-infectious cause of SIRS, as well as its value in serial assessment to determine the duration of antimicrobial therapy. Kibe et al. showed a favorability for procalcitonin over CRP in the diagnosis and prognosis of sepsis but only in conjunction with clinical parameters.[23] Karzai et al. also confirmed its value in predicting a systemic infectious process, although the cutoff value seemed to differ based on the disease process.[18] Ciriello et al., in their comparison of a wide assembly of biomarkers in trauma patients, found the only procalcitonin to be of benefit in predicting sepsis. Persistently high levels correlated well with increased mortality and severity scores.[24] Agarwal and Schwartz demonstrated that serial PCT measurements in ICU contributed to a significant reduction of ICU days and the duration of antimicrobial therapy.[25]

Selberg et al. in their study demonstrated that plasma concentrations of procalcitonin (PCT), C3a, and IL-6 obtained up to 8 hours after the clinical onset of sepsis or SIRS were significantly higher in patients with infectious etiologies. PCT, IL-6, and C3a were more reliable in distinguishing SIRS from sepsis.[26]

LACTATE

Lactic acid elevation can be a **type A lactic acidosis** with excessive production from tissue hypoperfusion related anaerobic metabolism or **type B lactic acidosis** from inadequate clearance due to liver dysfunction. The use of epinephrine as a vasopressor agent can also lead to excessive lactate production due to the alteration of the pyruvate cycle.

INTERLEUKIN 6

An IL-6 level of greater than 300 pg/ml correlates with an increased incidence of MODS and death. Similarly, a reduction in level by the second day of antimicrobial therapy has been shown to be a positive prognostic sign.[27][28]

LEPTIN

Serum Leptin levels above a cutoff of 38 mcg/L correlate serum levels of IL-6 and TNF-alpha and helps in differentiating between infectious and noninfectious causes of SIRS with a sensitivity of 91.2% and a specificity of 85%.[29][30] It is a centrally acting hormone generated by adipocytes acting on the hypothalamus.

ENDOTHELIAL MARKERS

Angiopoietin 1 and 2 are ligands for the Tie-2 receptor in endothelial cells. During acute inflammation, there is increased binding of Angiopoietin 2 (Ang-2) with Tie-2 receptor, triggering microvascular thrombosis, and capillary permeability. The circulating levels of Ang-2 appears to correlate with 28-day mortality in SIRS as well as with severity scores like APACHE and SOFA.[31][32] Similar significance has been attached to soluble E-selectin and P-selectin levels, which can help distinguish between septic and non-septic etiologies of SIRS. Pablo et al. in a study of 92 SIRS patients found soluble E selectin to be most useful in identifying early SIRS and prognosticating severity. Soluble Intracellular adhesion molecule (s-ICAM 1) helped in distinguishing septic and non-septic patients.[20] However, none of their analytic methods are standardized and cut off levels still need to be established to bring them into the market anywhere soon.

EMERGING BIOMARKERS

Other emerging biomarkers in research to distinguish septic and non-septic etiology of SIRS include triggering receptor expression on myeloid cells 1 (TREM-1), Decoy receptor 3 (DcR3) (belongs to the tumor necrosis factor family) and suPAR (soluble urokinase-type plasminogen activator receptor).[33][34][35] Among them, suPAR correlated particularly well with disease severity scores and the identification of nonsurvivors in the sepsis group.

TRANSCRIPTOME ANALYSIS

In recent years there has been an emerging idea behind SIRS pathophysiology suggesting immune dysregulation as a key phenomenon than a mere inflammatory surge in SIRS and sepsis. Utilizing high-throughput sequencing of cDNAs from mononuclear cells, a genetic profile of endotoxin tolerance (called endotoxin tolerance signature or ETS) has been identified which is expressed more often in septic patients, and was more commonly associated with organ failure

and disease severity. It may thus provide an opportunity of identifying a subpopulation of septic patients early for ICU admission and intensive therapy impacting mortality and morbidity.[36]

Treatment / Management

Systemic inflammatory response syndrome is a conglomeration of clinical manifestations of a triggering cause; management focuses on the treatment of the primary triggering condition.

Management is thus designed around a parallel search for the underlying etiology and its resolution along with time-sensitive interventions that may not be cause-specific, but get targeted towards preventing end-organ injury. The goal is to disrupt progression along the continuum of shock and multi-organ dysfunction syndrome.

Ensuring hemodynamic stability is of utmost importance. In severe sepsis and septic shock, the surviving sepsis guidelines recommend an initial administration of isotonic crystalloids at a rate of 30 ml/kg bolus. Such an arbitrary establishment of volume standards across the patient spectrum with variable cardiac, renal, and intravascular protein reserve can be a topic of clinical debate. Therefore some practice standards are consistent with subsequent volume administration guided by dynamic measures of volume responsiveness. For a spontaneously breathing patient not in cardiac arrhythmia, the indices relied upon include measurement of pulse pressure variability or stroke volume variability with passive leg raising. For a patient on mechanical ventilator support, pulse pressure variability, stroke volume variability or IVC diameter variability with respiration is an option. In an era where Swan Ganz catheter is not commonly used, other newer devices can be used to measure some of these indices while newer less invasive ones are in the pipeline.

Vasopressors and inotropes are useful in shock nonresponsive to volume repletion. A detailed description of their use will fall in the purview of discussion of management of shock in specific.

Primary source control may involve surgical intervention, e.g., incision and drainage of wound infection, tube drainage of a contained abscess and collection, or more exploratory surgery.

When the clinician suspects sepsis as the cause of SIRS, and in specific predisposed individuals, e.g., generalized debilitation, immunosuppression, neutropenia or asplenia, broad-spectrum empiric antibiotic therapy is indicated immediately after collection of culture specimen.

Broad-spectrum antibiotics should still be guided by:

- Suspicion of community vs. hospital-acquired infection
- Prior microbiology patterns in the individual
- Antibigram for the facility

Prompt de-escalation is the recommendation once culture results are available.

Antiviral therapy is considered only with respiratory exacerbation and systemic inflammatory response syndrome in the influenza season. Neutropenic patients and those on total parenteral nutrition with central venous access may need empiric antifungal if they continue to show SIRS response after empiric antibiotics.

Glucocorticoids in low doses (200 to 300 mg hydrocortisone or equivalent) have been shown to improve survival and help in the reversal of shock in patients with persistent shock in spite of fluid resuscitation and vasopressor use. There is no evidence in serum cortisol level or ACTH stimulation testing to determine the indication for steroids in septic shock. The rationale is decreased responsiveness at receptor level rather than an absolute reduction in serum cortisol level as a cause of relative adrenal insufficiency in SIRS syndromes.

Blood glucose control- Van den Berghe et al. in their landmark study in surgical ICU patients reported a reduction of in-hospital mortality rates with intensive insulin therapy (maintenance of blood glucose at 80 to 110 mg/dL) by 34%. However, subsequently, the large NICE-SUGAR trial failed to replicate the outcome benefit of tight glucose control

with an increased incidence of complications of hypoglycemia and hypokalemia. The surviving sepsis guidelines recommend blood glucose control less than 180 mg/dl.[37]

Differential Diagnosis

Systemic Inflammatory response syndrome, being a highly sensitive definition, with the need to satisfy only two out of four criteria, comes with the invariable loss of specificity. A combination of two SIRS criteria can reflect a host of clinical presentations in an acute setting, which may not reflect an underlying inflammatory state, that SIRS signifies. Some common ones include:

TACHYPNEA AND TACHYCARDIA

- Acute status asthmaticus with frequent administration of beta-agonists
- Acute salicylate toxicity
- Acute alcohol intoxication
- Acute ketoacidosis (diabetic, starvation, dehydration)
- Panic attack

TACHYCARDIA WITH HYPERTHERMIA

- Thyrotoxic crisis
- Acute intoxication with substance abuse (hallucinogens, psychotropic stimulants)
- Serotonin syndrome
- Malignant hyperthermia
- Neuroleptic malignant syndrome

HYPERTHERMIA AND LEUCOCYTOSIS

- Neurogenic emergency with acute hemorrhagic stroke (pontine).

The sustained presence of clinical criteria over time with repeated interval assessment, as well as corroboration with laboratory indices help distinguish them from an inflammatory milieu.

Prognosis

A systemic inflammatory response syndrome score of 2 or more on day 1 of hospitalization are more likely to develop multiorgan dysfunction syndrome (MODS), have more prolonged ICU stay and have a higher need for mechanical ventilation, vasopressor support, blood and blood products.

The median time interval from SIRS to sepsis in the continuum is inversely related to the number of SIRS criteria met on admission.[38]

Interestingly the mortality rates in Rangel-Fausto et al. study were 7% (SIRS), 16% (sepsis), 20% (severe sepsis), and 46% (septic shock).

Whereas in a similar study on in-hospital mortality, Shapiro et al. reported mortality rates of 1.3% (sepsis), 9.2 % (severe sepsis), and 28% (septic shock).[39]

The difference reflects upon a change in practice patterns over a decade (Rangel – Fausto study was in 1995 while the Shapiro et al. study was published in 2006) with more adherence to early goal-directed therapy, and use of proven risk

reduction approaches like DVT prophylaxis, blood glucose control, lung-protective tidal volume in mechanical ventilation, daily awakening and early ambulation.

Another interesting observation of the study by Shapiro et al. was that the presence of SIRS criteria alone did not have any correlation with in-hospital or 1-year mortality. Organ dysfunction did prove to be a better predictor of mortality, thus validating the significance of SOFA and q SOFA scores.

Complications

Complications of a systemic inflammatory response syndrome can include the progression of the disease state along the continuum of sepsis (for infectious etiology) to severe sepsis to shock and multiorgan dysfunction syndrome. Complications can also be related to individual end-organ dysfunction. Some important ones are as below

CENTRAL - Acute encephalopathy

RESPIRATORY - Acute respiratory distress syndrome (ARDS), acute aspiration pneumonitis related to encephalopathy

CARDIAC - Demand perfusion mismatch causing troponin elevation, tachyarrhythmia

GASTROINTESTINAL - Stress ulcer, acute transaminitis

RENAL - Acute tubular necrosis and acute kidney injury, metabolic acidosis, electrolyte abnormalities.

HEMATOLOGICAL – Thrombocytosis or thrombocytopenia, disseminated intravascular coagulation, hemolysis, deep venous thrombosis.

ENDOCRINE Hyperglycemia, acute adrenal insufficiency

Deterrence and Patient Education

Time being of supreme essence in the outcome of SIRS and sepsis, early identification holds the key to a favorable outcome. Education and awareness among predisposed patients and caregiving families about early warning signs should be a priority. A relevant subgroup is of individuals with underlying primary or acquired immunosuppression.

During management, educating the close family members and patients who can participate, about individualized prognosis, complications, treatment benefits, and risks helps to assuage detrimental sympathetic stress response.

It is also important to assess patient/family member's coping ability and apprehension regarding diagnostic and therapeutic interventions with which they are not familiar. If necessary, enlisting the help of palliative care personnel, or pastoral care to provide emotional support and assistance can certainly be more helpful than we often think.

Enhancing Healthcare Team Outcomes

As newer inroads are underway towards the understanding of this complex pathophysiology, etiology and pharmacotherapy targets of SIRS and sepsis, the race against time for early identification of individuals prone to more severe disease manifestation is now the priority. Along with the utilization of highly sensitive clinical definition to identify the susceptible patient, newer clinical scores and laboratory indices are being considered to quickly separate infectious from noninfectious etiologies, as well as to identify the risk of organ dysfunction and death early.

Such an orchestrated time-sensitive intervention involves prompt and effective execution from the level of triage to the emergency room to the intensive care unit, all functioning as a cohesive interprofessional team. It probably starts even earlier in susceptible individuals at the point of early recognition of instability by self or family with appropriate education and awareness.

Given the challenges of precise diagnosis and the gravity of the condition, diagnosis, and management of systemic inflammatory response syndrome requires an interprofessional team approach. A variety of clinicians to include

primary care/family doctors, specialists in a variety of fields (hematology, infectious disease), specialty-trained nursing staff, and pharmacists must all make unique contributions to the management of these patients. Clinician interventions have been the subject of much of this article. Nursing staff will often have the responsibility to monitor the patient as well as administering the medications needed to stabilize the patient. Given the wide variety of drugs that may be necessary, pharmacists should be consulted to ensure proper dosing regimens, and to assess the potential for drug interactions, making themselves available to both clinicians and nursing staff to assist with coordination of care and patient education. All members of the team need to chart their findings and maintain open lines of communication for consult and reporting so that everyone on the care team operates from the same information base. Only through this type of collaborative interprofessional paradigm can these patients receive the timely and proper therapy needed.

[Level V]

Uniform scoring systems endorsed by clinical societies, as well as hospital-wide sepsis or SIRS programs and bundles renders uniformity to the interventions. Most hospital systems across the US have been utilizing checklists and have incorporated it in their quality control measures to achieve perfection in execution.

CMS/Medicare supervision of healthcare system performance has added incentive to the effort along with opening up new debates and discussion for improvisation.

Continuing Education / Review Questions

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