Letter from the Editors

Dear Readers:

It is our distinct pleasure to continue the long tradition of the Albany Medical Review (AMR) with the release of the spring 2018 edition. Since its inception, the Medicine House Staff has contributed case reports of significant interest and high educational value. As the newest editors of the AMR, we would like to express our gratitude to Dr. Raymond Smith and Michelle Snively for their efforts in co-editing the presented case reports. In addition, we are thankful for the contributions made by the authors of the current edition of the AMR. We hope that you find this issue both enjoyable and educational. Thank you.

Case Report: Intravascular lymphoma presenting as an acute abdomen with intestinal perforation

Ali Wazir MD, PGY-3 Resident, Internal Medicine, Albany Medical College; Lezah McCarthy, MD, Pathology, Stratton VA Medical Center; Syed Mehm, MD, Section of Hematology/Oncology, Stratton VA Medical Center.

Introduction: Intravascular lymphoma is a rare subtype of Diffuse Large B cell lymphoma. It is characterized by intravascular (usually capillaries) proliferation of clonal lymphocytes, usually B cell. There is a striking sparing of surrounding tissue including lymph nodes and lymphatics.1

The disease was first described in 1959 by Pleger & Tappeiner. They termed the disease “angioendotheliomatosis proliferans”.2 The same disease has also been called “Malignant angioendotheliomatosis”, “Angiotropic large cell lymphoma”, “Diffuse large B-cell lymphoma” but most contemporary authors adhere to WHO terminology of Intra vascular Lymphoma.3

Intravascular lymphoma can have a varied presentation based on the organ in which the clonal cells proliferate. It usually presents in advanced ages (median age 67 years, range 41-85 years) and has a slight male predilection (male to female ratio 1.1:1). Even with aggressive therapy prognosis continues to be poor.3

Case Report: The patient was a 69-year-old caucasian male with past medical history of rheumatoid arthritis, COPD, atrial fibrillation, DVT and a pulmonary embolism. He presented to the hospital with severe abdominal pain and a high grade fever. On presentation he was awake, alert but encephalopathic. A chest x-ray revealed free air under the diaphragm. A subsequent CT scan of the abdomen was performed which revealed small bowel obstruction, wall thickening of the small bowel suggestive of an ischemic process [Figure 1] and multiple foci of intraperitoneal free air. A small amount of free fluid was noted in the pelvis.

Laparotomy revealed frank peritoneal contamination with a 1 cm. perforation on the anterior aspect of the cecum. The patient underwent an abdominal wash out and an ileectomy with primary anastomosis. He received broad spectrum antibiotics and the abdominal fluid demonstrated a polymicrobial infection.

Tissue specimens showed atypical lymphoid proliferation, colonic ulceration & perforation with serositis [Figure 2]. Immune histochemical testing showed aberrant expression of CD 20, CD 43, CD 30 and an increased Ki-67 proliferation index. A presumptive diagnosis of intravascular lymphoma was made. Because of his critical condition, he was not considered a candidate for chemotherapy.

His condition worsened requiring further abdominal washouts and escalation of care. After discussion with his health care proxy, palliative measures were instituted and he died during the hospitalization.

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Case Report: Intravascular lymphoma presenting as an acute abdomen with intestinal perforation (continued)

Ali Wazir MD, PGY-3 Resident, Internal Medicine, Albany Medical College; Lezah McCarthy, MD, Pathology, Stratton VA Medical Center; Syed Mehdi, MD, Section of Hematology/Oncology, Stratton VA Medical Center.


Discussion: Intravascular lymphoma can have a varied presentation depending on the organs involved. It has been referred to as “the oncologists’ great imitator”. Patients on presentation have advanced disease. One large case series reporting that 91% of the patients presented with clinical stage III or IV disease. Two major variants have been described. The western variant (classic variant) is characterized by CNS and skin involvement. In contrast, the Asian variant presents with multi-organ failure, hepatosplenomegaly, pancytopenia and sometimes hemophagocytic syndrome. The presentations are varied and many patients have presentations that do not fall in these two groups, limiting the utility of this classification.

The most common symptoms in one large series were fever (45%), cutaneous symptoms (39%) followed by neurological symptoms (34%). Pain from abdominal involvement was also fairly common (21%). Other symptoms reported less frequently included nonspecific symptoms such as fatigue, edema, dyspnea, urinary symptoms, and weight loss. The cutaneous symptoms vary in appearance from painful indurated erythematous eruptions to palpable purpura, poorly circumscribed violaceous plaques, large solitary plaques, erythematous, desquamation and a cellulitis like appearance.

Neurological symptoms can vary from stroke-like symptomatology (hemiparesis, aphasia, dysarthria) or new onset seizures, to fluctuation in consciousness and encephalopathy.

There are no standard diagnostic criteria for intravascular lymphoma. As discussed in our case, an important first step is demonstration of large number of lymphoid cells in small and medium sized blood vessels. The surrounding tissue is usually spared. Immunohistochemistry & molecular methods are useful adjuncts to establish clonally of lymphoma cells. Flow cytometry and bone marrow biopsy may be needed to establish clonality.

T cell and less commonly NK cell clones have also been described in intravascular lymphoma.

No randomized controlled therapy studies have been done in intravascular lymphoma. A widely used regimen is RCHOP. One retrospective series of 62 patients who received anthracycline-based chemotherapy reported a mean survival of 13 months.

Conclusion: Intravascular lymphoma is a rare diagnosis with protean manifestations. A high degree of clinical suspicion is needed to establish a diagnosis. Clinical manifestations are varied depending on organ systems involved. Prognosis continues to be poor even with aggressive chemotherapy. Randomized controlled trials and multicenter registry data are necessary to establish standardized treatment guidelines.
Meralgia Paresthetica as a presenting symptom of Ewing’s Sarcoma

Jing Tang, MD PGY3, Internal Medicine, Albany Medical College

Introduction: Meralgia paresthetica is a painful mononeuropathy of the lateral femoral cutaneous nerve. It is commonly due to focal entrapment of this nerve as it passes through the inguinal ligament. Common underlying causes include obesity, diabetes mellitus, old age, pregnancy, surgery, trauma or increased intra-abdominal pressure. The incidence in general population is 33 per 100,000. The condition is usually self-limiting.2 However, in certain cases, it has been found to be associated with abdominal or pelvic tumors. Given that these are possible underlying etiologies, are imaging studies always indicated? Here I report a case of persistent meralgia paresthetica as the only early presentation in a case of Ewing’s Sarcoma.

Case Description: A 26 year-old Caucasian male presented to the primary care clinic with right lateral thigh numbness for 3 months prior to presentation. Physical examination revealed a body mass Index of 25 and examination was consistent with lateral cutaneous femoral nerve mononeuropathy. Otherwise he was a healthy, physically active young man. Other review of systems and physical examination were unremarkable. Electromyography was performed and confirmed the diagnosis of meralgia paresthetica. A hip x-ray was negative for fractures or dislocation. The patient was instructed to avoid tight belts and follow up in the clinic. Two months later, he returned to the clinic with worsening burning pain of the lateral thigh that worsened with right hip flexion and was associated with right lower quadrant abdominal discomfort and self-reported right lower quadrant abdominal mass. CT of abdomen and pelvis with contrast showed a large heterogeneous mass in the right retroperitoneal pelvis extending into the right groin [Figure A], as well as sclerotic lesions within the bony pelvis. PET scan showed a large soft tissue mass with necrosis concerning for a high-grade tumor as well as lung metastasis. A needle biopsy pathologically diagnosed Ewing’s sarcoma. The patient then underwent neo-adjuvant chemotherapy and was scheduled to have a surgical evaluation.

Discussion: Meralgia paresthetica is a clinical diagnosis. It is a relatively common condition typically seen in obese, diabetic adults, with the incidence 7 times higher in the diabetes population.3 In the majority of cases, it is a self-limiting, benign disease and no intervention is required. Weight control and avoidance of tight belts and pants is a conservative treatment tried before consideration of steroid injections or surgical decompression. For persistent symptoms lasting more than one month in non-obese, non-diabetic young patients, additional underlying etiologies should be considered.4 In this case, the patient had a fast growing tumor. There have been cases of different intra-abdominal processes such as renal cell carcinoma, lipoma, hemangiomatosis,5 acute or chronic appendicitis 6, 7 as well as peritoneal dialysis reported as causes of meralgia paresthetica. Due to these rare but serious conditions, it is always advisable to extend the study with imaging tests.


Asymptomatic underlying Crohn’s disease diagnosed in a patient with a cecal mass

Yousef Nassar MD, PGY2 Resident, Internal Medicine; Arsa Batool MD, Division of Gastroenterology, Albany Medical College

Case presentation: A 67-year-old male presented to Albany Medical Center with syncope. He was at his doctor’s office and had syncope during his routine physical. He went to the emergency department at an outside hospital, where he received intravenous fluids as well as a blood transfusion and was discharged home. He continued to have weakness and lightheadedness and had another syncope episode at home, which prompted his presentation to Albany Medical Center. He denied any chest pain, palpitations, or dyspnea on exertion. He also denied having any abdominal pain, nausea, vomiting, change in bowel habits, melena or hematochezia. He reported a history of peptic ulcer disease 35 years ago. Colonoscopy was 5 years ago which demonstrated benign polyps which were resected at that time. Workup during this hospital admission revealed a hemoglobin level of 8.9 g/dL hematuria 28.8, MCV 80.4, Total Iron 358, TIBC < 378, Iron saturation > 95%. Other lab studies were normal. The patient underwent a colonoscopy to investigate anemia. Colonoscopy revealed a partially obstructing tumor in the cecum (figure 1), which was diagnosed as adenocarcinoma by pathology. Subsequently, a right hemicolectomy was performed.

During the procedure, the terminal ileum appeared thickened and “fat creeping” was noted. The distal 30 cm of the small intestine appeared thickened and inflamed. Pathological report showed inflammatory changes of both small intestine and portions of the resected large intestine suggestive of a possible Crohn’s disease. Magnetic Resonance enterography per-
Asymptomatic underlying Crohn’s disease diagnosed in a patient with a cecal mass (continued)
Yousef Nassar MD, PGY2 Resident, Internal Medicine; Arwa Batool MD, Division of Gastroenterology, Albany Medical College

formed one month after the hemi-colectomy procedure showed no findings to suggest active Crohn’s disease.

Biopsy revealed Crohn’s disease. The patient remained asymptomatic at the time of follow up colonoscopy. CRP level was 0.7, complete blood count and chemistry were all normal on follow up. He was started on mesalamine therapy for his active but asymptomatic disease. Repeat colonoscopy a year after starting mesalamine treatment again revealed an area of moderately altered vascular, congested, erythematous and friable mucosa at the site of the ileocolic anastomosis with normal ileum and colon. At this follow up, he was started on immunomodulatory therapy with 6-mercaptopurine.

**Discussion:** Crohn’s disease and ulcerative colitis are chronic idiopathic inflammatory disorders of the gastrointestinal tract. It is estimated that 1.2 million people in the United States suffer from inflammatory bowel diseases. Crohn’s disease can affect any part of the gastrointestinal tract from the mouth to the perianal area. Presenting symptoms vary greatly among patients but typically include fatigue, prolonged diarrhea, weight loss and fever. Patients with inflammatory bowel diseases are at an increased risk of colorectal cancer, the risk being higher in ulcerative colitis whereas patients with Crohn’s disease are at an increased risk of small intestinal cancer and anal carcinoma when compared with Ulcerative colitis. This case illustrates that patients may present with active disease that is asymptomatic. This is an atypical presentation of inflammatory bowel disease found on surgical specimen originally and subsequently seen on biopsies from the anastomotic site. C-reactive protein can sometimes help assess active inflammation if it is elevated, but in our patient, it was normal.

A study by Kiran et al of 240 inflammatory bowel disease patients suggested that the median duration of disease prior to the diagnosis of colorectal cancer was similar for Crohn’s disease and ulcerative colitis at 15 and 18 years, respectively. In our case, a previous colonoscopy 5 years ago did not reveal any evidence of malignancy or inflammatory bowel disease and the patient did not have any symptoms to suggest inflammatory bowel disease.

**Diagnosis:**

**Introduction:** Heart Failure with Preserved Ejection Fraction (HFpEF) is a common condition (1.1-5.5%) that accounts for significant individual and societal burden. It represents 40-70% of all heart failure cases and its incidence continues to rise. Its increasing incidence has been attributed to the rising prevalence of hypertension, obesity, atrial fibrillation as well as prolonged life expectancy of the population and improved recognition. When compared to heart failure with reduced ejection fraction (HFrEF), HFpEF patients are usually older and more commonly female. Their mortality and length of hospitalization approaches that of HFrEF patients in observational studies, although it has been lower in clinical trial populations.

Despite the increasing prevalence and significant societal burden of HFpEF, understanding of the underlying pathophysiology mechanisms is limited. Most pathophysiologic abnormalities in patients with HFpEF are related to the diastolic phase of the cardiac cycle with impairment of ventricular relaxation and ventricular stiffness leading to compromise of the ventricular filling and subsequently elevated diastolic pressures. The systolic function of the ventricles remains normal and the ejection fraction (EF) is preserved. The clinical outcome of these physiologic changes presents as symptoms and signs of heart failure.

The diagnosis of HFpEF is challenging and is generally based on clinical evidence of heart failure, a non-dilated LV with EF>50 percent, evidence of diastolic dysfunction on non-invasive echocardiographic or invasive cardiac catheterization assessment, and exclusion of other causes of HF. However, the diagnostic criteria used by observational studies and clinical trials vary widely creating confusion when interpreting their outcomes.

Asymptomatic diastolic dysfunction is much more common than HFpEF. Thus, it is important to recognize that the presence of diastolic dysfunction and an EF>50 percent does not necessarily indicate HFpEF unless the clinical syndrome of heart failure is present. This is illustrated by a community-based survey that evaluated 2042 subjects ≥45 years of age. The overall prevalence of clinical heart failure in this study was 2.2% of these, almost half had HFpEF. Among

Diagnostic Challenges and Management of Heart Failure with Preserved Ejection Fraction: What Have the Last Decades Brought to Us? (continued)

Efstathios Kourompakis, MD, PGY3 Resident, Internal Medicine, Gianni Bono, MD, PGY2 Resident, Internal Medicine Michael Francke, BS, MS4, Mikhael Tozrueff, MD, Division of Cardiology, Albany Medical College.

subjects without HF, 28.1 percent had some degree of diastolic dysfunction using Doppler echocardiographic criteria. The development of worsening diastolic dysfunction is associated with an increased risk of developing HF. 1, 6

Clinical trials have largely failed to show improvement in morbidity and mortality of HFrEF patients. The current review focuses on the most recent updates in regards with diagnosis and management of HFrEF.

Methods: A comprehensive literature review was performed in March 2017 within Pubmed. The search included the terms: heart failure with preserved ejection fraction, heart failure with normal ejection fraction, diastolic heart failure, diagnostic criteria, diagnosis and management. Only English literature was included. Additionally, the references section of relevant papers was manually searched and appropriate studies were retrieved and reviewed. Two investigators searched the literature individually and their findings were combined.

Diagnosis of HFrEF: The diagnosis of HFrEF has evolved significantly over the last three decades as new laboratory and imaging modalities have developed (Table 1). The diagnostic criteria that have been used in observational studies and clinical trials vary widely and this contributes to the failure of these studies to show significant improvement in prognosis of the disease. Currently, the diagnosis of HFrEF is based on clinical evidence of heart failure, a non-dilated LV with EF≥50, evidence of diastolic dysfunction on tissue Doppler imaging or elevated end-diastolic pressure on cardiac catheterization, and exclusion of other causes of HF with EF≥50 percent (mainly cardiomyopathies, valvular heart disease and pericardial disease). 7 Recently, expert societies recognized that patients with an LVEF in the range of 40–49 percent represent a 'gray area', and they were distinguished as heart failure with mid-range ejection fraction (HfMFRF). 

The European Society of Cardiology in their most recent guidelines used the following diagnostic criteria for HFrEF: 1) Symptoms and signs of heart failure, 2) LVEF≥50 percent, 3) elevated levels of natriuretic peptides (BNP >35 pg/mL and/or NT-proBNP >125 pg/mL), and 4) objective evidence of other cardiac functional and structural alterations. Key structural alterations are a left atrial volume index (LAVI) >34 mL/m² or a left ventricular mass index (LVMI) ≥135 g/m² for males and ≥115 g/m² for females. Key functional alterations are an E/e′ ratio >14, LA maximum volume index >34 mL/m², and peak TR velocity >2.8 m/sec. 8 If more than half of these criteria are met, then LV diastolic dysfunction is present. Of note, it was recommended that age appropriate cutoff values should be considered when evaluating older individuals given the physiologic myocardial changes with aging.

Finally, presence of certain comorbidities increases diagnostic confidence as HFrEF is closely associated with them. These include chronic hypertension, obesity, chronic kidney disease, diabetes, and atrial fibrillation.

Management of HFrEF: The management of HFrEF lacks the plethora of evidence seen for HFrEF. Multiple randomized controlled trials have failed to show clear improvement in morbidity and mortality (Table 2). This could be partially attributed to the heterogeneity of the disease and the lack of strict diagnostic criteria used in the trials. The management of HFrEF is therefore currently focusing on controlling the underlying comorbidities associated with HFrEF, including hypertension, chronic kidney disease, obesity, atrial fibrillation and diabetes as well as treatment of the acute decompensations. If coronary artery disease is suspected, stress testing and cardiac catheterization should be performed.

The most recent American College of Cardiology Foundation/American Heart Association guidelines recommend systolic and diastolic blood pressure control (Class IB indication) as well as symptomatic treatment with diuretics in patients with HFrEF and volume overload (Class IC indication). 9 In patients with coronary artery disease in whom angina or demonstrable myocardial ischemia is present, coronary revascularization is recommended (Class IIaC indication). Management of atrial fibrillation per published clinical practice guidelines is also proposed (ClassIIaC indication). ARBs could be considered to decrease hospitalization (ClassIIb indication). Nutritional supplementation is not recommended in HFrEF. Omega-3 polysaturated fatty acid (PUFA) supplementation is reasonable to use as adjunctive therapy in HFrEF patients with NYHA class II–IV symptoms, unless contraindicated, to reduce mortality and cardiovascular hospitalizations (Class IIaB).

The European Society of Cardiology guidelines published in 2016 make similar recommendations. The discordance between the inclusion criteria used in the clinical trials and the recent classification of patients with LVEF 40–49 percent to a separate category by international guidelines is worth attention.

Final Remarks: HFrEF is a challenging diagnosis. Evidence of diastolic dysfunction on imaging does not equal HFrEF in the absence of the clinical syndrome. Management of HFrEF should currently focus on controlling the underlying comorbidities and treating the exacerbations of the disease. Uniform use of strict diagnostic criteria in clinical trials is required.

Table 1: Evolution of diagnostic criteria for heart failure with preserved ejection fraction over the last three decades

<table>
<thead>
<tr>
<th>Years</th>
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<th>Diagnosis Criteria</th>
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<tbody>
<tr>
<td>1996</td>
<td>Fuster et al. 1996</td>
<td>LV dilation and EF ≥ 50, evidence of LV diastolic dysfunction, and 2 of the following: 1) LVF ≥ 1.1 L/m² in women or ≥ 1.3 L/m² in men; 2) LVEF &lt; 35% in men or &lt; 40% in women; 3) NT-proBNP ≥ 1000 pg/mL; 4) Transthoracic echocardiography: LA dilatation ≥ 40 mL/m²; 5) LVMI ≥ 135 g/m² for males and ≥ 120 g/m² for females.</td>
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<td>1999</td>
<td>Fuster et al. 1999</td>
<td>LV dilation and EF ≥ 50, evidence of LV diastolic dysfunction, and 2 of the following: 1) LVF ≥ 1.1 L/m² in women or ≥ 1.3 L/m² in men; 2) LVEF &lt; 35% in men or &lt; 40% in women; 3) NT-proBNP ≥ 1000 pg/mL; 4) Transthoracic echocardiography: LA dilatation ≥ 40 mL/m²; 5) LVMI ≥ 135 g/m² for males and ≥ 120 g/m² for females.</td>
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<tr>
<td>2006</td>
<td>Fuster et al. 2006</td>
<td>LV dilation and EF ≥ 50, evidence of LV diastolic dysfunction, and 2 of the following: 1) LVF ≥ 1.1 L/m² in women or ≥ 1.3 L/m² in men; 2) LVEF &lt; 35% in men or &lt; 40% in women; 3) NT-proBNP ≥ 1000 pg/mL; 4) Transthoracic echocardiography: LA dilatation ≥ 40 mL/m²; 5) LVMI ≥ 135 g/m² for males and ≥ 120 g/m² for females.</td>
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<td>2016</td>
<td>Fuster et al. 2016</td>
<td>LV dilation and EF ≥ 50, evidence of LV diastolic dysfunction, and 2 of the following: 1) LVF ≥ 1.1 L/m² in women or ≥ 1.3 L/m² in men; 2) LVEF &lt; 35% in men or &lt; 40% in women; 3) NT-proBNP ≥ 1000 pg/mL; 4) Transthoracic echocardiography: LA dilatation ≥ 40 mL/m²; 5) LVMI ≥ 135 g/m² for males and ≥ 120 g/m² for females.</td>
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Key structural alterations are a left atrial volume index (LAVI) >34 mL/m² or a left ventricular mass index (LVMI) ≥135 g/m² for males and ≥115 g/m² for females. Key functional alterations are an E/e′ ratio >14, LA maximum volume index >34 mL/m², and peak TR velocity >2.8 m/sec. 8
Diagnostic Challenges and Management of Heart Failure with Preserved Ejection Fraction: What Have the Last Decades Brought to Us? (continued)

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Table 2: Clinical trials on management of heart failure with preserved ejection fraction.

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Authors</th>
<th>Journal</th>
<th>Year</th>
<th>Type of HF</th>
<th>Clinical Setting</th>
<th>Intervention</th>
<th>Outcomes</th>
<th>Follow-up</th>
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<tbody>
<tr>
<td>CHARM-Added</td>
<td>Anstrom KJ, Levine JA, et al.</td>
<td>JAMA 2006;295:2813-28</td>
<td>2006</td>
<td>HFpEF</td>
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Review of 3rd International Consensus Definitions for Sepsis and Septic Shock- SEPSIS-3

Hau Chiang, DO, PGY3 Internal Medicine, Albany Medical College

The definition of sepsis was last revised in 2001 by the SEPSIS 2 Task Force. Since then, there have been several attempts to better understand the pathophysiology and management of sepsis that warranted a reexamination of the sepsis definition. Severe Inflammatory Response Syndrome (SIRS) Criteria was described about 23 years ago to analyze the clinical expression of a host’s inflammatory response. SIRS Criteria has many limitations, most pronouncedly the low specificity for an infection. The use of 2 or more SIRS criteria to identify sepsis has poor discriminant validity, meaning that SIRS can present in many hospitalized patients including those with an infection. 1 A retrospective study conducted by Govindan et al. in Annals of Internal Medicine on specificity of SIRS showed that it missed one out of eight patients with severe sepsis. Patient with SIRS negative severe sepsis had a lower but still a substantial mortality compared to SIRS positive severe sepsis counterparts. 2 Kaukonen et al. ’s analysis of ICU patients with infection and organ dysfunction revealed that 12% did not meet SIRS criteria. 3 Because SIRS Criteria lacks both the discriminant and convergent validities, the SEPSIS 3 Task Force has suggested to abandoned current approach to sepsis with SIRS Criteria and established a new set of recommendation.

The Third International Consensus Definition for Sepsis and Septic Shock was published in JAMA and presented at the 45th annual SCCM Critical Care Congress in Orlando on February 22, 2016 with the objective to re-examine and update the definitions of sepsis and septic shock. 4 The definitions of sepsis have gone through extensive multispecialty and multinational research and innovation over the past few decades [Figure 1]. Sepsis remains a major leading cause of morbidity and mortality. It also contributes to an increasing health care cost, approximately $20 billion or 5.2% of total hospital cost in 2011. 5 Incidence of sepsis diagnosis is on the rise, likely due to an aging population with more morbidities, better understanding and recognition of sepsis and better reimbursement and financial incentive for a particular sepsis coding. In the 1991 Sepsis-1 conference, Bone et al. developed the initial definition of sepsis as a host’s systemic response to an infection. Sepsis with organ dysfunction was characterized as severe sepsis which can progress to septic shock if hypoten sion persisted despite adequate fluid resuscitation. In 2001, the SEPSIS-2 Task Force reassembled to expand the list of diagnostic criteria, however the definitions of sepsis, severe sepsis and septic shock remained unchanged for another 2 decades. 6 The Task Force involved in SEPSIS-3 endorsed by the Society of Critical Care Medicine and the European Society of Intensive Care Medicine included 19 mem-
Review of 3rd International Consensus Definitions for Sepsis and Septic Shock- SEPSIS-3 (continued)

Hau Chiang, DO, PGY3 Internal Medicine, Albany Medical College

bers comprised of intensivists, infectious disease specialists, pulmonology, medicine and surgery selected for their expertise in sepsis pathobiology, clinical trials, translational research and epidemiology. The Task Force evaluated several scores, signs and symptoms in a cohort of 1.3 million medical records of 12 community and academic hospitals. Confirmatory analysis was done in 4 external US and non-US data set containing data from more than 700,000 patients. They found that the Sequential Organ Failure Assessment (SOFA) score is the most effective in identify patients with high mortality in ICU settings (Figure 2). Therefore, the Sepsis-3 Task Force recommended the use of the SOFA score to assist with identifying critically ill patients. For infected patients outside the ICU, on general medicine floor and the ED, a quick SOFA (qSOFA) score was developed. This score allocates one point for each of the following: Respiratory rate of 22/min or greater, altered mental status [GCS <15], systolic BP of 100 mmHg or less. It is important to understand that qSOFA does not, however, define sepsis outside of the ICU. It is rather a quick way to identify patients suspected of an infection that are more likely to have poor outcome especially if they have at least 2 points on the qSOFA assessment.

Sepsis was redefined as life threatening organ dysfunction caused by a dysregulated host response to infection. Organ dysfunction can be assessed using the SOFA score of 2 points or more, which is associated with mortality of greater than 10%. Septic shock is redefined as a subset of sepsis and is associated with a greater risk for mortality than sepsis alone. Patients with septic shock are identified by the need for vasopressors to maintain MAP > 65mmHg and serum lactate level of >2mmol/L in absence of hypovolemia. A combination of the two is associated with an hospital mortality of >40%. Septic shock is no longer used in the new definition. The Task Force concluded that the new definition and clinical criteria should be implemented in the assessment of septic patients due to greater consistency with epidemiologic studies and clinical trials. It also assists in earlier recognition and hence a timely response to patients with sepsis or at risk of developing sepsis.

Since the publication of SEPSIS-3 consensus definition of Sepsis, the response gathered from the health care community has not been uniform. The new definition of sepsis reflects an up-to-date view of sepsis biology and organ dysfunction. With the SOFA and qSOFA scoring, clinicians are now able to monitor organ dysregulation and the consequence risk for mortality, which is very different from the prior SEPSIS 1 and 2 approaches of ruling in or out sepsis by counting SIRS criteria. There are concerns about the revision of old SIRS Criteria. Given that positive SIRS identifies approximately 88% of patient with sepsis, and the incidence of sepsis related death has been declining worldwide. In addition, there are concerns that the new definition is better suited for identifying and managing patients in the ICU rather than non-ICU settings given its strong emphasis on organ dysfunction. To apply SOFA scoring, it is necessary to obtain laboratory data (ABG, urine creatinine, CBC, CMP, Lactic acid etc). Certain laboratory testing e.g. serum lactate level done routinely but not universally, especially in developing countries. The adoption of SEPSIS 3 may require additional laboratory tests that may be costly.

Sepsis syndrome is not completely understood. There are no simple clinical criteria, biological, imaging or lab features that are unique to a septic patient. We must remain aware of any clinical manifestation suggestive of sepsis and formulate treatment plan base on our level of suspicion. The Sepsis-3 consensus reemphasized the importance of early identification and better risk stratification of patients with sepsis. With the new definition still under the review of clinicians world-wide, it is unclear how this will impact our clinical judgement and affect future diagnosis and treatment guideline development for patients with sepsis. The SEPSIS 3 Task Force acknowledges that the sepsis definition should be reviewed and updated again in the near future as we learn more about the disease process. The new definition opens up more room for discussion and calls for additional research on sepsis with the hope to reduce sepsis related mortality.

Key concepts of sepsis from the SEPSIS 3 consensus.

- Sepsis is the primary cause of death from infection, especially when not recognized early.
- Sepsis is a syndrome shaped by the host’s epidemiologic factors [age, sex, race, genetic determinant, age, comorbidities, environment].
- What differentiates sepsis from infection is dysregulated host response and presence of organ dysfunction.
- Organ dysfunction induced by sepsis can be occult. Organ dysfunction should be considered in patients with an infection. Conversely, an unexplained organ dysfunction should also raise the possibility of an underlying infection.
- Comorbidities, medical intervention, preexisting acute illness can affect the clinical and biological phenotypes of sepsis.
- Infections may cause local organ dysfunction without generating a dysregulated systemic response.

New Terms and Definitions derived for the SEPSIS 3 Consensus.

- Sepsis is a life-threatening organ dysfunction caused by dysregulated host response to infection.
- Organ dysfunction is identified as an acute change in total SOFA score>2 points as consequence of an infection. Baseline SOFA is assumed zero in a patient without pre-existing organ failure. SOFA >2 reflects an increased mortality risks of 10% in general hospital population with an infection.
- Patients with a suspected infection who are likely to have a prolonged ICU stay or with a high in-hospital mortality may quickly identified at bedside with qSOFA.
- Septic shock is now a subset of sepsis. It is defined as persisting hypotension requiring vasopressors to maintain MAP > 65 mm Hg and having a serum lactate level of >2 mmol/L despite adequate volume resuscitation. In these patient, the estimated hospital mortality is 40% or greater.
- Severe sepsis is no longer a term to be used.
Review of 3rd International Consensus Definitions for Sepsis and Septic Shock- SEPSIS-3 (continued)

Hau Chieng, DO, PGY3 Internal Medicine, Albany Medical College

The Efficacy of Urate-Lowering Therapy in Preventing the Recurrence of Gout Attacks

Sathya K. Velkuru, DO, PGY3 Internal Medicine; Bija Bhatt, MD Rheumatology Fellow; Albany Medical College

New guidelines have surfaced from the American College of Physicians (ACP) in regards to urate-lowering therapy (ULT) in the management of gout. In the most recent guidelines published in the Annals of Internal Medicine in 2017, there was high-quality evidence that showed that ULT did not reduce the risk of gout attacks within the first 6 months. However, observational evidence revealed that patients who achieved lower urate levels after 1 year of ULT had fewer gout flares. Based on this evidence, it is difficult to determine if the benefits of long-term use (greater than 12 months) in patients with a single or infrequent gout attacks (<2 per year) reduces the risk of gout attacks. They suggest that ULT is not recommended in cases where the patient would have no or infrequent occurrences but do recommend considering ULT in cases of recurrent gout (>2 episodes per year) or problematic gout, such as gout associated with tophi or urolithiasis. The caveat in this situation is that it is impossible to determine which patients will have recurrent attacks even though patients with higher urate levels (>8 mg/dL) are shown to have a greater risk. Some patients and providers may prefer to initiate long-term ULT while others may prefer to treat flares if they occur. If ULT is chosen, allopurinol and febuxostat are both equally effective in decreasing serum urate levels.

Another emphasis in the new guidelines is that there is insufficient evidence to recommend escalating urate-lowering therapy to reach a serum urate target level. Despite there being an association between lower urate levels and the reduced incidence of gout flares, the authors state that other underlying patient characteristics could have accounted for the reduction in flares. They prefer an approach to base the intensity of ULT on overall patient characteristics vs only serum urate level to avoid recurrent gout attacks and to consider the costs versus the benefits of ULT.

However, the new ACP guidelines differ from the American College of Rheumatology’s (ACR) guidelines from 2012 in some key aspects. The ACR recommends treatment with urate lowering therapy for any patients with gouty arthritis in addition to tophi, or frequent attacks (>2 attacks/year), or CKD stage 2 or worse, or past urolithiasis. In addition, the ACR recommends targeting a urate goal of <6 mg/dL for all patients and regular monitoring of serum urate levels during ULT titration and to assess for compliance. Serum urate levels can be monitored every 6 months once an optimal dose of ULT is achieved. If palpable and visible tophi are still present on exam, they recommend attempting to achieve a urate goal of less than 5 mg/dL.

These differences in ULT guidelines pose many questions in regards to ULT in gout management. Since the primary care provider is likely to manage the first occurrence of gout, the ACP guidelines may be more directed to primary care physicians who may not be adequately trained in managing complicated gout cases, monitoring serum urate levels, and focusing on patient compliance with ULT medications, such as allopurinol and febuxostat. It is also likely that complicated gout cases will be referred to a rheumatologist for further management, which may lead to the ACR’s recommendation of strict urate level monitoring. These differences will need further clarification by conducting more studies to elucidate the most appropriate duration of ULT if this route is chosen.

Test Your Knowledge with our Electrocardiogram Quiz

Adam Austin MD, Pulmonary/Critical Care Medicine Fellow, Albany Medical College

48 year old male presented to the hospital with syncope one day prior to admission while ambulating in his kitchen. The patient was in his routine state of health when he had a sudden loss of consciousness. He denied any incontinence of bowel or bladder following the incident, tongue biting, or weakness. The patient did not endorse any chest discomfort, palpitations, headache, visual changes, nausea, emesis, diaphoresis, dyspnea, or pleuritic chest pain.

His medical history was pertinent for Diabetes Mellitus Type II, controlled with metformin. He was a nonsmoker but had a history of alcoholism, but was in remission for several years. He was employed as a school bus driver.

On physical examination, he was morbidly obese, afebrile with blood pressure 110/75, heart rate 105 and regular, respiratory rate 16, Oxygen saturation was 92% while receiving oxygen at 2L/minute by nasal cannulae. Cardiopulmonary examination demonstrated normal s1/s2, no murmurs, rubs or gallops appreciated, and no wheezing or crackles. No pitting edema, or lower extremity asymmetry and erythema were identified on examination. On neurological examination was normal.

EKG was performed and is shown:

What is the Diagnosis?

Answer: McGinn-White Pattern with Anterior Subepicardial Ischemic Changes in Submassive Pulmonary Embolism

Discussion: Pulmonary Embolism (PE) is a feared entity and its missed diagnosis is of great concern, be it in the emergency room or intensive care unit, due to the potential to cause obstructive shock and cardiovascular collapse. Thus, PE has to be considered in the working differential diagnosis for syncope. In a recent prospective study, pulmonary embolism was even found to be the causative etiology in the first episode of syncope in approximately 17% patients, or roughly 1 in 6, presenting with this symptom to the hospital.1

McGinn and White first described the S1Q3T3 in 1935 in the setting of acute cor pulmonale in the presence of a pulmonary embolism2, in which an S-wave in lead I, and a Q-wave and T-wave inversion in lead III were present. However, symmetric T-wave inversions in conjunction with S1Q3T3 can also help highlight right heart strain and subepicardial ischemia in leads V1-V4, as seen in this patient’s EKG (Figure 1). Ferrari et al. demonstrated that precordial T-wave inversions were the most common EKG finding in PE, and is associated with massive and severe PE.3 The appearance of this EKG may be misleading without the clinical history of PE, or identification of the S1Q3T3, and be thought of as simply anterior ischemia in an acute coronary syndrome, often referred as Wellen’s sign.


RESEARCH NEWS:

- Dr. Paul Feustel Ph.D. Professor of Neurosciences and Experimental Therapeutics here at AMC will be giving us a talk on Introduction to Biostatics geared towards individuals starting a research project. It is scheduled from May 17th at 12:00 pm in ME-100.

- Also, do you know that AMC Schaffer library provide EndNote™ for free installation to all the residents and students. End Note EndNote is reference management software with features to keep all your references and reference-related materials in a searchable personal library and use them in word-processing documents to create formatted citations and bibliographies or independent reference lists. You may contact librarytechhelp@amc.edu for installation instructions.