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Mini-Symposium: Controversies in the Evaluation and Treatment of Sickle Cell Disease

Systemic Corticosteroids in Acute Chest Syndrome: Friend or Foe?

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EDUCATIONAL AIMS

THE READER WILL:

- Learn the the pathophysiology of the Acute Chest Syndrome (ACS) and its various triggers
- Review the inflammatory responses elicited by the various triggers of the ACS
- Be able to evaluate the evidence on the benefit of systemic steroids in the treatment of Acute Chest Syndrome (ACS) and of the potential side effects

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SUMMARY

Acute chest syndrome(ACS) is the most common pulmonary complication of sickle cell disease (SCD), the second most common cause of hospitalization and the primary cause of death in patients with sickle cell disease. Its highest prevalence is in early childhood. The pathogenesis of ACS is unknown but many predisposing conditions and mechanisms have been implicated including infections, pulmonary fat embolism, asthma and ischemic reperfusion injury. These conditions are associated with inflammation and therefore, the use of corticosteroids has been advocated because of their anti-inflammatory properties. Although, significant benefits from their use have been shown, there is great reluctance in using them because of reports of serious adverse effects, such as readmission to the hospital due rebound pain crisis, stroke, renal infarction, coma and even death. The current article reviews the evidence in favor and against the use of corticosteroids in ACS. Emphasis is given on the potential benefits vs. risks among the different types of corticosteroids, the importance of the dosing regimen and the role of underlying co-morbidities.

INTRODUCTION

Acute chest syndrome (ACS) is the most common form of acute pulmonary disease among patients with sickle cell disease (SCD), occurring in as many as 50% of patients [1]. It is the second most common cause for admission to the hospital (after vaso-oclusive crises) and the leading cause of death accounting for up to 25% of SCD-related deaths [2]. ACS occurs in all ages but it is more common in children with the highest prevalence occurring between the ages of 2 and 5 years [3]. Several conditions and mechanisms are known to predispose, exacerbate or complicate the pathogenesis of ACS but the exact cause remains unknown [4]. As a result there is no specific therapy for ACS. Instead its management has focused on the treatment of presumed bacterial infection with broad spectrum antibiotics, judicious administration of intravenous fluids, and pain medications in order to alleviate the patient's discomfort and to prevent atelectasis caused by the patients' hypoventilation secondary to splinting. Simple or exchange blood transfusions decrease the percentage of sickled red blood cells, improve oxygenation and often stop the progression of ACS.

Given the increasing evidence that inflammation is an important factor in the presentation of ACS [5,6], treatment with immunomodulatory agents such as systemic corticosteroids has been advocated [7]. However, reports of serious side effects has made many clinicians reluctant to use corticosteroids. The current article reviews the available evidence in favor and against the use of systemic corticosteroids in SCD.

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ACS & Inflammation

The pathogenesis of ACS has been attributed to many diverse mechanisms in which the presence or development of inflammation feature prominently [4–6]. These conditions are briefly summarized below.

Infection

Patients with SCD develop functional asplenia due to infarction of the organ 'in situ' that predisposes them to infections especially by encapsulated organisms [eg pneumococcus]. Other mechanisms that may affect the immunity of patients with SCD have been also proposed including evidence from transgenic sickle mice that altered baseline immunity may be secondary to morphologic abnormalities of the splenic tissue [8]. Finally, there is clinical evidence of abnormal function of the complement system although the results have been contradictory [9]. Infants and young children are at higher risk for infections because of their naturally immature immune system.

ACS is a syndrome defined on the basis of a combined clinical and radiographic characteristics (development of a new pulmonary infiltrate involving at least one complete lung segment; fever; and any other constellation of pulmonary symptoms including hypoxemia, dyspnea, tachypnea, wheezing, chest pain, or cough) that is often difficult to distinguish from a typical bacterial pneumonia in a patient without SCD [2].

Although inflammation is characteristic of both entities, patients with SCD and ACS seem to develop a much more rapidly progressive and severe presentation suggesting a propensity to develop a more significant inflammatory response than non-SCD individuals. Indeed, studies in transgenic sickle mice have shown that those with SCD tend to mount a much more violent inflammatory response, and they seem to be much more susceptible to injury from the inflammatory mediators that are being released than compared with the non-SCD mice [10–13]. In other words, it is possible that patients with SCD may suffer not only by the increased susceptibility to infections but also by their own exaggerated inflammatory response that may then become the main trigger for the ACS.

Pulmonary fat embolism

Pulmonary fat embolism (PFE) is currently recognized as one of the major mechanisms associated with ACS [14]. Fatty bone marrow may be released into the blood as a result of bone marrow necrosis caused by a vaso-occlusive bony crisis. Embolic fat activates secretory phospholipase A2 (sPLA2), an enzyme that cleaves phospholipids and liberates free fatty acids and generates arachidonic acid that in turn produces inflammatory leukotrienes and prostaglandins. These fatty acids injure the pulmonary endothelium, increase the expression of VCAM-1 and promote the adhesion of erythrocytes to endothelium in vitro providing evidence for pathologic adhesive interactions in PFE. The concentration of sPLA2 in peripheral blood has been proposed as a laboratory marker of ACS, because it correlates with the course and severity of ACS. Specifically, the sPLA2 increases before ACS becomes clinically apparent, it peaks at the onset, and declines during resolution [15].

The basis for the PFE as a mechanism for the development of ACS has been based on the presence of lipid-laden macrophages (LLM) in bronchoalveolar lavage fluid in patients with ACS [16]. However, increased numbers of LLMs are not pathognomonic of fatty bone marrow embolization. Increased numbers of LLMs can also be found in cases of aspiration of fat containing food products, and most importantly they can be released from injured cells (e.g. in severe pneumonia or ARDS) [17]. Thus, it is possible that the presence of increased LLMs in the BAL may be due to cellular damage secondary to the ACS and not the underlying pathogenic mechanism of ACS.

Asthma

Several epidemiologic studies have reported an unusually high prevalence of airway hyperresponsiveness and asthma among children and adults with SCD compared with the general population (even after adjusting for race, socioeconomic conditions etc) [18,19]. Patients with SCD and asthma seem to have a much higher (as high as 6-fold) risk of recurrent ACS compared with those without history of asthma [19–22]. Most importantly patients with SCD who are admitted to the hospital for pain crises are more likely to develop ACS if they have asthma, and they seem to improve after treatment with bronchodilators [19–22]. Asthma is a classic inflammatory disease and its association with ACS suggests a possible synergistic effect by the presence of inflammation.

Animal data in transgenic sickle mice have shown that experimentally induced asthma is associated with greater mortality due to increased allergic lung inflammation (elevations in eosinophils, eosinophil peroxidase, and IgE levels) compared with control mice without asthma. Eosinophils (a major source of leukotrienes in asthma) and elevations of LTB4 and LTC4 in blood and LTE4 in urine also occur in patients with sickle cell disease [5].

Ischemia/reperfusion injury

SCD has traditionally been considered a disorder of microvascular vaso-occlusion secondary to mechanical obstruction by of deformed RBCs and subsequent tissue hypoxia [23] However, more recently a modified paradigm has emerged suggesting that the wide spectrum of clinical manifestations of SCA results from recurrent episodes of ischemia-reperfusion injury [5]. Ischemia-reperfusion triggers a multifactorial cascade including inflammatory response characterized by increased leukocyte and sickle erythrocyte adhesion to vascular endothelium and activation of coagulation, platelets and neutrophils. The data suggest that acute lung vaso-occlusive injury causes an inflammatory response that triggers chemotaxis of leukocytes and secondary injury [24–27].

SYSTEMIC CORTICOSTEROIDS AND ACS

Corticosteroids are powerful anti-inflammatory medications with pleiotropic beneficial effects in a variety of diverse clinical conditions including cancer (pain control and mood-elevation), in trauma (decrease the risk of fat-embolism) and complications/mortality from ARDS. [28–30] ACS shares many of the manifestations and pathology with these conditions (e.g. pain, fat embolism, hypoxemia and acute lung injury). Thus, there has been great interest in the role of systemic corticosteroids as the means of inhibiting the inflammatory response that accompanies tissue ischemia/infarction. Several clinical studies using different preparations and doses of corticosteroids have held promising results. Griffin et al. [31] used high dose methylprednisolone in vaso-occlusive crisis and reported significant reduction in the duration of analgesic therapy and hospitalization.

Bernini et al. [32] investigated the efficacy of a lower dose of a longer acting glucocorticoid, dexamethasone in 43 children with mild to moderately severe ACS in a randomized, double-blind, placebo-controlled trial. They showed reduction in the length of hospitalization by about 40%, in the need for transfusion due to worsening anemia, in the duration of fever, and in need of oxygen requirement and pain treatment.

Unfortunately, the successes associated with the use of corticosteroids in the setting of SCD have been accompanied by reports of complications ranging from recurrence of pain requiring readmission to the hospital, to episodes of severe vaso-occlusive