Therapeutic aspects of fat embolism syndrome

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Summary¹ Signs and symptoms of clinical fat embolism syndrome (FES) usually begin within 24–48 hours after trauma. The classic triad involves pulmonary changes, cerebral dysfunction, and petechial rash. Clinical diagnosis is key because laboratory and radiographic diagnosis is not specific and can be inconsistent. The duration of FES is difficult to predict because it is often subclinical or may be overshadowed by other illnesses or injuries. Medical care is prophylactic or supportive, including early fixation and general ICU management to ensure adequate oxygenation and ventilation, hemodynamic stability, prophylaxis of deep venous thrombosis, stress-related gastrointestinal bleeding, and nutrition. Studies support early fracture fixation as a method to reduce recurrent fat embolism and FES. The main therapeutic interventions once FES has been clinically diagnosed are directed towards support of pulmonary and neurological manifestations and management of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS).

Introduction
Fat embolism syndrome (FES) has been reported to occur in several clinical conditions including bone marrow transplant, pancreatitis, fatty liver and liposuction [1, 2]. However, FES is most commonly associated with long bone fractures. Although fat embolism may occur in up to 90% of trauma patients [3], FES occurs in only 2–5% of patients with long bone fractures [4]. FES is characterized by both pulmonary and systemic fat embolism [2, 5, 6, 7] and includes a spectrum of subclinical, mild to fulminate presentations [7, 8].

Clinical FES typically involves multiple organ systems; however, the pulmonary, neurological, hematological, and dermatological systems involvement is the most common.

In addition to fat embolization from the initial trauma, long bone fixation may result in additional embolizations and FES. During intramedullary nailing, the intramedullary canal pressure can reach 1000 mm Hg [9]. This elevated pressure during reaming appears to be temporally associated with embolization to the pulmonary circulation when studied with echocardiography [10]. Once fat is liberated into the circulation and embolizes, the pulmonary microvasculature becomes occluded.

Depending on the size of fat globules, smaller globules may traverse the pulmonary microvasculature and reach the systemic circulation, leading to the common neurological manifestation of FES. Although the pulmonary, cerebral, retinal, and skin microcirculations are typical clinical manifestations of FES, fat embolization can affect any microcir-
Discussion

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) may result from fat emboli occluding pulmonary capillaries [2, 12–16] and biochemical alterations that produce lung injury that directly damages the pulmonary capillary endothelium [2, 12, 13, 17, 18].

Although many patients with long bone fractures develop fat embolism, far fewer develop FES, suggesting that additional factors may be necessary in the development of lung injury. Biochemical fat embolization is associated with the release of free fatty acids (FFAs) [19]. FFAs in the lung are locally hydrolyzed in pulmonary circulation by lipoprotein lipase, which releases toxic substances that injure the capillary endothelium. The release of FFAs increases vascular permeability, producing alveolar hemorrhage, edema, and inactivate the surfactant molecules [20–26]. Ultimately, these pulmonary alterations lead to respiratory failure, resulting in ALI and ARDS.

As fat accumulates in the pulmonary microcirculation and lipoprotein lipase liberates FFAs, disseminated intravascular coagulation (DIC) and platelet aggregation further compound capillary disruption and systemic inflammation.

Fat emboli that pass through the pulmonary vasculature result in systemic embolization, most commonly in the brain and kidneys [27]. Cerebral FES is a rare, yet potentially lethal, complication of long bone fractures. Neurological symptoms vary from confusion with diminished Glasgow Coma Scale (GCS) to encephalopathy with coma and seizures. A clinical diagnosis may be difficult as cerebral FES may be masked by other clinical scenarios [28]. Diffuse encephalopathy, petichial hemorrhages, localized cerebral edema, and white matter changes have also been seen in patients diagnosed with FES. Magnetic resonance imaging (MRI) may be necessary to show the characteristic cerebral lesions of the acute state of FES as opposed to a CT scan, which appears normal [29, 30, 31].

Treatment

A specific treatment for FES does not currently exist [32]. Treatments with heparin, dextran, and corticosteroids have not been shown to reduce the morbidity or mortality as treatments for FES [1, 33]. However, when given prophylactically, corticosteroids (methylprednisolone) may have beneficial effects [34–38]. The mainstay of treatment for FES is supportive [32], therefore, prevention, early diagnosis, and adequate symptom management are paramount.

Although long bone fracture fixation is the main cause of fat embolism and FES, early fracture fixation may be critical in reducing recurrent liberation of fat into the circulation as a result of fracture movement [39].

Early fixation of long bone fractures within 24 hours has documented a reduction in the incidence of FES in patients who are stable enough to undergo surgery [40]. In addition, as patients with polytrauma are at risk of other forms of respiratory failure (atelectasis, pneumonia) and multiple system organ failure (MSOF), early fixation and patient mobilization may reduce complications [41]. Experimentally, increasing intramedullary pressure [42] has been shown to increase fat embolization. Methods to reduce intramedullary pressure and embolization during reaming have been developed, which include venting or applying a vacuum during reaming to limit the elevation of intramedullary pressure and thus reduce the incidence of fat embolization [43, 44].

Respiratory failure from FES is characterized as permeability edema with decreased compliance similar to oleic acid lung injury [15]. Gas exchange abnormalities include shunt and increased dead space from atelectasis and alveolar flooding comparable to ALI and ARDS from other causes [45–47].

The general goals of ALI and ARDS management focus on maintaining acceptable gas exchange while limiting ventilator-associated lung injury (VALI).

Supportive pulmonary therapies may include enhancement of spontaneous breathing and cough, early patient mobilization, utilization of positive end-expiratory pressure (PEEP), and a reduction in the use of sedation and neuromuscular blocking agents (NMBAs). By utilizing ventilator modes that allow spontaneous breathing and cough, patients are not mandated to conform to a clinician-set I:E ratio; rather, the patient may spontaneously breathe freely and interact with the ventilator. Traditionally, spontaneous breathing in patients with ALI or ARDS is discouraged, forcing the patient to adapt to predetermined ventilator settings. Controlled ventilation frequently requires heavy sedation or NMBAs to synchronize the patient with the ventilator, particularly in the management of patients diagnosed with FES and associated neurological manifestations.

Forms of ventilation that require excessive sedation and NMBAs preclude detailed assessment...
and the ability to perform serial neurological examinations. In addition, excessive sedation or NMBAs usage eliminates spontaneous breathing and the diaphragm's potential to facilitate dependent lung ventilation [48,49]. Data suggest spontaneous breathing may play a vital role during mechanical ventilation. Improvements in V/Q matching, alveolar recruitment, and cardiac output are often seen when effective spontaneous breathing is introduced during mechanical ventilation [48, 50, 51]. Elimination of spontaneous breathing and cough may result in additional ventilator days, adverse hemodynamic effects, ventilator-associated complications, and cost [52–54].

Recent data suggest PEEP may protect and even delay the onset of VALI [55]. Required PEEP levels to maintain end-expiratory lung volume in ALI or ARDS and limit shear forces may be substantial (>20 cmH₂O). Although the exact level of PEEP required to completely eliminate cyclic airway closure and shear force is unknown, studies demonstrate a wide spectrum of airway pressures exist within the acutely injured lung [56–60]. These studies suggest recruitment is a 'pan inspiratory' phenomenon and may require pressures of 30 cmH₂O or greater to fully recruit lung regions and prevent tidal shear stress [61]. An alternative to controlled ventilation is Airway Pressure Release Ventilation (APRV) which combines spontaneous breathing and an open lung method to optimize lung volume [62]. APRV allows patients to breathe comfortably, decreasing sedation needs and facilitating neurological examinations. Spontaneous breathing improves ventilation to dependent lung regions recruiting these regions without increasing applied airway pressure [48–51]. Patients with severe chest trauma and fat embolism have been successfully managed with APRV at R Adams Cowley Shock Trauma Center in Baltimore, Maryland as standard of care for multi-trauma patients since 1994. In addition to mechanical ventilation, more severe pulmonary dysfunction may benefit from prone positioning or extracorporeal membrane oxygenation [63].

Support of patients with FES and neurological complications is directed towards neurological examinations, including frequent monitoring of GCS and the patient's status. Patients with FES may develop cerebral edema, leading to rapid deterioration [64]. In such cases, ICP monitoring may be beneficial and should be considered [65]. In general, trauma patients should not have their neurological examination obscured by excessive sedation or NMBAs in order to allow them to tolerate mechanical ventilation [66]. Therefore, sedation and analgesia should be chosen carefully to optimize patient comfort while preserving neurological examination. Furthermore, the utilization of a sedation/agitation scale may provide consistency of examinations for neurological function as affected by sedation or analgesia.

Fat from long bones and subcutaneous tissue is composed of neutral fat including triglyceride, glycerol, and long chain fatty acids. Unsaturated fatty acids constitute 60–80% of acid elements [67]. FFAs are normally bound to serum albumin with only 1% in the unbound state [46]. They can produce tissue injury and inflammation, and are particularly toxic to capillary endothelium [15, 45, 68]. Oleic acid has been implicated as a key component in fat embolism and the development of ALI and ARDS [69–71]. Although albumin can bind oleic acid and render it non-toxic, albumin binding may be prevented or limited during fat embolization [69, 70].

Oleic acid may have a role in ARDS. Elevated plasma and broncoalveolar lavage oleic acid levels have been documented in patients with ARDS and are associated with increased vascular permeability, increased extravascular lung water, and inhibition alveolar fluid reabsorption [72].

Generally, the management of patients with FES includes adequate resuscitation to limit or prevent persistent shock states. Also, overaggressive reaming of the femoral canal should be avoided in femoral shaft fractures. Resuscitation remains a key element in the management of critically ill, polytrauma patients. Intraoperatively, these patients should be handled carefully and prolonged surgeries > 6 hours duration should be avoided.

Although the form of volume expansion used for resuscitation may or may not be relevant, some data suggest that albumin binding to oleic acid diminishes its edemogenic potential [73, 74]. Goodman found that human serum albumin has several binding sites for FFA and estimated that each gram of albumin can bind up to 110 mg of long-chain fatty acid [75].

Since fatty acids, such as oleic acid, are one of the factors involved in the development of ALI and ARDS, fluid resuscitation with albumin solutions may be beneficial. In addition, the use of albumin when combined with furosemide in patients with ALI and ARDS tends to improve oxygenation and may decrease ventilation duration. A recent meta-analysis of albumin therapy in general suggests improved mortality of acutely ill hospitalized patients [76].

In patients with fulminate FES causing obstructive shock and right ventricular failure, hemodynamic support with dobutamine, in addition to volume, may be superior in restoring RV-PA coupling and cardiac output over norepinephrine [77]. Other
agents to consider may include nitric oxide to lower pulmonary arterial pressure and unload the right ventricle.

**Conclusion**

The outcome in patients with FES who receive supportive care is generally favorable with mortality rates of less than 10% [78].

Pulmonary, neurological, and retinal abnormalities generally resolve completely. General management is supportive in nature and focuses on early fixation and mobilization. Organ support includes shock resuscitation and gas exchange support, which balances lung recruitment and limits the potential for VALI. Ideally, neurological support would include the ability to conduct a clinical neurological examination.

**Bibliography**


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