Fat embolism syndrome: A comprehensive review and update

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Abstract:
Fat embolism syndrome (FES) is a life-threatening situation, which warrants greater emphasis than it receives in the literature. FE occurs following various medical and surgical conditions leading to a cascade of systemic inflammatory process affecting multiple organs of the body, which may lead to end-organ failure. It has high mortality and morbidity. Despite advancement in science and technology, diagnosis of this fatal syndrome is mainly based on clinical symptoms and signs and no major definitive diagnostic tool and treatment method is available. At present, treatment of this disastrous medical condition is only supportive. In this review, we summarize the incidence, etiology, pathophysiology, and management of FES.

Keywords:
Fat embolism syndrome, organ failure, polytrauma

Introduction

Although a rare clinical condition, fat embolism syndrome (FES) is an alarming multidisciplinary phenomenon difficult to diagnose but if missed, may lead to death. Historically known from very past, it was first described by Zenker in 1861 that it is associated with long-bone fractures and often presents as a combination of neurological, pulmonary, dermatological, and hematological symptoms and observed fat deposition in the pulmonary capillaries during autopsy. Later in 1873, the first clinical case of FES was described by Bergmann in a patient of distal femur fracture. The actual incidence of FES is unknown as it varies significantly according to the cause and mild cases remain unnoticed very often but incidence of FES ranges from 0.5% to 29% in different studies. As reported by Bulger et al., in their retrospective study, incidence of FES was <1% whereas by Fabian et al. in their prospective study, it was 11%–29%. Overall mortality from FES had been reported from 5% to 15%. It would be wise to know that two clinical conditions “Fat Embolism” and “Fat Embolism Syndrome” although closely related but have completely different meaning. The term FE is described as the asymptomatic mechanical blockage of vascular channels by circulating fat globules in the lung parenchyma and peripheral circulation and term FES is described as the serious consequences of fat emboli producing a distinct pattern of clinical manifestations. Hence, the FES is a rare clinical entity in which circulating fat emboli or fat macroglobules lead to multisystem dysfunction which typically presents 24–72 h after the initial injury.

Etiology

FES may be associated with a variety of clinical conditions both traumatic as well as nontraumatic. Various clinical conditions complicated by FES are enumerated as follows.

Conditions associated with FE:
1. Trauma related
   a. Long-bone fractures
   b. Pelvic fractures

c. Fractures of other marrow-containing bones
d. Orthopedic procedures
e. Soft-tissue injuries (e.g., chest compression with or without rib fractures)
f. Burns
g. Liposuction
h. Bone marrow harvesting and transplant

2. Nontrauma related
   a. Pancreatitis
   b. Diabetes mellitus
c. Osteomyelitis and panniculitis
d. Bone tumor lyse
   e. Steroid therapy
   f. Sickle cell hemoglobinopathies
g. Alcoholic (fatty) liver disease
   h. Lipid fusion
   i. Cyclosporine A solvent.

Various risk factors have been identified in the recent studies for increases the risk for development of FES in a patient [Table 1].

It is reported in a study that patients with a single long-bone fracture have a 1%–3% chance of developing the FES, but it increases up to 33% in patients with bilateral femoral fractures.

Pathophysiology

Although FES genesis is an extremely complex phenomenon, various theories had been given in the past regarding this.

Gauss’ mechanical theory

In 1924, Gauss established the mechanical theory which points out the necessity of three factors for the development of FES. 

1. Injury to adipose tissue
2. Rupture of veins within the injury area
3. Passage of free fat into the open ends of the blood vessels.

According to this theory, the highest incidence of FES in long-bone fractures may be because of the disruption of venules in the marrow, which remain tethered open by their osseous attachments. Detection of FE in the form of passage of “echogenic material” by transesophageal echocardiography (TEE) during an orthopedic procedure supports this.

As FE is initially a venous phenomenon, so it is naturally expected that the lungs will be the first as well as most commonly affected organs. These fat emboli must migrate from venous circulation to arterial circulation to involve other body organs which can happen in various ways.

Lehman’s Biochemical Theory

In 1927, Lehman proposed a theory which states that production of toxic intermediates from plasma-derived fat molecules is responsible for development of FES. There are a number of biochemical mechanisms which are involved in FES. The embolized neutral fat globules as found in bone marrow do not cause acute lung injury (ALI). These are degraded into various ways.
toxic intermediates such as free fatty acids (FFAs), C-reactive proteins, and catecholamines which initiate the inflammatory cascade causing end-organ injury at various sites such as the brain and lungs. C-reactive proteins cause lipid agglutination which may obstruct blood flow in the microvasculature. It also agglutinates chylomicrons, low-density lipoproteins, and the liposomes of nutritional fat emulsions. In addition, catecholamines release due to circulating FFAs increases further lipolysis. The mobilization and lysis of excess triglycerides lead to the incomplete binding to albumin and eventual triglyceride entry into the circulatory system forming fat globules. Agglutination of chylomicrons into fat globules is enhanced by various mediators such as catecholamines, FFAs, protein degradation products, and C-reactive proteins. FFAs have also been associated with cardiac dysfunction, a probable feature of FES.

This theory explains the delay in development of clinical FES from initiating events as onset of symptoms may coincide with the degradation and agglutination of fat and onset of inflammatory cascade. This theory also explains the development of nontraumatic FES. This theory is further supported by animal studies which reported that neutral fat does not injure the lung; however, if it is hydrolyzed over the course of hours to several products, including FFAs, it may cause ALI or acute respiratory distress syndrome (ARDS).

Hence, from these different theories development of FES can be explained in two different phases, the first phase “Mechanical Phase” and the second phase “Biochemical Phase.”

**Clinical Presentation and Diagnostic Criteria**

FES is purely a clinical diagnosis. It usually occurs in the second and third decade of life and typically presents 24–72 h after the initiating injury. Rarely, cases can occur as early as 12 h or as later as 2 weeks. Patients of FES typically present with a clinical triad of pulmonary involvement, neurological involvement, and dermatological involvement.

Hypoxia is the most common clinical presentation, and very often, it is presented an hour before the onset of other clinical symptoms. Other manifestations of pulmonary involvement include tachypnea, dyspnea, and cyanosis and may lead to respiratory failure in 10% of the cases. This clinical picture must be distinguished from pneumonia and acute respiratory distress syndrome (ARDS) or ALI. In most of the cases of FES, pulmonary involvement requires mechanical ventilation or positive end-expiratory pressure (PEEP) ventilation.

Neurological features may be present either because of hypoxia or because of actual injury to brain parenchyma by circulating fat globules. Neurological involvement often occurs after the involvement of the respiratory system and is seen in up to 86% of the cases. Often patients with neurological symptoms present in a state of acute confusion, but it can vary from mild confusion to severe seizures and a level of altered consciousness. Various neurological features described in multiple studies are irritability, anxiety, agitation, confusion, drowsiness, delirium, convulsions, coma, hypotonia, rigidity, and decerebration. Focal neurological manifestations such as anisocoria, aphasias, apraxia, hemiplegia, paraplegia, tetraplegia, scotomas, and eye conjugate deviation although less common but have been reported. Almost all neurological deficits are transient and completely reversible most of the times.

Dermatological involvement with characteristic petechial rashes constitutes the last component of the FES clinical triad. These are noticed in up to 60% of cases and can be seen in the conjunctiva, oral mucous membrane, and skin folds of the upper body, especially the neck and axilla. It is observed that petechial rashes do not appear because of abnormality in platelet functions but appears as a result of embolization of small dermal capillaries leading to extravasation of erythrocytes. Typical petechial rashes usually appear within the first 36 h of development of FES and disappear completely within 7 days.

Meningococcal septicemia should be ruled out in differential diagnosis of other clinical signs may be present due to released toxic mediators due to initial injury or dysfunctional metabolism. These may include pyrexia, tachycardia, myocardial depression, electrocardiogram (ECG) changes suggestive of right heart strain, Purtscher’s retinopathy, coagulation abnormalities as in disseminated intravascular coagulopathy (DIC), and kidney involvement presenting as oliguria, lipiduria, proteinuria, or hematuria.

As described earlier that FES is purely a clinical diagnosis; various clinical manifestations (respiratory failure, neurological features, and petechial rashes) are not pathognomonic of FES as it may be seen in other polytrauma patients and also various laboratory tests and imaging findings are nonspecific, so various diagnostic criteria were given time to time for making the diagnosis of FES. Gurd and Wilson proposed clinical criteria for diagnosing FES [Table 2]. Lindeque proposed a diagnostic criteria for FES based only on the respiratory status of the patient [Table 3].

More recently, Schonfeld proposed FE Index for diagnosing FES which is a quantitative measure comprised of seven clinical features, each one is given a...
particular score and a score of >5 is required for making the diagnosis of FES [Table 4].\cite{40}

Diagnosis of FES is usually made on the basis of clinical findings, but biochemical investigations are also of value.

### Laboratory Investigations and Imaging Techniques

As emphasized earlier, various laboratory changes are typical of FES, they are not unique or diagnostic of this syndrome. Anemia, thrombocytopenia, coagulopathies, decrease in hematocrit, and increase in erythrocyte sedimentation rate various nonspecific findings which occur within 24–42 h and attributed to intraalveolar hemorrhage. It is well known that decrease in hematocrit is most common manifestation after a severe trauma, but it usually reaches at its lowest within 1–2 days of trauma and then become stable but a sudden drop in hematocrit after this may be contributed by pulmonary hemorrhages secondary to fatty acids toxicity. Thrombocytopenia is also a feature of FES which can be noted in about 30% of cases.\cite{31} Cases of FES may present laboratory changes similar to DIC and changes often described are reduction of serum calcium and platelets, increase of platelet adherence, prolonged times of activated partial prothrombin and thromboplastin, release of FDPs (fibrin degradation products), and reduction of circulating fibrinogen.\cite{29,31,41} As complement cascade have been suspected to be involved in the pathogenesis of FES due to activation of inflammatory cascade, so various laboratory investigations can detect the increase in complement activity; however, it is nonspecific and found in a lot of clinical conditions. An increase in serum level of FFAs, triglycerides, and AGLs is also noticed. These circulating AGLs are bonded to albumin molecules, so decrease in serum level of albumin may also be noticed. Although the most common pattern is the increase of circulating AGL after severe orthopedic injuries, serum levels of AGL have not been correlated to diagnosis or severity grading of FES.\cite{41,43} It is also noticed in various studies that the levels of lipase enzyme are increased between the 3rd and 5th day after trauma reaching their peaks around the 8th day, but it also lack diagnostic importance in FES.\cite{41,43} Fat droplets in the blood, urine, and sputum either in free form or inside the macrophages detected with Sudan or Oil Red O staining are noticed in FES, but these findings are also insensitive. It is a very common misconceptions that finding of fat globule in urine, sputum, or blood obtained from wedge pulmonary artery catheter is necessary for diagnosing FES, but in fact, their presence is of uncertain significance because we discussed at the beginning that presence of fat globules in urine or blood define FE, but it does not conclude FES diagnosis since majority of patients of FE do not progress with clinical features of this syndrome.\cite{4,5,31} Although early detection of FES may be done by preliminary investigations for the presence of fat globules in pulmonary capillary blood obtained from a wedged pulmonary artery catheter.\cite{44} Fat droplets may also be noticed in bronchoalveolar lavage but its use to aid in the diagnosis or to predict the likelihood of FES is still controversial due to its presence even in patients with sepsis, hyperlipidemia, or in patients on lipid infusions.\cite{45} Arterial blood gas analysis (ABG) with an unexplained increase in pulmonary shunt fraction and an alveolar-to-arterial oxygen tension difference within 24–48 h of trauma is strongly suggestive of FES. ABG will demonstrate hypoxia, with a PaO<sub>2</sub> of <60 mmHg along with the hypocapnia. Therefore, monitoring of arterial gases and of transcutaneous arterial saturation of hemoglobin are extremely important measures for follow-up of newly hospitalized FES-suspected patients.\cite{41,46,47}

Chest radiography is the initial basic imaging modality and is mandatory in cases of trauma patients. It is

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**Table 2: Gurd and Wilson’s criteria**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Score</th>
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<tbody>
<tr>
<td>Petechiae</td>
<td>5</td>
</tr>
<tr>
<td>Chest X-ray changes</td>
<td>4</td>
</tr>
<tr>
<td>Hypoxemia (PaO&lt;sub&gt;2&lt;/sub&gt;&lt;9.3 kPa)</td>
<td>3</td>
</tr>
<tr>
<td>Fever (&gt;38°C)</td>
<td>1</td>
</tr>
<tr>
<td>Tachycardia (&gt;120 bpm)</td>
<td>1</td>
</tr>
<tr>
<td>Tachypnea (&gt;30 bpm)</td>
<td>1</td>
</tr>
<tr>
<td>Confusion</td>
<td>1</td>
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For making the diagnosis of FES, presence of one major and four minor criteria are required. ESR=Erythrocyte sedimentation rate, FES=Fat embolism syndrome

**Table 3: Lindeque’s criteria**

<table>
<thead>
<tr>
<th>Lindeque’s criteria</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sustained PaO&lt;sub&gt;2&lt;/sub&gt; &lt;8 kPa</td>
<td>1</td>
</tr>
<tr>
<td>Sustained PCO&lt;sub&gt;2&lt;/sub&gt; of &gt;7.3 kPa or a pH &lt;7.3</td>
<td>1</td>
</tr>
<tr>
<td>Sustained respiratory rate &lt;35 breaths min despite sedation</td>
<td>1</td>
</tr>
<tr>
<td>Dyspnea, tachycardia, anxiety</td>
<td>1</td>
</tr>
</tbody>
</table>

**Table 4: Schonfeld’s criteria**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Score</th>
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<tr>
<td>Petechiae</td>
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For diagnosis of FES score should be more than 5. FES=Fat embolism syndrome
found often normal initially but certain findings may be observed in FES in 30%–50% of cases such as diffuse bilateral pulmonary infiltrates, snow-storm appearance, increased bronchovascular markings, and dilatation of the right side of the heart, but these findings cannot be considered as pathognomic of FES because these can also be noticed in cases of pulmonary congestion, pulmonary contusion, tracheobronchial aspiration of gastric contents, or ARDS.[48,49]

Pulmonary ventilation/perfusion imaging may be executed for the suspicion of FES but findings from this imaging may be normal or may demonstrate a mottled pattern of subsegmental perfusion defects.

Spiral chest computerized tomography scan (CT-scan) may be found normal or may demonstrate focal areas of ground-glass opacities with interlobular septal thickening, centrilobular or subpleural nodules or parenchymal changes similar lung contusion, ALI, or adult respiratory distress syndrome (ARDS).[44]

CT scan of the head although represents a valuable test in many neurological conditions, but it does not add value to the diagnosis of FES and may be found normal. However, it may be used to rule out the cranial trauma or other head injuries which may deteriorate consciousness level. CT scan of the head may reveal diffuse white matter petechial hemorrhages because of microvascular injury of brain parenchyma.[50]

Magnetic resonance imaging (MRI) brain is more sensitive than CT scan and demonstrates earlier and specific damage to brain parenchyma because of circulating fat microemboli. The typical findings of MRI in FES are the low-intensity signs at T1 and high-intensity signs at T2 imaging. Characteristically, cerebral FES lesions are always located in the deep white substance of the basis, brainstem, and cerebellum ganglia. MRI of the brain may also reveal multiple hyperintense punctate lesions disseminated throughout the cerebral white matter on T2-weighted axial images and a so-called starfield pattern on diffusion-weighted images.[34,51]

Transcranial Doppler sonography may indirectly reveal the most common lesion in cerebral FES that is perivascular edema by its ability detect the slowness of cerebral blood flow secondary to the increase of vascular resistance.[90]

ECG may reveal signs suggestive of the right-sided heart strain.[52,53]

Intraoperative TEE may be helpful in evaluation of release of bone marrow contents in the bloodstream during intramedullary reaming of the long bones. The density of the echogenic substances going through the right atrium and ventricle of the heart correlates with the level of reduction in arterial oxygen saturation.[84]

As should have been obvious, with respect to what we have evaluated up until now, there is neither pathognomonic clinical picture nor an investigation facility that could close a demonstrative of FES. FES analysis depends, accordingly, on an entire informational collection, and history, signs and symptoms, and imaging tests ought to be constantly considered.

**Treatment and Prevention**

There is no specific treatment modality for the management of FES; however, early diagnosis, continuous monitoring, supportive treatment, and prevention are the mainstay of treatment. As discussed earlier, hypoxia is the most common and earliest feature of FES, continuous pulse oximetry monitoring in the high-risk patients may help in detecting desaturation early allowing early identification of problem and institution of preventive or supportive measures.

Supportive therapy constitutes the mainstay of treatment as no specific treatment modality is available. It constitutes the early management of shock by volume resuscitation with crystalloids fluids or blood, mechanical ventilation and PEEP for maintenance of adequate oxygenation and ventilation, maintenance of stable hemodynamics, use of vasoactive drugs for maintenance of cardiac output and to decrease the preload on the heart, prophylaxis of deep vein thrombosis and stress-related gastrointestinal bleeding, and maintenance of adequate nutrition.[55] FES affects pulmonary functions severely, however, patients responding great to mechanical ventilation, the inflammatory process of FES is generally settled inside 3–7 days.[91]

Historically, various drugs were instituted in patients of FES as specific pharmacotherapy for management of FES but none show promising results. Ethyl alcohol showed the ability of reducing serum lipase activity and consequently reducing the release of FFAs in circulation and thus indicated as treatment of FES but no useful results were obtained.[156] Hypertonic glucose was also tried as 50 g oral or intravenous (IV) infusion as it reduces the concentration of FFAs within 30 min but results were still disputable.[57,58] Dextran-40 was also introduced as pharmacotherapy of FES because of the idea that by promoting hemodilution, it would reduce the aggregation of platelets and erythrocytes. Even though its utilization was appeared to be valuable in keeping up or recuperating volemia in polytraumatic patients, no advantage was indicated with respect to incidence reduction or patients’ advancement,
and its utilization for these reasons was soon left aside. Although its use was shown to be useful in maintaining or recovering volemia in polytraumatic patients, no benefit was shown regarding incidence reduction of FES or patients’ evolution and its use for these purposes was soon left aside. Heparin was initially thought of some importance in treatment of FES as it stimulates the lipase and reverses lipemia, but it causes an undesirable increase of circulating fatty acids and creates a high risk of hemorrhage in polytraumatic patients, and hence, it became formally contraindicated for FES treatment.

In the past, FES therapy was targeted toward reduction of lipemia and coagulation changes but today treatment targets the maintenance of oxygen levels and the cardiac output.

Recently, use of human albumin IV was found to reduce the incidence and severity of FES occurring in orthopedic surgeries because of its FFA-chelating property and thus avoiding their toxicity. In light of this evidence, the utilization of albumin IV was proposed and tried for FES treatment, yet it has not been embraced because of the absence of noteworthy evidence. Aprotinin (Trasylol) is also being tried for management of FES because of its platelets aggregation inhibiting, serotonin release reducing, and proteases actions blocking property. Recently, Aspirin has also been used for the management of FES due to some of its beneficial effects in patients of FES.

Corticosteroids mainly methylprednisolone are also considered for treatment of FES because of their anti-inflammatory actions both local and systemic (inhibiting the release of proteolytic enzymes of neutrophils’, lysosomes, complement activation, systemic inflammatory response, and platelet aggregation), but their efficacy is considered of no more use in the treatment of FES. However, methylprednisolone use shows promising results for the prophylaxis of FES and reducing the severity and mortality of FES.

Preventive measures

Early immobilization of the fractures of long bone and pelvis decreases the occurrence of FES. The hazard is additionally diminished by operative intervention, as opposed to nonoperative management. Externally fixator application or open reduction and internal fixation with plates and screws produces lesser lung injury than nailing the medullary canal. Constraining the rise of intraosseous pressure during orthopedic procedures likewise prevent FE disorder by decreasing the intravasation of intramedullary fat and different debris material. Various modifications have been described during orthopedic surgeries as preventive measures to reduce to the incidence and severity of FES such as cleaning of the medullary cavity with saline solution, followed by aspiration of medullary content, use of fluted intramedullary rods in place of cylindrical rods, overdrilling of entrance port, distal venting by performing a 4–6 cm hole in diaphysis distal to prosthesis, retrograde filling of medullary cavity with cement, using low viscosity cement, using proximal vacuum, using prosthesis without cement, use of narrow reamers, slow insertion of nail, reamed intramedullary femoral shaft stabilization in patients with associated chest injuries, and use of reamer irrigator aspirator devices.

Corticosteroids prophylaxis

Due to low incidence, unclear risk factors, low mortality, and a good outcome with conservative management, corticosteroid prophylaxis is controversial, but a number of studies report decreased incidence and severity of FES when corticosteroids were given prophylactically as also no complications related to use of corticosteroids observed. Today’s rationale would be to give prophylactic steroid therapy only to those patients at high risk for FES, and for this, methylprednisolone 1.5 mg/kg IV can be administered every 8 h for six doses.

Prophylactic placement of the inferior vena cava filters has been advocated as a method to reduce the volume of fat that reaches to the heart and lungs and thus decreasing the chances of FES but this has not been adequately studied and there is a paucity of literature. Moreover, risk of the surgery for placing inferior vena cava filters should be weight against benefits.

Hyperbaric oxygen (HBO) therapy is defined by the Undersea and Hyperbaric Medical Society as a treatment in which a patient intermittingly breathes 100% oxygen under a pressure that is greater than the pressure at sea level. Adequacy of early HBO treatment on cerebral FE has been affirmed. It expands blood oxygen pressure and oxygen content and in addition outspread dissemination of oxygen in the brain capillaries to enhance microcirculation. It likewise stimulates growth of capillaries which helps in establishing collateral circulation.

Conclusion

Most patients with FES recover fully without residual deficits. Mortality rate varies from 5% to 15% in various studies. However, patients with older age, numerous comorbid medical conditions, and diminished physiologic reserve have more terrible results. The fulminant form of FES displays as acute cor pulmonale, respiratory failure or embolism, and prompting to death of patient inside few hours of injury.
Hence in short, a high index of suspicion is needed to diagnose FES and a combination of clinical criteria is needed to accurately diagnose it and early supportive therapy is the mainstay of treatment.

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Conflicts of interest
There are no conflicts of interest.

References


