



# Neurologic Complications of Fat Embolism Syndrome

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## Abstract

**Purpose of Review** Fat embolism syndrome (FES) is a rare disorder with potentially devastating neurologic complications. This article reviews the history, pathophysiology, clinical features, diagnosis, and treatment of FES with a focus on its neurologic aspects.

**Recent Findings** The neurologic complications of FES are more commonly recognized with current diagnostic testing and increase awareness of the disorder. FES may present initially with neurologic manifestations. Prompt diagnosis of FES and of its neurologic manifestations could be lifesaving. This includes respiratory support and management of neurological complications.

**Summary** The classic clinical triad of pulmonary insufficiency, neurologic disturbances, and petechial skin rash typically presents 24 to 72 h following an initial insult, most commonly a traumatic long bone fracture. Early onset (< 24 h) and delayed onset (> 72 h) have been described. Neurologic manifestations may include ischemic/hemorrhagic strokes, retinal ischemia, seizures, autonomic dysfunction, and diffuse brain injury. Diagnosis remains clinical. Management consists mainly of supportive care.

**Keywords** Fat embolism syndrome (FES) · Fat emboli · Cerebral embolization

## Introduction

Fat embolism syndrome (FES) is a rare disorder most commonly manifested with respiratory insufficiency following orthopedic trauma. The classical triad of FES consists of respiratory insufficiency/distress, neurologic impairment, and petechial skin rash. Neurologic involvement in FES is the result of a major cause of morbidity and mortality, migration of fat globules to the central nervous system (CNS). The term cerebral fat emboli (CFE) is used to imply FES affecting the brain. Neurologic complications of CFE include ischemic and hemorrhagic strokes, seizures, convulsive and non-convulsive status epilepticus, autonomic impairment, acute encephalopathy, and coma.

## History

Fat embolism was first described in an animal model more than three centuries ago [1]. Mechanical obstruction of small blood vessels by fat globules and pulmonary edema was first demonstrated by Magendie in an animal study using intravenous oil.

The first human case of FES was confirmed by the post-mortem presence of fat globules in pulmonary capillaries [2]. Fracture immobilization as a plausible preventive measure for FES was first posited in 1914 by Tanton [1].

## Pathophysiology

FES has been attributed to either mechanical or biochemical pathophysiologic mechanisms. The mechanical pathophysiology proposed by Gauss in 1924 had three essential components: (1) adipose tissue damage, (2) rupture of venous channels, and (3) passage of fat globules into open-ended venous channels [3]. A biochemical pathophysiology proposed by Lehman in 1927 suggested plasma intermediaries promoting fat mobilization from body storage with subsequent formation of fat globules into the intravascular compartment. Figure 1 illustrates the mechanical theory of FES.

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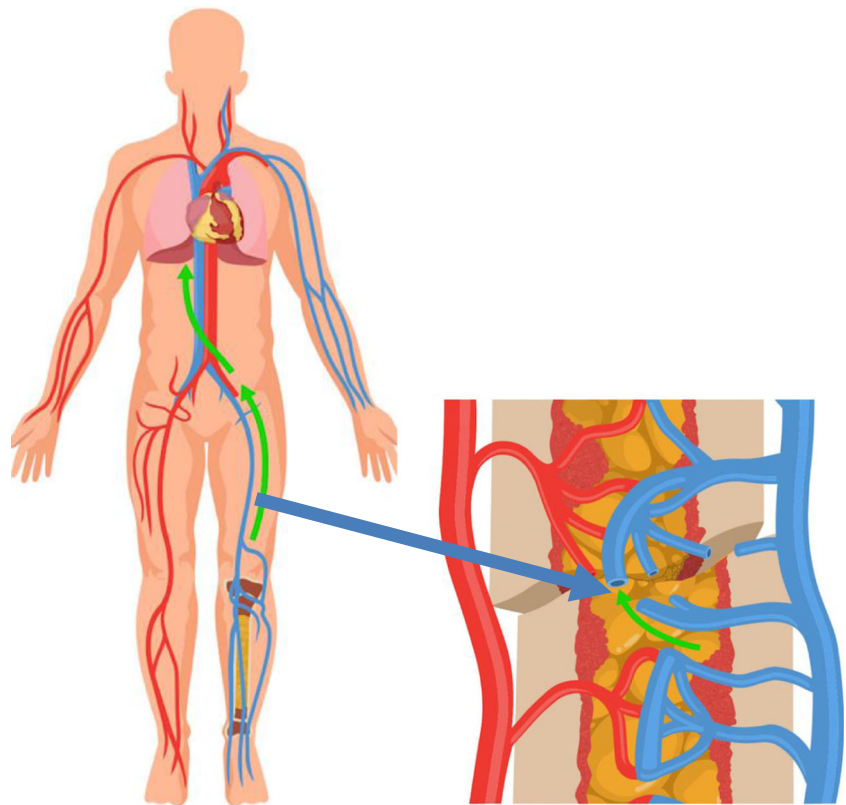
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**Fig. 1** This illustration depicts transection of venous vessels with embolization of fat globules into the systemic circulation following a femoral shaft fracture



## Etiology

Orthopedic trauma is the most common cause of FES. Table 1 provides a list of the underlying causes of FES.

### Traumatic

The reported risk of FES following orthopedic trauma ranges between  $< 1$  and  $> 30\%$ . Traumatic femoral shaft fracture (excluding isolated neck fractures) carries an almost inevitable risk for FES. FES is less common ( $< 1\%$ ) with isolated tibial or fibular fractures or with isolated fractures of the femur. Other fracture sites (e.g., pelvic and ribs) also appear to have a low incidence of FES [4].

Albeit rare, FES may complicate hip arthroplasty, revision of hip arthroplasty, knee arthroplasty, intraosseous procedures, intraosseous infusions as well as surgical interventions including percutaneous vertebroplasties [5–10].

Adipose tissue damage could be the initial trigger for the development of FES. Adipose tissue damage may follow a variety of procedures and interventions, including cosmetic procedures involving the gluteal region such as liposuction, cosmetic filler injections, autologous fat transfer, depot drug delivery, and implants. Dermal fillers or fat cosmetic injections may also result in ophthalmic artery embolism. High-risk regions of injection sites include the periosteum, the nasal dorsum, and the nasolabial fold [11].

Trauma without bony fractures, so-called non-orthopedic trauma, may also result in FES [12]. Some conditions where non-orthopedic trauma is thought to play a role in FES include lung transplantation, and coronary artery bypass graft (CABG). Off-pump CABG, as compared to on-pump techniques, appears to have a much lower risk of FES than on pump [13]. FES following multiple vertebral compression fractures has been described after lung transplantation [14]. FES has also been observed following renal transplantation [15].

### Non-traumatic

Non-traumatic causes of FES are heterogeneous and include pancreatic diseases, bony or soft tissue infections, bone marrow disorders, hemoglobinopathy malignancies, and drugs [16–22]. Mechanisms for the development of FES vary in each of the listed conditions. In instances of renal angiomyolipomas, these rare tumors may invade the inferior vena cava resulting in FES; resection of renal angiomyolipomas could be an effective preventive treatment of FES [11].

Medications and interventions associated with FES include corticosteroids, cis-platinum, cyclosporine solvent, lipid infusion, and cell-salvage devices [23–25]. Cell salvage is the collection of a patient's own blood during surgery. The continuous cell salvage device removes fat to a higher extent as

**Table 1** Causes of fat embolism syndrome

|   |
|---|
| Traumatic   |
| Bone fractures  |
| Long bone fractures (e.g., femur)   |
| Other: pelvic fractures and rib fractures                                   |
| Orthopedic intervention, procedures and surgeries                           |
| Intraosseous access   |
| Arthroplasty (hip or knee)  |
| Adipose tissue damage   |
| Soft tissue trauma  |
| Plastic surgeries and cosmetic interventions                                |
| Liposuction   |
| Fat grafting  |
| Lipoinjections  |
| Cosmetic filler injections  |
| Depot drug delivery   |
| Implants  |
| Other   |
| Lung transplantation  |
| CABG  |
| Renal transplantation   |
| Chest compressions without rib fractures                                    |
| Burns   |
| Non-traumatic   |
| Pancreatic and liver disorders  |
| DM  |
| Pancreatitis  |
| Fatty liver   |
| Infections  |
| Osteomyelitis   |
| Panniculitis  |
| Hemoglobinopathies  |
| Sickle cell disease   |
| Thalassemia   |
| Bone marrow disease   |
| Bone marrow necrosis or osteonecrosis                                       |
| Cancer-related  |
| Metastasis from fatty tumors  |
| Bone tumor lysis  |
| Tumor invasion (e.g., renal angiomyolipoma invading the inferior vena cava) |
| Medications and other interventions   |
| Corticosteroid therapy  |
| Chronic cyclosporin A solvent   |
| Lipid infusion  |
| Intraoperative cell salvage   |

compared to discontinuous devices. Of particular interest to neurologists is the risk of FES with chronic corticosteroid use. Duchenne muscular dystrophy (DMD) also poses an increased risk for FES [26••]. This is thought to be secondary

to osteopenia with associated non-traumatic fractures secondary to chronic corticosteroid use. Thus, FES should be considered among the plausible causes of respiratory insufficiency in patients with DMD.

## Epidemiology

Trauma, in particular, long bone fractures, carries the highest risk for FES. FES is more common among men between 10 and 40 years of age. Elderly patients with high body mass index (BMI) or high bone marrow fat content appear to be at increased risk for pulmonary fat embolism during total knee arthroplasty [27].

## Clinical Features

The most common manifestation of FES is respiratory distress and usually occurs 24 to 72 h following initial insult. Early onset FES (< 24 h) usually occurs within 12 to 24 h following the initial insult [28]. Delayed onset (> 72 h) has been described post-CABG and as a late complication of trauma-related FES [29].

## Pulmonary Manifestations

Respiratory distress is usually the first and most common clinical manifestation of FES. Patients may develop dyspnea, tachypnea, hypoxemia, or a full-blown acute respiratory distress syndrome (ARDS)-like picture.

## Dermatologic Manifestations

Most commonly, a petechial rash involves the head, neck, axilla, anterior thorax, and subconjunctiva [30]. Dermatologic manifestations occur on average in one-third of patients.

## Miscellaneous Manifestations

It may include fever, anemia, thrombocytopenia, lipiduria, cardiomyopathy, and arterial hypotension [31].

## Neurologic Manifestations

Neurologic manifestations typically follow the pulmonary manifestations and may include cerebral and/or spinal cord ischemia, hemorrhagic stroke, seizures, autonomic dysfunction, and diffuse brain injury leading to acute encephalopathy or coma. In addition, ocular manifestations,

such as retinal ischemia, could be considered as part of neurologic manifestations.

CFE is a rare cause of ischemic and hemorrhagic stroke [32]. Aside for traumatic orthopedic and other causes mentioned above for FES, CFE may also occur following reconstructive eye surgery [33]. FES should be considered in patients with sickle cell disease and thalassemia presenting with multifocal cerebral embolism. Findings include a star field pattern on brain MRI [34]. Susceptibility-weighted images (SWI) are of particular value for the suspicion of FES in patients with sickle cell disease and other hemoglobinopathies [35, 36].

AC best rare, paraplegia due to spinal cord infarction (SCI), could be the initial presentation of FES [37, 38].

Focal seizures with or without secondary generalization usually follow other manifestations of FES. FES may ensue after seizures complicating long bone fractures, as well as seizures without associated orthopedic trauma [39]. The mechanism of post-seizure FES without bony fractures is thought to be secondary to soft tissue trauma. Refractory status epilepticus and non-convulsive status epilepticus could be the main neurologic manifestations of FES [40].

Paroxysmal sympathetic hyperactivity syndrome (PSHS) characterized by the sudden occurrence of arterial hypertension, tachycardia, diaphoresis, and fever may be associated with FES [41]. Episodes may be manifested spontaneously or induced by stimulation (e.g., turning, bathing, aspiration of secretions, and pain). PSHS is commonly underdiagnosed and delayed recognition is associated with increased morbidity [41].

Fat emboli may invade the subarachnoid space in patients with FES [42]. Subarachnoid fat droplets may occur without FES as a sequela of ruptured dermoid cysts [43].

Ocular fat embolism syndrome occurs most commonly when fat globules result in retinal ischemia [44]. Furthermore, iris segmental infarction has been described following autologous fat injection into the lower eyelid tissues [45].

Unresponsiveness could be the initial manifestation of FES [46]. FES should be considered in the differential diagnosis of rapid onset of coma following long bone fracture [47]. Delayed coma could also be the initial clinical manifestation of FES in trauma patients with head injury [48].

## Evaluation and Diagnosis

Diagnosis of FES is primarily clinical. FES should be suspected among high-risk patients before all manifestations

**Table 2** Proposed diagnostic criteria of FES by Gurd and Wilson [49]

| Gurd's and Wilson's criteria   |  |
|--|--|
| Major criteria   |  |
| Axillary or subconjunctival petechiae                                |  |
| Hypoxemia PaO <sub>2</sub> ,60 mmHg; FIO <sub>2</sub> 1/4 0.4)       |  |
| CNS depression disproportionate to hypoxemia                         |  |
| Pulmonary edema  |  |
| Minor criteria   |  |
| Tachycardia > 110 bpm  |  |
| Fever  |  |
| Retinal emboli   |  |
| Fat globules in urine  |  |
| Fat globules present in the sputum                                   |  |
| Elevated ESR   |  |
| Sudden inexplicable drop in hematocrit or platelet values increasing |  |

are evident. Tables 2, 3 and 4 provide the diagnostic criteria proposed by Gurd, Schonfeld's, and Lindeque.

The classic clinical triad usually does not occur simultaneously and the petechial rash is present in less than half of the cases. The hemodynamic status should be closely monitored since patients with FES may develop acute arterial hypotension. Funduscopy may show evidence of retinal scotomata (Purtscher's retinopathy).

Laboratory studies may show evidence of anemia and thrombocytopenia. Chest roentgenogram and CT of the chest are usually normal in most patients. However, on occasions, air space disease, ground-glass opacities, or centrilobular nodules may be present.

MRI of the brain may show diffuse hyperintense punctate lesions on DWI that tend to correlate with hypointense signal changes on SWI/GE. Diagnostic criteria have been developed to support the clinical diagnosis. Transcranial Doppler ultrasound may predict the development of neurologic symptoms in patients with long bone fractures; the presence of microembolic signals to the brain has been noted to be more frequent among patients with cardiac right to left shunts [51].

**Table 3** Proposed diagnostic criteria of fat embolism syndrome by Schonfeld [3]

| Schonfeld's criteria                               |            |
|--|------------|
| Petechia   | – 5 points |
| Chest X-ray changes (diffuse alveolar infiltrates) | – 4 points |
| Hypoxemia (PaO <sub>2</sub> , 9.3 kPa)             | – 3 points |
| Fever (> 38.8 °C)                                  | – 1 point  |
| Tachycardia (> 120 bpm)                            | –1point    |
| Tachypnea (> 30 bpm)                               | – 1 point  |
| Cumulative score 5 required for diagnosis          |            |

**Table 4** Proposed diagnostic criteria of fat embolism syndrome by Lindeque [50]

| Lindeque's criteria  |
|--|
| Sustained pO <sub>2</sub> < 60 mmHg                        |
| Sustained pCO <sub>2</sub> > 55 mmHg                       |
| Sustained respiratory rate > 35 bpm spite of sedation      |
| Increased work of breathing, dyspnea, tachycardia, anxiety |

A hypodense middle cerebral artery on CT could serve for diagnostic suspicion for cerebral fat embolism [52, 53].

Ancillary tests support but do not confirm FES diagnosis. Autopsy may not be necessarily confirmatory of FES as fat may be seen incidentally at autopsy. Hence, the clinical significance of this finding is uncertain. Nonetheless, a high percentage of fat in alveolar macrophages on bronchoalveolar lavage, high amount fat globules on wedged pulmonary artery sample, or fat globules during autopsy could settle the diagnostic suspicion of FES.

## Differential Diagnosis

Main differential diagnoses include ARDS and pulmonary embolism. Neurological differential diagnoses depend on the initial manifestation of disease. Most importantly is to investigate and exclude other causes of cerebral embolism. Embolization syndromes that could present with respiratory distress and CNS involvement include amniotic fluid embolism syndrome, tumor embolism, air embolism, foreign body embolism, food embolism, and vasculitic cutaneous disorders [54–56].

## Management, Prevention, and Therapeutic Considerations

Appropriate therapy requires prompt recognition and supportive care. Most clinicians advocate early correction of long bone fractures to prevent FES, and also during established FES in order to prevent recurrent embolization.

Supportive care is aimed at respiratory and neurologic care. Patients may need immediate mechanical respiratory support. Neurocritical care, including management of increased intracranial pressure (ICP), may be warranted. In addition, hemodynamic and cardiac interventions (vasopressors, extracorporeal membrane oxygenation etc.) may be necessary.

It is unclear if systemic corticosteroid administration is beneficial or in patients with FES. Corticosteroids could be potentially beneficial. However, the use of prophylactic corticosteroids in high-risk patients with long bone fractures remains controversial. A metaanalysis of 104 studies concluded

that corticosteroids may be beneficial in preventing FES and hypoxia without increasing the risk of infection. However, there was no impact on mortality [57]. At present, there is no high level of evidence supporting corticosteroid use for the management or prevention of FES.

Heparin may increase lipid clearance from the intravascular compartment. However, the routine administration of heparin for FES is not recommended.

High-dose statins following CFE may improve outcomes [58]. However, more data are needed to validate the potential efficacy of statin in the management of CFE.

There is no clear indication to screen for the presence of patent foramen ovale (PFO), prior to lower extremities orthopedic surgeries [59].

## Prognosis

Most patients with FES have spontaneous full recovery. A case report of nine patients reported a mortality rate of 22% at approximately 5 years of follow-up, and minor or no neurologic impairment in the remainder [60••].

## Conclusions

Neurologists should be familiar with the clinical triad of FES (pulmonary insufficiency, neurologic disturbances, and petechial rash). Physicians are commonly aware of FES in high-risk patients mostly following long bone fractures. Neurologists should be mindful of atypical causes of FES as well as initial neurologic insult (e.g., stroke) as the initial manifestation of this disease. Prompt therapeutic interventions, including neurocritical care, could be lifesaving.

## Resources

For patients with Muscular Dystrophy: <https://www.parentprojectmd.org/care/care-guidelines/by-area/bone-and-joint-care/fat-embolism-syndrome/>

## Compliance with Ethical Standards

**Conflict of Interest** Sarkis Morales-Vidal declares no potential conflict of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of major importance

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- infarction secondary to fat embolism syndrome should be considered in high risk population (e.g. femur fractures).**
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