Fat Embolism Syndrome

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Injury/Disease Demographics

- Definitions
  - *Fat embolism* – fat within the circulation, which can produce embolic phenomena with or without clinical sequelae. Estimated to occur in 90% of patients with long bone fractures.
  - *Fat embolism syndrome* – fat within the circulation associated with an identifiable clinical pattern of symptoms and signs. Occurs in 2-5% of patients with long bone fractures.

- Three conditions required for fat to appear in the bloodstream
  - 1) Damage to fat tissue stores (e.g. long bone fracture or subcutaneous bruising)
  - 2) Rupture of surrounding veins
  - 3) Increased local interstitial tissue pressure, which allows fat globules to access the circulation

- Etiologies
  - ***Traumatic injury***: Embolization into vasculature through ruptured medullary venous sinuses after bone fracture. Higher risk in patients with ISS >16, multi-system trauma, open fractures, bilateral femoral fractures, femoral shaft fractures, concomitant thoraco-abdominal and/or pelvic trauma; and requirement for massive transfusion or hypotension on presentation.
  - ***Surgical***: Fixation of long bones with intramedullary nails can trigger embolization and result in fat embolism syndrome. Intramedullary canal pressures can reach 1000 mmHg during reaming, liberating fat into the circulation through venous openings. High intramedullary pressure can occur during hip or knee arthroplasty, exacerbated by the use of orthopedic cement. Simultaneous intramedullary nailing of multiple long-bone fractures, including bilateral femoral fractures, significantly increases the risk of fat embolism syndrome.
  - ***Non-traumatic etiology*** – (5% of patients)
    - **Disease-related**: fat or marrow necrosis, or increased concentration of lipids in blood. Seen in patients with burn injury, pancreatitis, panniculitis, sickle cell C variant, alcoholic hepatitis and altitude illness.
    - **Drug-related**: secondary to infusion of lipids (TPN, Propofol, long-term steroid use) at rates greater than the normal clearance capacity of lipids. Agglutination of lipid emulsion particles with fibrin causes fat emboli.
    - **Procedure-related**: intraosseous fluid and drug administration; ECMO/cardiopulmonary bypass; bone marrow transplant, liposuction, lymphography.

- Two major pathophysiologic theories
  - 1) Mechanical: Fat embolism syndrome results from fat and intramedullary contents that are released from the fracture and enter the systemic circulation through arteriovenous shunts. Veins in bone marrow are held apart by osseous attachments, allowing fat globules to enter with ease. These particles can embolize into the pulmonary circulation and cause respiratory dysfunction, ventilation-perfusion mismatch, low PaO_2 and low SaO_2; and severe neurologic complications. [Husebye]
  - 2) Biochemical: Degradation of embolized fat into harmful free fatty acids (olein and triglyceride triolein) which are hydrolyzed in the pulmonary circulation by catecholamine-activated

lipoprotein lipase. This causes a neutrophil-mediated release of toxic, pro-inflammatory intermediaries, inducing a chemical pneumonitis caused by injury to the capillary endothelium and pneumocytes, as well as inactivation of pulmonary surfactant. Acute phase reactants cause agglutination of chylomicrons (1 μ in diameter) into larger particles (10-40 μ), which become trapped in pulmonary and other tissue capillary beds and results in fat embolism syndrome and/or end-organ dysfunction. [Mellor and Soni]

- Paradoxical embolism occurs with patent foramen ovale (PFO) or other connection between venous and arterial systems. In the absence of these connections, fat emboli enter the arterial circulation via micro embolism, in which emboli are small enough to pass from venous to arterial circulation through the lungs.

- Incidence/Prognosis
    - Four-fold higher risk in males versus females
    - Higher risk in younger patients (10-40 years)
    - Lower risk in elderly patients (typically low-impact mechanism involving the femoral neck)
    - Lower risk in children < 10 years (lower marrow fat and olein content)
    - Poorer prognosis in patients with neurologic manifestations
    - Mortality less than 1.2%
- Survivors usually have excellent prognoses, and most fully recover within 3-7 days. In rare cases fat embolism syndrome can lead to long-term renal dysfunction, pulmonary fibrosis, or COPD; permanent cerebral dysfunction or permanent cardiac conduction abnormalities. The embolization of fat particles that cause obstruction of small pulmonary and systemic vessels can lead to organ dysfunction, with clinical presentation and course dependent on the extent of the particular organ affected. [Akhtar]
- The exact morbidity and mortality associated with FES is difficult to determine, as it is often challenging to differentiate FES from other traumatic causes of acute lung injury, ARDS, or renal failure. [Akhtar]

Clinical Presentation

- Classic triad of fat embolism syndrome - occurs in 3-4%, usually 24-72 hours after inciting trauma or event:
    - **Petechial rash** (96% of patients) on chest, oral mucosa, skin folds of neck and axillae (**Figure 1**), and conjunctiva (**Figure 2**) due to engorgement of dermal vessels, clotting factor depletion and increased platelet and endothelial damage resulting from free fatty acids. The observed pattern of non-dependent involvement is hypothesized to result from accumulation of fat droplets in the aortic arch prior to embolization. [Mellor and Soni] Petechial rash is pathognomonic for Fat Embolism Syndrome.

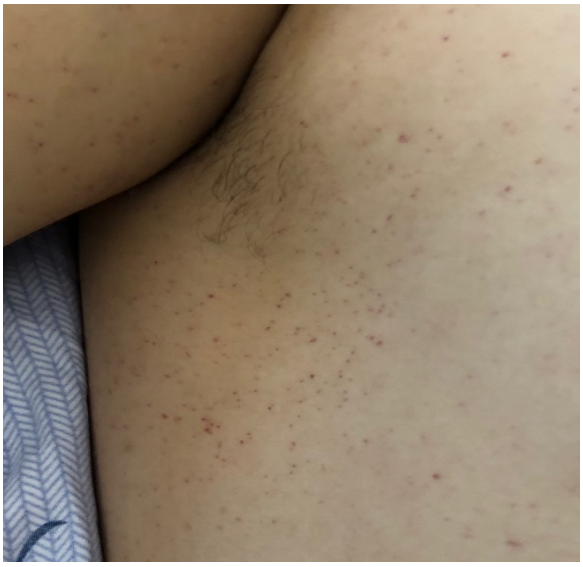

Figure 1. Petechial rash of the axilla

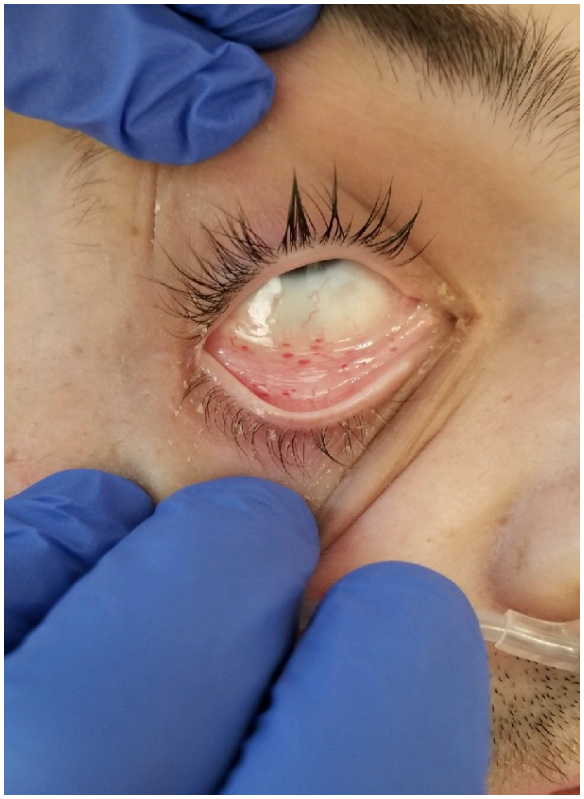

Fig 2. Conjunctival petechia

- **Pulmonary/respiratory failure** (75% of patients) that may be indistinguishable from ARDS. Hypoxemia is the most prominent manifestation of pulmonary fat embolism syndrome. The buildup of pro-inflammatory cytokines and free radicals may explain delay, or "lucid interval"

between embolization and onset of symptoms. This leads to pulmonary edema and decreased compliance with gas exchange abnormalities, including shunting and alveolar flooding. There is no correlation between type of injury and severity of pulmonary symptoms. [Habashi]

- **Neurological dysfunction** (86% of patients) termed cerebral fat embolism. Symptoms are variable, non-specific, and non-lateralizing; and may include lethargy, headache, confusion, acute anxiety, rigidity, stupor, seizure, and coma. Risk increases with surgery greater than 3 hours. Spinal cord embolism is described, but rare. Diagnosis complicated by concomitant brain contusion or hypoxic-ischemic injury.

- Non-specific symptoms include fever, tachycardia, tachypnea, and anemia.
- Serum abnormalities may include hypokalemia, hypoalbuminemia (from free fatty acid binding), thrombocytopenia, or anemia (from platelet activation and consumption due to disseminated intravascular coagulation).
- Purtscher retinopathy (50% of patients with fat embolism syndrome and 4% of patients with long bone fractures) is characterized by cotton-wool spots and flame-like hemorrhages surrounding the optic disc due to microvascular injury and microinfarction of the retina. Lesions disappear after a few weeks, although scotomas may persist.
- Emboli may result in an increase in pulmonary artery pressure due to increased perfusion pressure in the lungs resulting in right heart strain and inadequate preload. This may lead to acute cor pulmonale, cardiopulmonary collapse, and death.
- Acute kidney injury is described in 30-60% of patients and manifests as oliguria, lipiduria, and elevated creatinine.
- Fulminant fat embolism syndrome (occurring within minutes to hours) is characterized by profound hypoxemia, hypotension, cardiovascular collapse, and shock secondary to massive mechanical blockage of pulmonary vessels by fat emboli.

Evaluation/Diagnostics/Imaging

- No gold standard exists for diagnosis. The diagnosis is clinical, and one of exclusion.
- Fat globules can be seen on cytologic examination of urine, blood, or sputum, but none of these tests are reliable and cannot be used solely for diagnosis of fat embolism syndrome.
- Quantification of macrophages containing fat droplets in bronchoalveolar (BAL) fluid within the first 24 hours of trauma have been shown to correlate with fat embolism syndrome. However, difficulty in obtaining a sufficient sample and low sensitivity and specificity, makes this clinically impractical. If a BAL is obtained, absence of fat-laden macrophages should prompt a search for alternative etiologies of hypoxemia. [Mellor and Soni]
- Multiple diagnostic indices exist to assist in the diagnosis of fat embolism syndrome (**Table 1**).

Table I: Three indices used to define fat embolism syndrome

Criterion	Features
Gurd and Wilson (fat embolism syndrome = 1 major + 4 minor + fat microglobulinemia [Talbot and Schemitsch]	*Major criteria* Respiratory insufficiency Cerebral involvement Petechial rash *Minor criteria* Tachycardia

	Retinal changes Pyrexia Jaundice Anuria Oliguria Thrombocytopenia (drop of >50% of admission platelet level) Elevated ESR Fat macroglobulinema
Lindeque criteria (fat embolism syndrome = femur fracture +/- tibial fracture + 1 feature) [Mellor and Soni]	*Features* Sustained PaO_2 <60 mmHg Sustained $PaCO_2$ >50 mmHg or pH <7.3 Sustained respiratory rate >35 breaths per minute even after adequate sedation Increased work of breathing as determined by dyspnea, use of accessory muscles, tachycardia, and anxiety
Schonfeld fat emboli index score (fat embolism syndrome = >/ 5 points) [Talbot and Schemitsch]	Diffuse petechiae (5 points) Diffuse alveolar infiltrates (4 points) Hypoxemia PaO_2 <70 mmHg (3 points) Confusion (1 point) Fever > 38 degrees Centigrade (1 point) Heart rate > 120 bpm (1 point) Respiratory rate > 30 bpm (1 point)

- Imaging findings
    - Chest radiography reveals cardiomegaly, and patchy perihilar and basilar alveolar opacities which may resemble pulmonary edema without vascular congestion.
    - CT chest demonstrates ground-glass opacities and consolidation, which correlate with disease severity. Lobular sparing (due to variations in perfusion at the time of embolization) within the ground-glass opacities, helps to distinguish fat embolism syndrome from other post-traumatic complications and infection.
    - CT head is frequently normal, but may demonstrate diffuse encephalopathy and/or vasogenic edema (**Figure 3**) due to toxic effect of fatty acids on brain parenchyma or diffuse white-matter petechial hemorrhages, consistent with microvascular injury.

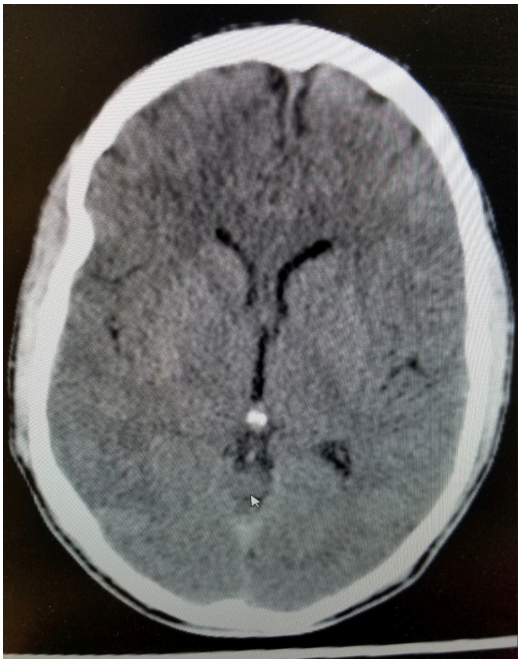

Figure 3. CT imaging demonstrating cerebral edema in a patient with fat embolism syndrome.

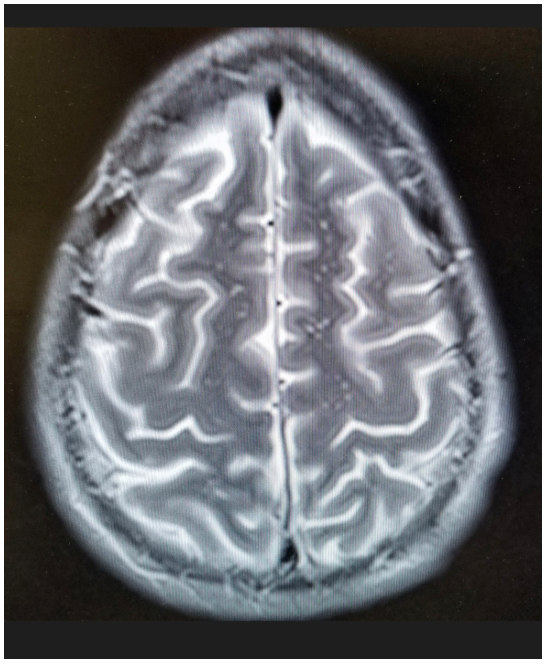

Figure 4. "Starfield" pattern distributed bilaterally in watershed zones of deep white matter on T2-weighted MRI image

- Cerebral MRI is the most sensitive imaging modality for diagnosis of fat embolism syndrome.
  - T1-weighted images demonstrate hypointense lesions.
  - T2-weighted images demonstrate multiple diffuse hyperintense lesions in deep white matter, basal ganglia, corpus callosum, periventricular region, and/or cerebellar hemisphere, associated with vasogenic edema.
  - The most common observed pattern on T2-weighted imaging is the "starfield pattern" (**Figure 4**) consistent with scattered cytotoxic edema observed in the acute phase of fat embolism syndrome, and characterized by scattered spot lesions distributed bilaterally in watershed zones of white matter and deep gray matter (centrum semiovale, basal ganglia, thalami). The pattern is seen in all types of embolic events, but is reversible in fat embolism syndrome.

- Trans-esophageal echocardiography (TEE) may be used intra-operatively during intramedullary nailing. TEE may demonstrate embolic particles, which appear as white snowflakes flowing through the right atrium.

Prevention/Prophylaxis

- **Early stabilization** is the single most important prophylactic measure recommended to decrease incidence of fat embolism syndrome and recurrent bouts of emboli. Some surgeons delay initial operative fixation in patients with suspected fat embolism syndrome from inciting trauma until clinical improvement has been observed.
- **Sildenafil** has been shown to decrease pulmonary pressures after bone marrow embolization in experimental models, while **N-acetylcysteine** has been shown to attenuate acute lung injury in animal studies. [Krebs, Liu]

- **Corticosteroids** are theorized to limit increased free fatty acids, stabilize lysosomal membranes, and inhibit complement-mediated leukocyte aggregation. Meta-analyses have demonstrated a 43% risk reduction of fat embolism syndrome in treatment groups; however small sample sizes, low quality studies, and small number of outcome events limit the use of corticosteroids as prophylaxis for fat embolism syndrome. No differences in mortality were found with administration of corticosteroids. [Habashi, Mellor and Soni, White]
- Reaming during intramedullary nail placement for fracture fixation distributes fat emboli and impairs immune reactivity. Simultaneous reaming/irrigation tools for intramedullary nailing (IMN) and ORIF with plates, reduce the incidence of fat embolism syndrome in animal models.

Treatment

- **Supportive care** is mainstay, so prevention, early diagnosis, and symptom management are paramount.
- Ventilator support, if necessary, should be used. Sedation and neuromuscular blockade should be limited to encourage spontaneous breathing and cough, and to facilitate frequent neurologic exams. As in severe ARDS or ALI, gas exchange support may involve high PEEP or proning and advanced ventilator strategies such as airway pressure release ventilation (APRV) or ECMO.
- **Early fracture fixation** is critical in reducing recurrent liberation of fat into the circulation as a result of fracture movement. Fixation within 24 hours reduces incidence of fat embolism syndrome five-fold.
- Adjuvant and experimental therapies such as cyclo-oxygenase inhibitors (decrease thromboxane (TXA) production), ethanol (reduces lipolysis), and dextrose (reduced free fatty acid mobilization) have little evidence to support their clinical use. [White]
- Free fatty acids (FFAs) in circulation can produce tissue and endothelial injury. While albumin can neutralize FFAs, binding may be reduced during FES. Thus, supplemental albumin has not been demonstrated to be beneficial in patients with fat embolism syndrome. [Habashi]

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Suggested Readings

Akhtar S. Fat embolism. Anesthesiology 2009;27:533-550.

Bulger EM, Smith DG, Maier RV. Fat embolism syndrome. Arch Surg 1997;132:435-439.

Joynt GM, Li TS, Wai JK, et al. Fat embolism syndrome. Crit Care & Shock 2008;11:83-93.

Mellor A & Soni N. Fat embolism. Anaesthesia 2001;56:145-154.

Habashi NM, Andrews PL, & Scalea TM. Therapeutic aspects of fat embolism syndrome. Injury, Int. J. Care Injured 2006;(37S):S68-S73.

Husebye EE, Lyberg T, Røise O. Bone marrow fat in the circulation: clinical entities and pathophysiological mechanisms. Injury, Int. J. Care Injured 2006;(37S):S8-S18.

Additional References

Bederman SS, Bhandari M, McKee MD, et al. Do corticosteroids reduce the risk of fat embolism syndrome in patients with long-bone fractures? A meta-analysis. Can J Surg 2009;52(5):386-393.

Blokhuis TJ, Pape HC, & Frolke JP. Timing of definitive fixation of major long bone fractures: Can fat embolism syndrome be prevented? Injury, Int. J. Care. Injured 2017;48S:S3-S6.

Caricato A, Russo G, Biasucci DG, et al. Fat embolism syndrome. Intensive Care Med 2017;43:1411-1412.

Ching Liang Ong S, & Balasingam V. Characteristic imaging findings in pulmonary fat embolism syndrome (FES), BMJ Case Rep 2017, 11 November 2017, http://dx.doi.org.ezproxy.library.unlv.edu/10.1136/bcr-2017-223007.

Cvetkovic D, Zivkovic V, Nikolic S. An unusual case of pulmonary fat embolism following blunt trauma, Forensic Science, Medicine, and Pathology, 5 November 2018, https://doi.org/10.1007/s12024-018-0053-0

Dunn RH, Jackson T, Burlew CC, et al. Fat emboli syndrome and the orthopaedic trauma surgeon: lessons learned and clinical recommendations. International Orthopaedics 2017;41:1729-1734.

Eriksson EA, Pellegrini DC, Vanderkolk WE, et al. Incidence of pulmonary fat embolism at autopsy: an undiagnosed epidemic. J Trauma 2011;71:312-315.

Gandhi RR, Overton TL, Haut ER, et al. Optimal timing of femur fracture stabilization in polytrauma patients: a practice management guideline from the Eastern Association for the Surgery of Trauma. J Trauma Acute Care Surg 2014;77(5):787-795.

Kearsley R, Galbraith J, Dalton D, et al. Spinal cord infarction as a rare complication of fat embolism syndrome following bilateral intramedullary nail of femur fractures, BMJ Case Rep, 27 August 2016, http://dx.doi.org/10.1136/bcr-2016-215690.

Krebs J, Ferguson SJ, Nuss K et al. Sildenafil prevents cardiovascular changes after bone marrow fat embolization in sheep. Anesthesiology 2007;107(1):75-81.

Kuo KH, Pan YU, Lai YJ, et al. Dynamic MRI imaging patterns of cerebral fat embolism: a systematic review with illustrative cases. Am J Neuroradiol 2014;35:1052-1057.

Liu DD, Kao SJ, Chen HI. N-Acetylcysteine attenuates acute lung injury induced by fat embolism. Crit Care Med 2008;36(2):565-571.

Newbigin K, Souza CA, Armstrong, et al. Fat embolism syndrome: Do the CT findings correlate with clinical course and severity of symptoms? A clinical-radiological study. European Journal of Radiology 2015;85:422-427.

Sen RK, Tripathy SK, & Krishnan Vibhu. Role of corticosteroid as a prophylactic measure in fat embolism syndrome: a literature review. Musculoskelet Surg 2012;96:1-8.

Shaikh N, Mahmood Z, Ghuori SI, et al. Correlation of clinical parameters with imaging findings to confirm the diagnosis of fat embolism syndrome. Int J Burn Trauma 2018;8(5):135-144.

Talbot M & Schemitsch EH. Fat embolism syndrome: history, definition, epidemiology. Injury, Int. J. Care Injured 2006;37S:S3-S7.

Whelan DB, Byrick RJ, Mazer D, et al. Posttraumatic lung injury after pulmonary contusion and fat embolism: factors determining abnormal gas exchanged. J Trauma 2010;69:512-518.

White T, Petrisor BA, Bhandari M. Prevention of fat embolism syndrome. Injury, Int. J. Care Injured 2006;37S:S59-S67.