Journal Homepage: -www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI:10.21474/IJAR01/16797
DOI URL: http://dx.doi.org/10.21474/IJAR01/16797

RESEARCH ARTICLE

FAT EMBOLISM AND FAT EMBOLISM SYNDROME: A REVIEW OF THE LITERATURE

Taha Hounain, Youssef Elouardi and Mohammed Khallouki
IBN-TOFAIL Hospital Surgical Intensive Care Unit Mohammed VI University Hospital Center, Marrakech, Morocco.

Manuscript Info

Manuscript History
Received: 28 February 2023
Final Accepted: 31 March 2023
Published: April 2023

Key words:-
Fat Embolism Syndrome, Fat Embolism, Trauma

Abstract

Fat embolism (FE) is defined as the presence of fat globules within the circulation [1]. Fat embolism is extremely common after trauma and occurs, to a variable extent, in the majority of patients suffering long bone or pelvic fractures [2]. In the majority of patients, fat emboli appear to have minimal physiological effects and most patients display no signs or symptoms. Fat embolism syndrome (FES) is a rare but potentially fatal consequence of FE resulting in a spectrum of end organ damage. Fat embolism syndrome was originally described by the symptomatic triad of respiratory distress, neurological impairment, and petechial rash [1]. Although first reported in humansby Zenker in 1862,the pathophysiology of FES remains incompletely understood. Despite an accumulating body of literature describing the occurrence of FES, there remains significant clinical uncertainty regarding its diagnosis, prevention, and management.

Introduction:-

Definition and Introduction

When fat enters the circulation, it can embolize and either generate clinical symptoms or not. This is known as a fat embolism [1]. Fat emboli entering the circulation have been linked to FES, a clinical condition with an imprecise definition. It typically manifests as traits related to the nervous system, the skin, and the respiratory system. It generally happens following long-bone fractures and total hip arthroplasty; burns and soft tissue injuries are less common causes [2]. Although early stabilization of long bone fractures is considered to reduce its incidence, the most efficient way to do so has not yet been established [3].

Epidemiology And Incidence

Although it has been reported in the literature that FES has happened after other traumatic conditions like burns, hepatic injury, cardiopulmonary resuscitation compressions, bone-marrow transplant, liposuction, lung transplant, caisson disease, extracorporeal circulation, caesarean section, and tetrachloromethane poisoning, it happens most frequently after orthopedic trauma. Rare non-traumatic causes of FESinclude injections of fat emulsion, corticosteroid therapy, pancreatitis, angiomyolipoma, intravenous lipid infusion, and hemoglobinopathies such as sickle cell disease (SCD) [4-8]. Depending on the series design, incidence of fat embolism and FES varies considerably throughout the literature. The lowest rates are reported by long-term retrospective reviews. According to Muller, fat embolism occurs in 0.9% to 2.2% of long bone fracture cases and tends to occur less frequently (0.5–0.8%) with intramedullary manipulation or instrumentation [9].

Corresponding Author: Taha Hounain
Address:IBN-TOFAIL Hospital Surgical Intensive Care Unit Mohammed VI University Hospital Center, Marrakech, Morocco.

While the incidence of FE at autopsy is much higher than the incidence of clinically suspected FES, prospective studies reveal significantly higher yet consistent rates of FES [9]. FES is a well-described syndrome that can result from aesthetic procedures like liposuction and gluteal vitamin E injections, and it has even resulted in fatalities [10-11]. Despite the relative safety of these aesthetic operations, doctors should be aware of the likelihood of FES in the postoperative period and use caution if their patient displays acute symptoms. With a death rate of 64%, FES caused by severe bone marrow necrosis in Sickle Cell Disease (SCD) is likewise a rare but well-described complication [12].Surprisingly, people with the "milder" form of SCD appear to be most at risk; in a review, 81% of patients did not have the HbSS genotype.

Gurd stated in his 1974 research that a sample of trauma victims had a 19% incidence of FES. An incidence of 0.9% was recorded in a 10-year review done by a significant trauma center in the United States[13]. Contrary to other studies that have found a significant correlation between "at-risk fractures" (fractures of the femur, tibial shaft, or pelvis) and incidence of FES, the authors of this study found no relationship between the severity, location, or pattern of patients' injuries and their likelihood of developing FES [14]. The number of fracture sites and the occurrence of FES were found to be correlated in the same study.

A prospective evaluation was conducted by one trauma center to ascertain the actual prevalence of FES following long bone or pelvic fractures. By measuring the alveolar/arterial PO2 gradient, they were able to identify patients with pulmonary shunts, and then further subclassified them to determine a minimum incidence of FES. They came to the conclusion that at least 10 individuals (11%) had FES related to a long bone or pelvic fracture since 49 out of 92 patients had a pulmonary shunt and 39 of them also had a pulmonary injury that was at least largely to blame for the shunt[15].

In one series, patients receiving simultaneous unilateral and bilateral total knee arthroplasty (TKA) had serial arterial and right atrial blood samples taken for histology[16]. The incidence of fat embolism was 46% in 100 individuals with a unilateral TKA and 65% in 100 patients with bilateral TKAs, according to the researchers' examination of fat cells at various time points.Two patients from the unilateral group and four patients from the bilateral group both had neurological symptoms that were compatible with FES.

Clinical Presentation

Because it is frequently accompanied by concurrent injuries or illnesses, FES is both a clinical diagnostic and a diagnosis of exclusion. This makes it challenging to gauge the severity of FES. FES symptoms and signs typically appear 24 to 48 hours after a trauma. Changes in the respiratory, nervous, and dermatological systems are how FES typically manifests. FES may potentially show more serious symptoms such right ventricular failure, cardiovascular collapse, and pulmonary and systemic fat embolisation. Pell described a very dramatic instance of fulminant FES that occurred intra-operatively. During open reduction and internal fixation of a femur fracture, a patient suddenly developed cor pulmonale. An autopsy revealed a patent foramen ovale, and FES was diagnosed posthumously [17].

Neurological

The clinical manifestations of neurological sequelae in FES can vary greatly, from moderate disorientation to drowsiness to a comatose condition. An otherwise healthy young woman who presented with catastrophic symptoms following reamed intramedullary nail repair of a femur fracture was the subject of a case report of cerebral FES published by DeFroda in 2016 [18]. There are a few known examples of severe cerebral fat embolisms that result in brain death [19]. A case study about a woman who passed away after experiencing non-convulsive status epilepticus following a total knee replacement was published in 2015. Before she passed away, she lingered in refractory status epilepticus for two weeks. Numerous brain infarcts connected to fat emboli were discovered during autopsy [20]. This was the first case of its kind to be described, which serves as yet another illustration of how little we know about the pathophysiology of FES. When neurological symptoms were present without respiratory symptoms, Scopa defined this as an unusual presentation of FES [21]. Bulger discovered that 59% of patients had neurological abnormalities. The most typical manifestation is little global impairment, however there have been catastrophic cases of blindness, convulsions, and hemiparesis with rapid onset. Fortunately, neurological symptoms of FES frequently go away on their own without leaving any lasting effects [22].

Cerebral fat embolism should be suspected in patients with long bone fractures who deteriorate neurologically without respiratory compromise, with the exception of those who have intracranial lesions, as early detection and

thorough treatment can improve prognosis [23]. For cerebral FES, magnetic resonance imaging is the preferred imaging technique [24].

Respiratory

The most common FES symptoms and indicators are respiratory in nature.This can range From transient respiratory distress to catastrophic respiratory failure. In an effort to properly identify FES, Bulger conducted a 10-year research in a major trauma center. Of the 27 patients who had FES, 12 (44%) needed mechanical ventilation [12]. In Lindeque's study, 16 of 28 patients with lower limb long bone fractures had a PaO2 of less than 7.3 kPa [7]. In a comparable study of patients with polytrauma, 90% of included patients had a PaO2 of less than 9.3 kPa. The degree of attention paid to a syndrome's signs or symptoms appears to be related to the diagnosis.

Ocular

Although uncommon, ocular fat embolism syndrome without heart defects has been recorded in a case report. Small fat droplets may reach the systemic circulation via passing through lung capillaries or pre-capillary shunts, according to the author's theory[25]. Ocular FES is a distinct condition from Purtscher's retinopathy, which is linked to acute pancreatitis or head/chest trauma [26].

Dermatological

The rash of FES is petechial in nature. Usually, the head, neck, anterior thorax, and axillae will exhibit this rash. According to Tachakra's theory, this pattern is brought on by fat droplets that gather in the aortic arch and subsequently embolize to non-dependent skin through the carotid and subclavian vessels [27]. Stasis, a lack of clotting factors, thrombocytopenia, and damage from FFAs to the capillary endothelium are all contributing factors in petechial rashes in FES patients [28].

Radiology

When there is a possibility of neurological involvement in FES, imaging may be important. However, magnetic resonance imaging (MRI) of the brain has been proven to be beneficial in early identification of cerebral fat embolism, high-intensity signals are seen in T2 weighted images as soon as four hours after symptoms start. In the acute context, computed tomography does not reveal any abnormalities [29]. MRI is a good potential tool for grading the severity of cerebral FES and its evolution/resolution since, in addition, MRI pictures seem to correlate with the severity of symptoms and with resolution [30]. Suzuki noted that the lesions typically occurred in the major vascular territories' boundary zones and proposed a connection between the hypoxic brain condition in FES and the mechanical aggregation of fat globules and complete brain capillary blockage[30]. In cases with polytrauma, these distinctive characteristics may help distinguish FES from primary intra-axial brain injury [31]. The three stages of cerebral fat embolism were recognized by five unique MRI imaging patterns in a more recent American comprehensive review: In the acute stage, there was scattered cytotoxic oedema; in the subacute stage, there was confluent cytotoxic oedema or vasogenic oedema; and in the long-term stage, there was identifiable brain atrophy and demyelination [32]. With all stages of cerebral FES, petechial hemorrhages with a confluent morphology were observed.Early detection of these tendencies may aid in choosing the best management. While not specific, diffuse, well-demarcated ground glass opacities or ill-defined centrilobular nodules on computed tomography might offer clinicians a reason to suspect FES in patients with respiratory compromise following trauma or an orthopaedic treatment [33]. To enable early diagnosis and appropriate care, radiologists, orthopaedic surgeons, and clinicians must be conversant with the clinical presentation and imaging of FES.

Criteria For The Diagnosis

Fat embolism is a disease in which fat cells enter the circulation, making autopsy the only conclusive or empirical way to prove the existence of this condition. The clinical expression of this process is FES. FES cannot be diagnosed with a single laboratory or radiographic test. To diagnose FES, a number of criteria have been developed. Of the three criteria suggested to support a diagnosis of FES, the Gurd and Wilson criterion (Table I) is the most widely used. Gurd first put up his initial standards in 1970, then revised them with Wilson in 1974 [4,5]. Gurd's criteria are frequently criticized for the fact that healthy volunteers' and trauma patients' blood frequently contains fat macroglobulinemia without any other indication of FES [34]. The criteria from Schoenfeld (Table II)and Lindeque (Table III) have also been employed in the past. When Lindeque et al. used their parameters on this, a reported incidence of 29% was obtained, which was greater than in any other comparable series [7]. None of the aforementioned diagnostic criteria are universally recognized or clinically validated. Another critique of these

criteria is that they are too general and will include many non-specific cases of respiratory failure. This may be the cause of the huge variation in incidence mentioned in the previous section.

Table I:- Gurd and Wilson Criteria for FES [3].

Two major criteria / one major criteria and four minor criteria suggest a diagnosis of FES	
Major Criteria	**Minor Criteria**
▪ Respiratory Distress ▪ Cerebral symptoms in non-head injury patients ▪ Petechial rash ▪ Renal Changes ▪ Retinal Changes ▪ Drop in haemoglobin ▪ New onset thrombocytopaenia ▪ Elevated erythrocyte sedimentation rate ▪ Fat macroglobulinemia	▪ Fever (>38.5°C) ▪ Tachycardia (>110 bpm) ▪ Jaundice

Table II:- Schoenfeld's scoring system for diagnosing FES [6].

Score >5 points diagnoses FES
Sign/ Symptom: • Petechial Rash (5 points) • Diffuse infiltrates on chest x-ray chest (4) • Fever (1) • Tachycardia (1) • Tachycardia (1) • Confusion (1)

Table III:- Lindeque's Criteria for FES [5].

Criteria:
• pO2 <8kpa • pCO2 >7.3kpa • Respiratory rate >35/min; despite sedation • Dyspnoea, tachycardia, anxiety

Differential Diagnoses

Given the nonspecific nature of the clinical presentation, it is crucial to rule out other possible diagnosis including pulmonary emboli, bacterial pneumonia, sepsis, ARDS, and COVID-19 infection.

Pathophysiology

FES's pathophysiology is still a mystery. The oldest theories have been around for close to a century.

Biochemical theory:

According to Lehman, a proinflammatory condition is what is to blame for the clinical symptoms of FES [35]. Acute Respiratory Distress Syndrome can result from the breakdown of adipose cells from bone marrow by tissue lipases, which produces glycerol and toxic free fatty acids (FFAs) such chylomicrons that harm pneumocytes and pulmonary endothelium cells. Lehman's idea could be useful in explaining non-traumatic FES events. Animal models of FES used in biochemical research provide credence to this notion. Peltier made the first scientific demonstration of the FFAs' toxicity in the 1950s [36]. Since then, FFA infusions have been employed in animal models to cause alterations in the lungs and circulation that mimic FES [37]. Research has been done to produce FES and look at a "second hit" using the FFA triolein in rat models. In comparison to rats subjected to a pulmonary

toxin alone, rats with a history of clinically resolved triolein-induced FES exhibited severe lung damage after receiving a pulmonary toxin injection [38]. Cell membrane proteins called aquaporins create pores in the membrane of living cells [39]. Zhang et al. demonstrated that the pulmonary oedema brought on by FES results in increased expression of an aquaporin known as AQP1 [40]. Additionally, this happened in accordance with how severe the pulmonary oedema was. According to Zhang, AQP1 may be controlled by FFAs and is consequently increased during FES, creating a possible opportunity to target AQP1 as a treatment for FES. Patients with ARDS have higher levels of oleic acid, the most prevalent FFA in human adipose tissue, in their plasma and bronchoalveolar lavage fluids [41]. It has been demonstrated in animal models to cause alveolar oedema, its creation, and inhibit its clearance, all of which contribute to the development of ARDS[42]. There are several FFA binding sites on human albumin[43]. This led to the hypothesis that hypoalbuminemia is a risk factor for FES in trauma and raises the mortality risk for patients who are hospitalized [44,45]. While crystalloid resuscitation has been linked to a lower death rate in trauma patients, the data from this trial was not powered to definitively prove that colloids are preferable to isotonic crystalloids in fluid resuscitation[46]. Divergent evidence suggests that fluid resuscitation using albumin solutions may be advantageous in the development of ARDS because the oleic acid will bind to albumin and reduce its ability to generate oedema [47-50]. Additionally, using albumin along with furosemide for ARDS patients seems to increase oxygenation and may shorten ventilation times[48].

Mechanical theory:

In 1924, Gauss suggested that the increased intramedullary pressure that follows trauma could allow fat cells from the bone marrow to enter venous sinusoids[49]. These adipose cells contain characteristics that are pro-inflammatory and pro-thrombotic. Before becoming imprisoned somewhere in the pulmonary arterial circulation when the vessels form capillaries, they induce accelerated platelet adhesion and enhanced fibrin production as they travel through the venous system back towards the heart. Interstitial hemorrhage, oedema, alveolar collapse, and a reactive hypoxemic vasoconstriction are brought on by capillary blockage. Massive fat emboli can potentially result in shock and macrovascular obstruction[50]. Through a patent foramen ovale or directly through the pulmonary capillaries, fat cells can enter the arterial circulation and result in FES's distinctive dermatological and neurological symptoms [51].

Management

Pharmacological Interventions

There is not a specific treatment for FES at the moment. After FE was produced by injecting fat intravenously, aliskiren, a renin inhibitor, was found to protect the lungs of rats from gross and histopathologic damage[52]. In order to prevent the respiratory effects of FES, additional research is required to determine whether aliskiren could be used both prophylactically before specific orthopaedic operations and therapeutically after severe trauma. Losartan was used on rat models of FES generated by triolein in a comparable animal study[53]. This study demonstrated how losartan assisted in preventing long-term pulmonary system impairment following FES. Additionally, it guarded the rats against the second occurrence discussed earlier. The potential for using the renin-angiotensin system to treat FES is supported by both investigations. Concomitant illnesses and injuries frequently make managing FES more challenging. Heparin and dextran were two treatments that were tried out in the middle of the 20th century, but neither showed any sign of reducing morbidity or mortality[54,55]. FES management is centered on supportive care, symptom control, and most importantly prevention because there is no specific treatment for the condition.

Fat Embolism During Intramedullary Nailing

Kuntscher was the first to describe how intramedullary nailing affects the entire body[56]. In vitro studies have demonstrated that increasing IM pressure increases fat embolization[57]. One year after surgery, Richards discovered that reamed intramedullary nails were a risk factor for cognitive decline[58]. Reaming using a vacuum or venting has been demonstrated to lower intra-medullary pressure, which in turn lowers fat embolization[58]. Volgas compared the use of a Reamer Irrigator-Aspirator (RIA) system with the conventional sequential reaming procedure while monitoring intracardiac fatty emboli using intraoperative transoesophageal echocardiography[59]. In the RIA group, he displayed considerably decreased levels of fatty emboli. Unfortunately, the RIA system's substantial cost and mass may prevent wider use. The suction tubing for intramedullary reaming is advanced to the end of the IM bone and suction is applied for two to three minutes once access to the medullary canal is gained.The procedure is then carried out, and suction is repeated in a similar manner afterward, according to a method described by Baig that could be used with conventional reaming equipment[60]. Transoesophageal echocardiography during TKA has also demonstrated that medullary cavity irrigation reduces the size of emboli[61]. Muller investigated intramedullary pressure in several reamer systems and discovered that pressures were greatly lowered when the flexible driver's

diameter was reduced from 9mm to 7mm. Using a 9.5mm hollow reamer and a driver with a 7mm diameter, he also reported that the operational intramedullary pressures were lowered by 61% to 66%[62]. In conclusion, improvements in technique and technology for frequently used reamer systems have made it possible to treat fractures more aggressively while reducing the risk of fat embolization and the emergence of FES.

The Different Orthopaedic Trauma Philosophies

Although there is evidence that corticosteroids can be administered prophylactically to prevent FES in high-risk individuals, such as those who have experienced long-bone fractures, their use in FES prevention is disputed[63]. However, a 2009 meta-analysis revealed that while corticosteroids did lower rates of FES and hypoxia, they did not lower death rates[64]. The authors came to the conclusion that a larger randomised trial is required as a result. Due to the ongoing controversy about when to operate on long bone fractures, which has just recently led to a consensus between Early Total Care and Damage Control Orthopaedics, a method known as Early Appropriate Care, these results cannot be generalized to contemporary trauma populations[65].

None of these randomised controlled trials also looked into the long-term side effects of steroid therapy. To enable best practice of evidence-based medicine, a sizable confirmatory randomised-controlled study will ultimately be required. The most frequent cause of FES is repair of long bone fractures, however timely and effective immobilization of fractures may be crucial in limiting the release of additional adipose cells into the circulation[66]. Tanton first suggested that adequate fracture immobilization would lower the incidence of FES in 1914–1919[67]. Following a shift in strategy to treat long bone fractures in the first days after injury, a big Finnish trauma center saw a trend in decreasing rates of FES[68].

In patients who were healthy enough for surgery, a prospective American studyfound that fixing long bone fractures within 24 hours decreased the risks of FES, ARDS, and pneumonia[69]. In fact, it has been demonstrated that delayed fracture repair increases the length of ICU stays [70]. Pape suggested that patients with chest injuries have un-reamed intramedullary nailing because a 10-year retrospective study shown that early fracture fixing of a patient with concurrent chest injury increased the frequency of FES. This contrasts Brundage's findings, which stated that polytrauma is not a contraindication to early fixation and that delaying fixation operation in patients with polytrauma was proven to increase incidence of FES as well as other sequelae[71]. Pinneyet al also shared similar findings[72].

Treatment of Related Lung Injuries

The most severe potential FES consequence is ARDS, which can result in respiratory failure and even death. Maintaining appropriate gas exchange while reducing the risk of ventilator-associated lung damage (VALI) is the goal of treating ARDS secondary to FES. Some of the supportive therapies used to accomplish this include improving spontaneous breathing and coughing, early mobilization, positive end-expiratory pressure (PEEP), reduced sedation, and neuromuscular blockade[73]. It's crucial to take into account how the immunological states linked to trauma overlap and how the influence of FES hasn't yet been clearly defined in this debate[74].

Frequent neurological observations are a key component in treating patients with FES and neurological sequelae. Although cerebral oedema in FES patients frequently recovers, it can occasionally result in significant morbidity[75]. Monitoring the intracranial pressure in such circumstances is advised[76]. While studies have indicated that MRI is helpful in cases when head trauma is not present in evaluating the severity of cerebral fat embolism and predicting long-term outcomes, clinical diagnosis is still seen to be the preferred diagnostic approach for FES[77]. For trauma patients, sedation and neuromuscular blockade must typically be adjusted so that the patient is kept comfortable, without impairing their serial neurological exams, and that they can tolerate mechanical ventilation[78].

Conclusion:-

Fat emboli entering the circulation generate FES, a poorly understood clinical condition. FES is less typically linked to other traumatic and atraumatic conditions; it usually develops as a result of orthopaedic trauma. The diagnosis of FES cannot be made with a single test. Due to its subclinical presentation or confusing injuries in patients who have been harmed more severely, FES diagnosis is sometimes missed. The mortality rate is less than 10% with supportive care, and pulmonary, neurological, and dermatological symptoms typically fully resolve. Even if prevention and top-notch supportive care are the cornerstones of its management, a high suspicion for FES in at-risk patient cohorts and early diagnosis improve prognosis. The effects of this disease will be lessened by improvements in the perioperative

care of polytraumatized patients as well as the intraoperative procedures. These advancements will also help us better grasp the role of the yet research-based "targeted" pharmaceutical remedies. Similarly, a better understanding of how FES affects lung damage immunomodulation would aid in determining the best course of action.

References:-

1. Kosova E, Bergmark B, Piazza G. Fat embolism syndrome. Circulation. 2015; 131(3): 317-20. doi: 10.1161/CIRCULATIONAHA.114.010835
2. Maitre S. Causes, clinical manifestations, and treatment of fat embolism. Virtual Mentor. 2006; 8(9): 590-2. doi: 10.1001/virtualmentor.2006.8.9.cprl1-0609
3. White T, Petrisor BA, Bhandari M. Prevention of fat embolism syndrome. Injury. 2006; 37(Suppl 4): S59-67. doi: 10.1016/j.injury.2006.08.041
4. Gurd AR. Fat embolism: an aid to diagnosis. J Bone Joint Surg Br. 1970; 52(4): 732-7.
5. Gurd AR, Wilson RI. The fat embolism syndrome. J Bone Joint Surg Br. 1974; 56B(3): 408-16.
6. Kwiatt ME, Seamon MJ. Fat embolism syndrome. Int J Crit Illn Inj Sci. 2013; 3(1): 64-8. doi: 10.4103/2229-5151.109426
7. Lindeque BG, Schoeman HS, Dommisse GF, Boeyens MC, Vlok AL. Fat embolism and the fat embolism syndrome. A doubleblind therapeutic study. J Bone Joint Surg Br. 1987; 69(1): 128-31. doi: 10.1302/0301-620X.69B1.3818718
8. Schonfeld SA, Ploysongsang Y, DiLisio R, Crissman JD, Miller E, Hammerschmidt DE, et al. Fat embolism prophylaxis with corticosteroids. A prospective study in high-risk patients. Ann Intern Med. 1983; 99(4): 438-43. doi: 10.7326/0003-4819-99-4-438
9. Muller C, Rahn BA, Pfister U, Meinig RP. The incidence, pathogenesis, diagnosis, and treatment of fat embolism. Orthop Rev. 1994;23(2):107-17.
10. Laub DR, Jr., Laub DR. Fat embolism syndrome after liposuction: a case report and review of the literature. Ann Plast Surg. 1990; 25(1): 48-52. doi: 10.1097/00000637-199007000-00011
11. Mendoza-Morales R, Camberos-Nava E, Luna-Rosas A, Garcés-Ramírez L, De la Cruz F, García-Dolores F. A fatal case of systemic fat embolism resulting from gluteal injections of vitamin e for cosmetic enhancement. Forensic Sci Intl. 2016; 259: e1-4. doi: 10.1016/j.forsciint.2015.11.012
12. Tsitsikas DA, Gallinella G, Patel S, Seligman H, Greaves P, Amos RJ. Bone marrow necrosis and fat embolism syndrome in sickle cell disease: increased susceptibility of patients with non-SS genotypes and a possible association with human parvovirus B19 infection. Blood Rev. 2014; 28(1): 23-30. doi: 10.1016/j.blre.2013.12.002
13. Bulger EM, Smith DG, Maier RV, Jurkovich GJ. Fat embolism syndrome. A 10-year review. Arch Surg. 1997; 132(4): 435-9. doi: 10.1001/archsurg.1997.01430280109019
14. Robert JH, Hoffmeyer P, Broquet PE, Cerutti P, Vasey H. Fat embolism syndrome. Orthop Rev. 1993; 22(5): 567-71.
15. Fabian TC, Hoots AV, Stanford DS, Patterson CR, Mangiante EC. Fat embolism syndrome: prospective evaluation in 92 fracture patients. Crit Care Med. 1990; 18(1): 42-6.
16. Kim YH. Incidence of fat embolism syndrome after cemented or cementless bilateral simultaneous and unilateral total knee arthroplasty. J Arthroplasty. 2001; 16(6): 730-9. doi: 10.1054/arth.2001.23723.
17. Pell AC, Hughes D, Keating J, Christie J, Busuttil A, Sutherland GR. Brief report: fulminating fat embolism syndrome caused by paradoxical embolism through a patent foramen ovale. N Engl J Med. 1993; 329(13): 926-9. doi: 10.1056/NEJM199309233291305
18. DeFroda SF, Klinge SA. Fat Embolism Syndrome With Cerebral Fat Embolism Associated With Long-Bone Fracture. Am J Orthop (Belle Mead NJ). 2016; 45(7): E515-E21.
19. Hayes I, Walshe C, Kossmann T, Iles L, Cooper J. Cerebral fat embolism syndrome causing brain death after long bone fractures and acetazolamide therapy. Crit Care Resusc. 2007; 9(2): 184.
20. Fernandez-Torre JL, Burgueno P, Ballesteros MA, Hernandez-Hernandez MA, Villagra-Teran N, de Lucas EM. Super-refractory nonconvulsive status epilepticus secondary to fat embolism: A clinical, electrophysiological, and pathological study. Epilepsy Behav. 2015; 49: 184-8. doi: 10.1016/j.yebeh.2015.04.045
21. Scopa M, Magatti M, Rossitto P. Neurologic symptoms in fat embolism syndrome: case report. J Trauma. 1994; 36(6): 906-8. doi: 10.1097/00005373-199406000-00030
22. Jacobson DM, Terrence CF, Reinmuth OM. The neurologic manifestations of fat embolism. Neurology. 1986; 36(6): 847-51. doi: 10.1212/wnl.36.6.847
23. Shaikh N. Emergency management of fat embolism syndrome. J Emerg Trauma Shock. 2009; 2(1): 29-33. doi: 10.4103/0974-2700.44680

24. Parizel PM, Demey HE, Veeckmans G, Verstreken F, Cras P, Jorens PG, et al. Early diagnosis of cerebral fat embolism syndrome by diffusion-weighted MRI (starfield pattern). Stroke. 2001; 32(12): 2942-4.
25. Nentwich MM, Remy M, Schaller UC. Ocular fat embolism syndrome. Int Ophthalmol. 2011; 31(1): 15-6. doi: 10.1107/s10792-010-9378-8
26. Agrawal A, McKibbin MA. Purtscher's and Purtscher-like retinopathies: a review. Surv Ophthalmol. 2006; 51(2): 129-36. doi: 10.1016/j.survophthal.2005.12.003
27. Tachakra SS. Distribution of skin petechiae in fat embolism rash. Lancet. 1976; 1(7954): 284-5. doi: 10.1016/s0140-6736(76)91408-2
28. Jaffe FA. Petechial Hemorrhages A Review of Pathogenesis. Am J Forensic Med Pathol. 1994; 15(3): 203-7. doi: 10.1097/00000433-199409000-00004
29. Erdem E, Namer IJ, Saribas O, Aras T, Tan E, Bekdik C, et al. Cerebral fat embolism studied with MRI and SPECT. Neuroradiology. 1993;35(3):199-201. doi: 10.1007/BF00588493
30. Takahashi M, Suzuki R, Osakabe Y, Asai JI, Miyo T, Nagashima G, et al. Magnetic resonance imaging findings in cerebral fat embolism: correlation with clinical manifestations. J Trauma. 1999; 46(2): 324-7. doi: 10.1097/00005373-199902000-00021
31. Suzuki S, Hayashi T, Ri K, Hashimoto T, Matsui S, Kitanosono T, et al. Brain CT and MRI findings in fat embolism syndrome. Nihon Igaku Hoshasen Gakkai Zasshi. 1996; 56(6): 390-8.
32. Kuo KH, Pan YJ, Lai YJ, Cheung WK, Chang FC, Jarosz J. Dynamic MR imaging patterns of cerebral fat embolism: a systematic review with illustrative cases. AJNR Am J Neuroradiol. 2014; 35(6): 1052-7. doi: 10.3174/ajnr.A3605
33. Newbigin K, Souza CA, Torres C, Marchiori E, Gupta A, Inacio J, et al. Fat embolism syndrome: State-of-the-art review focused on pulmonary imaging findings. Respir Med. 2016;113:93-100. doi: 10.1016/j.rmed.2016.01.018
34. Nolte WJ, Olofsson T, Schersten T, Lewis DH. Evaluation of the Gurd test for fat embolism. J Bone Joint Surg Br. 1974; 56B(3): 417-20.
35. Lehman EP, Moore RM. Fat embolism: including experimental production without trauma. Arch Surg. 1927; 14(3): 621-62. doi: 10.1001/archsurg.1927.01130150002001
36. Peltier LF. Fat embolism. III. The toxic properties of neutral fat and free fatty acids. Surgery. 1956; 40: 665-70.
37. Liu DD, Hsieh NK, Chen HI. Histopathological and biochemical changes following fat embolism with administration of corn oil micelles: a new animal model for fat embolism syndrome. J Bone Joint Surg Br. 2008; 90(11): 1517-21. doi: 10.1302/0301-620X.90B11.20761
38. Poisner A, Herndon B, Lankachandra K, Likhitsup A, Al Hariri A, Kesh S, et al. Fat embolism sensitizes rats to a "second hit" with lipopolysaccharide: An animal model of pulmonary fibrosis. J Trauma Acute Care Surg. 2015; 78(3): 552-7. doi: 10.1097/TA.0000000000000539
39. Agre P. The aquaporin water channels. Proc Am Thorac Soc. 2006; 3(1): 5-13. doi: 10.1513/pats.200510-109JH
40. Zhang Y, Tian K, Wang Y, Zhang R, Shang J, Jiang W, et al. The Effects of Aquaporin-1 in Pulmonary Edema Induced by Fat Embolism Syndrome. Int J Mol Sci. 2016; 17(7): 1183 doi: 10.3390/ijms17071183
41. Kokatnur MG, Oalmann MC, Johnson WD, Malcom GT, Strong JP. Fatty acid composition of human adipose tissue from two anatomical sites in a biracial community. Am J Clin Nutr. 1979; 32(11): 2198-205. doi: 10.1093/acjn/32.11.2198
42. Vadasz I, Morty RE, Kohstall MG, Olschewski A, Grimminger F, Seeger W, et al. Oleic acid inhibits alveolar fluid reabsorption: a role in acute respiratory distress syndrome? Am J Respir Crit Care Med. 2005; 171(5): 469-79. doi: 10.1164/rccm.200407- 9540C
43. Goodman DS. The interaction of human serum albumin with long-chain fatty acid anions. J Am Chem Soc. 1958; 80(15): 3892- doi: 10.1021/ja01548a024
44. Moylan JA, Birnbaum M, Katz A, Everson MA. Fat emboli syndrome. J Trauma. 1976; 16(5): 341-7. doi: 10.1097/00005373-197605000-00002
45. Mogensen KM, Robinson MK, Casey JD, Gunasekera NS, Moromizato T, Rawn JD, et al. Nutritional Status and Mortality in the Critically Ill. Crit Care Med. 2015; 43(12): 2605-15. doi: 10.1097/CCM.0000000000001306
46. Perel P, Roberts I. Colloids versus crystalloids for fluid resuscitation in critically ill patients. Cochrane Database Syst Rev. 2012; (6): CD000567. doi: 10.1002/14651858.CD000567.pub6
47. Amanullah S, Venkataraman R. The routine use of albumin for fluid resuscitation of critically ill patients is not warranted. Crit Care. 2004; 8: E2. doi: 10.1186/cc3006
48. Calfee CS, Matthay MA. Nonventilatory treatments for acute lung injury and ARDS. Chest. 2007; 131(3): 913-20. doi: 10.1378/chest.06-1743
49. Gauss H. The pathology of fat embolism. Arch Surg. 1924; 9(3): 593-605. doi: 10.1001/archsurg.1924.01120090110007

50. Husebye EE, Lyberg T, Roise O. Bone marrow fat in the circulation: clinical entities and pathophysiological mechanisms. Injury. 2006; 37(Suppl 4): S8-18. doi: 10.1016/injury.2006.08.036.
51. Pell AC, Christie J, Keating JF, Sutherland GR. The detection of fat embolism by transoesophageal echocardiography during reamed intramedullary nailing. A study of 24 patients with femoral and tibial fractures. J Bone Joint Surg Br. 1993; 75(6): 921-5. doi: 10.1302/0301-620X.75B6.8245083
52. Fletcher AN, Molteni A, Ponnapureddy R, Patel C, Pluym M, Poisner AM. The renin inhibitor aliskiren protects rat lungs from the histopathologic effects of fat embolism. J Trauma Acute Care Surg. 2017; 82(2): 338-44. doi: 10.1097/TA.0000000000001278
53. Poisner A, Herndon B, Bass D, Jain A, Fletcher A, Molteni A. Losartan protects the lung from chronic cellular damage induced by fat embolism (LB512). The FASEB Journal. 2014; 28(1): LB512. doi: 10.1096/fasebj.28.1_supplement.lb512
54. Lewis A, Pappas Am. Experimental fat embolism: evaluation of treatment with low molecular weight dextran. J Trauma Acute Care Surg. 1969; 9(1): 49-55.
55. Sage R, Tudor R. Treatment of fat embolism with heparin. British Med J. 1958; 1(5080): 1160. doi: 10.1136/bmj.1.5080.1160
56. Bick EM. The intramedullary Nailing of Fractures by G. Kuntscher. Translation of article in Archiv fur Klinische Chirurgie, 200:443,1940. Clin Orthop Relat Res. 1968; 60: 5-12.
57. Kropfl A, Berger U, Neureiter H, Hertz H, Schlag G. Intramedullary pressure and bone marrow fat intravasation in undreamed femoral nailing. J Trauma. 1997; 42(5): 946-54. doi: 10.1097/00005373-199705000-00028
58. Pitto RP, Koessler M, Kuehle JW. Comparison of fixation of the femoral component without cement and fixation with use of a bone-vacuum cementing technique for the prevention of fat embolism during total hip arthroplasty. A prospective, randomized clinical trial. J Bone Joint Surg Am. 1999; 81(6): 831-43. doi: 10.2106/00004623-199906000-00010
59. Volgas DA, Burch T, Stannard JP, Ellis T, Bilotta J, Alonso JE. Fat embolus in femur fractures: a comparison of two reaming systems. Injury. 2010; 41(Suppl 2): S90-3. doi: 10.1016/S0020-1383(10)70017-6
60. Baig MN, Curtin W. A Simple and Easy Intramedullary Lavage Method to Prevent Embolism During and After Reamed Long Bone Nailing. Cureus. 2017; 9(8): e1609. doi: 10.7759.cures.1609
61. Zhao J, Zhang J, Ji X, Li X, Qian Q, Xu Q. Does intramedullary canal irrigation reduce fat emboli? A randomized clinical trial with transesophageal echocardiography. J Arthroplasty. 2015; 30(3): 451-5. doi: 10.1016/j.arth.2014.10.006
62. Müller C, Frigg R, Pfister U. Effect of flexible drive diameter and reamer design on the increase of pressure in the medullary cavity during reaming. Injury. 1993; 24: S40-S7. doi: 10.1016/0020-1383(93)90006-r
63. Kallenbach J, Lewis M, Zaltzman M, Feldman C, Orford A, Zwi S. 'Low-dose' corticosteroid prophylaxis against fat embolism. J Trauma. 1987; 27(10): 1173-6.
64. Bederman SS, Bhandari M, McKee MD, Schemitsch EH. Do corticosteroids reduce the risk of fat embolism syndrome in patients with long-bone fractures? A meta-analysis. Can J Surg. 2009; 52(5): 386-93.
65. Tasker A, Kelly M. Managing trauma: the evolution from 'early total care'/'damage control'to 'early appropriate care'. JTO. 2014; 2(2): 66-70.
66. Pape HC. Effects of changing strategies of fracture fixation on immunologic changes and systemic complications after multiple trauma: damage control orthopedic surgery. J Orthop Res. 2008; 26(11): 1478-84. doi: 10.1002/jor.20697
67. Tanton J. L'embolie graisseuse traumatique. J de Chir. 1914; 12: 287-96.
68. Riska EB, von Bonsdorff H, Hakkinen S, Jaroma H, Kiviluoto O, Paavilainen T. Prevention of fat embolism by early internal fixation of fractures in patients with multiple injuries. Injury. 1976; 8(2): 110-6. doi: 10.1016/0020-1383(76)-90043-7
69. Bone LB, Johnson KD, Weigelt J, Scheinberg R. Early versus delayed stabilization of femoral fractures. A prospective randomized study. J Bone Joint Surg Am. 1989; 71(3): 336-40.
70. Behrman SW, Fabian TC, Kudsk KA, Taylor JC. Improved outcome with femur fractures: early vs. delayed fixation. J Trauma. 1990; 30(7): 792-7. doi: 10.1097/00005373-199007000-00005
71. Brundage SI, McGhan R, Jurkovich GJ, Mack CD, Maier RV. Timing of femur fracture fixation: effect on outcome in patients with thoracic and head injuries. J Trauma. 2002; 52(2): 299-307. doi: 10.1097/00005373-200202000-00016
72. Pinney SJ, Keating JF, Meek RN. Fat embolism syndrome in isolated femoral fractures: does timing of nailing influence incidence? Injury. 1998; 29(2): 131-3. doi: 10.1016/s0020-1383(97)00154-x
73. Habashi NM, Andrews PL, Scalea TM. Therapeutic aspects of fat embolism syndrome. Injury. 2006; 37(Suppl 4): S68-73. doi: 10.1016/j.injury.2006.08.042

74. Binkowska AM, Michalak G, Slotwinski R. Current views on the mechanisms of immune responses to trauma and infection. Cent Eur J Immunol. 2015; 40(2): 206-16. doi: 10.5114/ceji.2015.52835
75. Butteriss DJ, Mahad D, Soh C, Walls T, Weir D, Birchall D. Reversible cytotoxic cerebral edema in cerebral fat embolism. AJNR Am J Neuroradiol. 2006; 27(3): 620-3.
76. Sie MY, Toh KW, Rajeev K. Cerebral fat embolism: an indication for ICP monitor? J Trauma. 2003; 55(6): 1185-6. doi:10.1097/01.TA.0000100833.57027.1F
77. Georgopoulos D, Bouros D. Fat embolism syndrome: clinical examination is still the preferable diagnostic method. Chest. 2003; 123(4): 982-3. doi: 10.1378/chest.123.4.982
78. Bullock R, Chesnut RM, Clifton G, Ghajar J, Marion DW, Narayan RK, et al. Guidelines for the management of severe head injury. Brain Trauma Foundation. Eur J Emerg Med. 1996; 3(2): 109-27.