VILNIUS UNIVERSITY
FACULTY OF MEDICINE

Medicine

Clinic of Rheumatology, Orthopaedics, Traumatology and Reconstructive Surgery
Institute of Clinical Medicine

Ruben Frederic Ackermann
Year 6
Group 1

INTEGRATED STUDY MASTER'S THESIS

Fat Embolism Syndrome

Supervisor Assoc. Prof. Igoris Šatkauskas

Head of the department Prof. Irena Butrimienė, PhD

Vilnius, 2025

Student's email: ruben.ackermann@mf.stud.vu.lt

1. ABBREVIATIONS

FES - Fat embolism syndrome

FE - Fat embolism

DCO - Damage-controlled orthopedics

SDS - Safe definitive surgery

ETC - Early Total Care

EAC - Early Appropriate Care

RIA - Reamer-Irrigator-Aspirator

CT - Computer tomography

CFE - Cerebral fat embolism

MRI - Magnetic resonance imaging

DWI - Diffusion-weighted imaging

FFA - Free fatty acids

DIC - Disseminated intravascular coagulation

PFO - Patent foramen ovale

IL-1 - Interleukin 1

IL-6 - Interleukin 6

ECMO - Extracorporeal membrane oxygenation

RCE - Red cell exchange

TPE - Therapeutic plasma exchange

IMN - Intramedullary nailing

RIN - Reamed intramedullary nailing

URIN - Unreamed intramedullary nailing

RSR - Rinsing-suction reamer

LPV - Lung-protective ventilation

PEEP - Positive end-expiratory pressure

VILI - Ventilator-induced lung injury

RCT - Randomized controlled trial

e.g. - exempli gratia

2. SUMMARY

Although relatively underrecognized in daily clinical practice, fat embolism and its systemic manifestation, fat embolism syndrome, pose a significant threat in trauma and orthopedic surgery. Fat embolism refers to the entry of fat globules into the pulmonary or systemic circulation. In contrast, fat embolism syndrome describes the resulting clinical manifestations due to fat deposition in the microvasculature following a triggering event. Fat embolism syndrome is a potentially fatal complication most common after orthopedic surgical procedures or trauma-induced long bone fractures. While fat embolism is relatively common in cases involving long bone fractures, the progression of the clinical syndrome to fat embolism syndrome is much rarer but much more dangerous, as it has a much higher mortality rate. Despite a declining incidence over recent decades, fat embolism syndrome remains a diagnostic and therapeutic challenge. This is largely due to its highly variable clinical presentation, and that there is no possibility of using a sufficiently established biomarker routinely in standard clinical settings. The purpose of this thesis was to give an overview of the etiopathogenesis of fat embolism syndrome as understood at the current time and to critically examine evidence-based measures of prevention in orthopedic trauma care. For this purpose, an organized literature review was performed using the PubMed database, using peer-reviewed literature published in 2014 - 2024. Selection was based on relevance to pathophysiological mechanisms, risk factors, and prevention strategies in trauma- and surgery-based settings.

The results highlight that the development of fat embolism syndrome involves a complex interplay of mechanical, biochemical, and coagulative factors. Clinically, fat embolism syndrome most commonly presents with a triad of respiratory distress, neurological impairment, and petechial skin manifestations. Major risk factors include multiple or bilateral long bone fractures, delayed fracture fixation, and comorbidities such as obesity or advanced age. Effective prevention strategies include early fracture stabilization, preferably within 48 hours, applying damage control orthopedics and safe definitive surgery, as well as technical measures such as intramedullary lavage and using the Reamer-Irrigator-Aspirator system. Additional strategies, including lung-protective ventilation and selective pharmacological interventions like corticosteroid therapy, remain under investigation due to limited clinical evidence. In conclusion, effective prevention of fat embolism syndrome relies on trauma management strategies tailored to the patient’s physiological status and injury pattern, particularly concerning surgical strategies and the choice of intramedullary techniques. While supportive care remains the cornerstone of fat embolism syndrome treatment, advances in intraoperative strategies have contributed to a measurable decline in incidence. Nevertheless,

significant gaps persist in early diagnostic capabilities and long-term outcome data. Moving forward, future research should aim to establish standardized diagnostic criteria, investigate promising molecular targets such as the renin-angiotensin system, and critically evaluate surgical innovations in prospective clinical studies.

2.1. Keywords

Fat embolism syndrome (FES), Etiopathogenesis, Trauma-related FES, Surgical Prevention, Reamed vs. Unreamed Nailing, Damage Control Orthopedics (DCO) / Safe Definitive Surgery (SDS)

3. INTRODUCTION

Although often underdiagnosed (1), fat embolic phenomena represent a potentially severe complication that is frequently encountered in the context of orthopedic trauma. Fat embolic manifestations refer to a spectrum of conditions, ranging from Fat emboli within the vascular system (Fat embolism) to the clinically significant fat embolism syndrome (FES), characterized by the onset of recognizable signs and patterns. While fat embolism (FE) occurs in over 90% of long bone fracture cases, only a fraction develops into the full clinical picture of (FES) (2). Despite FES remaining a feared complication associated with long bone trauma and orthopedic surgery, a notable decline in its incidence has been observed over the past decades, from approximately 8% in the period 1960 - 1979 to only 2% in the years 2000 - 2019 (Figure 1) (3).

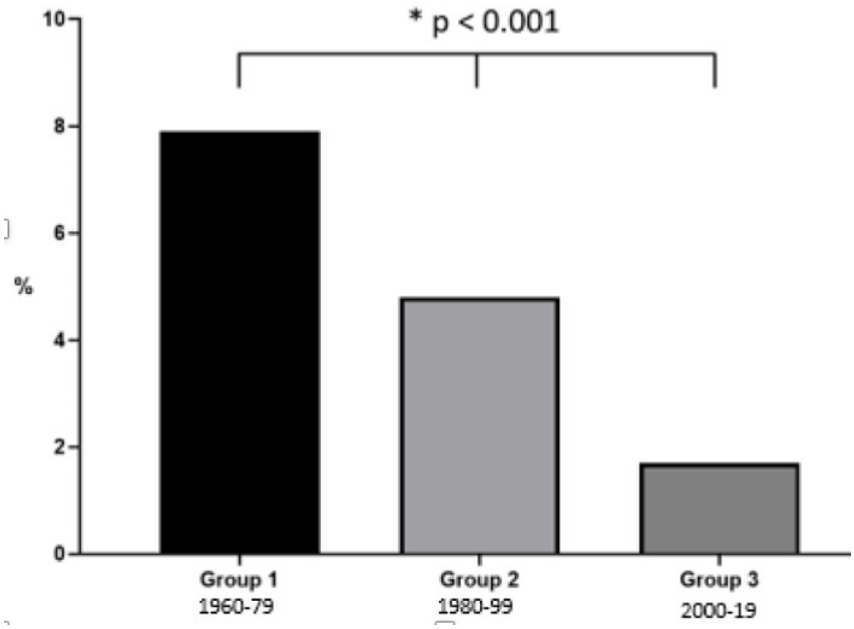

Figure 1. *Changes in the rate of clinically identified fat embolism syndrome over time (level of significance gr1 versus gr2 and gr3) (3).*

This reduction may suggest both improved prevention strategies and advances in management of the syndrome. However, the precise reasons behind this decline are still debated, and the underlying pathophysiology of FES remains incompletely understood.

This thesis aims to evaluate the etiopathogenesis as well as intraoperative prevention strategies for FES in the context of long bone fractures. To achieve this aim, the thesis will begin by providing a comprehensive overview of the syndrome, followed by a detailed examination of prevention strategies and both surgical and anesthetic treatment approaches. Recent studies emphasize the increasing importance of preventive strategies, including the choice of reaming techniques, optimal timing of fixation, and the application of systems such as the Reamer-Irrigator-Aspirator (RIA).

3.1. AIMS AND OBJECTIVES

This thesis primarily aims to summarize the key aspects of the current scientific understanding of FES, with a particular focus on its etiopathogenesis and evidence-based prevention strategies in the context of surgical trauma care. Given the clinical relevance of FES in patients with injuries involving long bones and during surgical orthopedic interventions, a good understanding of its underlying mechanisms and risk-reducing interventions is essential for improving outcomes and guiding surgical decision-making.

To achieve this aim, the objectives of the thesis are defined as follows: First, to establish a clear understanding of the pathophysiological mechanisms contributing to the development of FES, including mechanical, biochemical, and coagulation-based theories. Second, to identify and categorize relevant risk factors, both trauma-related and patient-specific, that may predispose individuals to the syndrome. Third, to evaluate the impact of surgical timing, specifically within the frameworks of Early total care (ETC), Damage-controlled orthopedics (DCO), and Safe definitive surgery (SDS), on the prevention of FES. Fourth, to assess the influence of different intramedullary nailing techniques, with particular attention to the comparison between reamed and unreamed approaches, on the risk of fat embolization. Fifth, to summarize and critically discuss current intraoperative prevention strategies, including the use of RIA systems, intramedullary lavage, suction techniques, and emerging experimental interventions. Lastly, the thesis aims to highlight persisting knowledge gaps and to outline future directions for research, particularly regarding diagnostic standardization and intraoperative prevention strategies.

4. LITERATURE SEARCH STRATEGY AND METHODOLOGY

The methods used in this thesis are based on a structured literature review designed to identify, evaluate, and synthesize current scientific evidence on the etiopathogenesis and prevention of FES, particularly in the context of orthopedic trauma care. This approach was selected to offer a thorough and current perspective on the subject, considering both the limited availability of prospective clinical data and the complex, multifactorial pathophysiology of FES. The review process aimed at ensuring methodological transparency and reproducibility, following clear and structured guidelines.

The primary data source for the literature review was PubMed, selected for its extensive coverage of peer-reviewed clinical and medical literature. A comprehensive literature search was performed utilizing both Medical Subject Headings (MeSH) and non-indexed keywords, such as “Fat Embolism Syndrome,” “Etiopathogenesis,” “Intramedullary Nailing,” “Reamed vs. Unreamed,” “Fracture Fixation,” and “Surgical Prevention.” Boolean operators (AND, OR) were employed to systematically narrow and enhance the relevance of the search findings. Several different variations of search terms were used during searching to achieve sensitivity and specificity. Screening of titles and abstracts for relevance was followed by an examination of the full text.

To guarantee research relevance and integrity, inclusion/exclusion criteria were established. Publications were considered eligible if they were published in English between 2014 and 2024, were peer-reviewed, and fell into one of the following categories: clinical trials, prospective population studies, retrospective comparative studies, systematic reviews, or experimental/animal studies. Included studies focused on trauma- and non-trauma-related causes of FES, pathophysiological mechanisms, and surgical prevention strategies, particularly in orthopedic trauma care.

Exclusion criteria include publications before 2014, non-English articles, and non-peer-reviewed literature such as case reports, letters, or abstracts without full text. Studies focusing exclusively on other forms of embolism without direct relevance to FES, as well as articles lacking clinical or experimental evidence related to FES pathophysiology or prevention, were also excluded. Duplicate entries were removed using reference management software, and reference lists of key articles were manually screened for additional relevant publications.

This methodology allowed for a systematic and targeted evaluation of current evidence, providing a structured basis for analyzing both established and emerging approaches to the prevention of FES in orthopedic trauma care.

5. RESULTS

5.1. Description of the condition

5.1.1. Clinical Manifestations and Diagnosis of FES

FES typically presents with a latent period following the initial traumatic event, during which no clinical symptoms are observed. This delay in symptom onset is a recognized feature of the condition and can pose challenges for its identification. Symptoms generally begin within 12 to 72 hours post-injury, with an average onset around 48 hours. In rare cases, however, FES can manifest even sooner, appearing in under 12 hours (4). The clinical presentation may arise intraoperatively or be delayed up to 2 weeks following the inciting event (5). Once clinical manifestations begin, FES can affect multiple organ systems, presenting with impaired respiratory function, sudden neurological disturbances, hematologic findings such as anemia and thrombocytopenia, as well as systemic signs including tachycardia, fever, and, in some cases, a petechial rash (6).

The progression of symptoms follows a characteristic clinical triad. Initially, pulmonary symptoms appear, often marking the first clinical sign. These are then followed by neurologic manifestations, while the petechial rash, a hallmark feature of FES, is usually the last component to develop (7). Importantly, not all features of FES present simultaneously; the full triad is seen in only a minority of cases (8). Among the less common clinical features are fever, myocardial ischemia or infarction, cor pulmonale, and obstructive shock (9). The petechial rash appears later during the syndrome, typically 24 to 72 hours after the initial traumatic event. In some presentations, it may not become apparent until several days after the onset of respiratory symptoms. Some studies suggest that the rash may not develop until 3 to 5 days after respiratory compromise begins (8). As a result, the early absence of a petechial rash does not rule out FES, emphasizing the need for clinical caution even in its absence (8). Typically, petechial exanthema occurs in non-dependent regions, including the conjunctivae, head, neck, anterior thoracic wall, and axillae (10).

As already mentioned, pulmonary symptoms are the initial and most prominent features of FES, occurring in approximately 75% of cases (9,11). The key respiratory manifestations include dyspnea and tachypnea, with patients experiencing rapid breathing and shortness of breath as initial signs of pulmonary involvement. They may appear anxious and exhibit increased work of breathing (6,12). Hypoxemia is another common finding, as most FES patients develop low oxygen

saturation, which may present clinically as restlessness, cyanosis, or altered mental status due to inadequate oxygenation (11). Hypoxemia occurs in up to 96% of cases and is therefore the most common clinical sign of FES (10). In severe cases, respiratory failure may advance to Acute respiratory distress syndrome (ARDS) (10), characterized by diffuse pulmonary infiltrates and edema. Patients may develop crackles on lung examination and require high-flow oxygen or mechanical ventilation (13). The severity of respiratory distress in FES varies, ranging from mild, transient hypoxia to acute severe respiratory failure (13). Because these pulmonary findings appear as the earliest symptoms after injury (11), they are critical early indicators of FES. Chest imaging has proven to be neither a sensitive nor a specific diagnostic tool for FES. A retrospective analysis described a range of findings, such as ground-glass opacities, septal thickening, nodules, and areas of consolidation, none of which are specific to FES. Furthermore, the authors noted that even with the use of contrast agents, vascular filling defects typically indicative of embolic events were rarely observed (6). Despite its limited specificity, chest imaging may still reveal abnormalities in a considerable number of cases: up to 30–50% of patients with FES show abnormalities on chest radiographs. Among available imaging modalities, high-resolution chest computer tomography (CT) has emerged as the most effective tool for evaluating pulmonary involvement in FES (9).

Neurological manifestations are a common feature of FES, occurring in up to 86% of patients, with symptoms ranging from mild confusion to drowsiness to severe conditions such as convulsions or coma (11,13). Also, headaches, aggressive behavior, dementia, or hallucinations are reported (14). Interestingly, these neurological signs can present even in the absence of other major features of FES (4), again highlighting the broad spectrum in clinical presentation. Impaired consciousness is frequently observed, and while some patients exhibit only an acute confusional state unrelated to hypoxemia, others may develop focal deficits such as hemiplegia, pupillary dilation, or conduction aphasia (4). In some cases, those neurological symptoms can be severe and life-threatening. For example, a case report describes a previously well 42-year-old woman who developed severe cerebral symptoms following reamed intramedullary nailing of femoral and tibial shaft fractures in a single procedure. Postoperatively, she presented with diffuse extremity weakness and an inability to speak. The initial diagnosis was a stroke, later determined to be diffuse encephalopathy caused by cerebral fat embolism (CFE) (13,15). In addition, isolated reports describe severe cases of CFE culminating in brain death (13). Also, a case of refractory non-convulsive status epilepticus post-total knee arthroplasty resulted in fatal cerebral infarcts caused by fat embolism, emphasizing the potential severity of FES-related neurological involvement (16). Despite these extreme cases, neurological symptoms often resolve spontaneously without long-term consequences (13,15). This is explained by the physical properties of fat vacuoles, which remain in a liquid state, allowing them

to deform, fragment into smaller droplets, and re-enter the pulmonary circulation, ultimately enabling reperfusion of previously affected tissue (14). However, in patients with long bone fractures who experience sudden neurological deterioration without respiratory distress, CFE should be strongly suspected unless intracranial pathology is present (13). Magnetic resonance imaging (MRI) is considered the preferred diagnostic modality for detecting cerebral involvement in FES, whereas CT contributes little to the identification of typical findings (6,13). This is primarily due to its limited sensitivity; however, in rare cases, CT may reveal scattered, round hypodense lesions with a specific density of fat. In cases where MRI findings are nonspecific, assessing the density of these lesions on CT can assist in establishing the correct diagnosis (14). Diffusion-weighted imaging (DWI) has demonstrated the ability to detect the characteristic “starfield” pattern (Figure 2) suggestive of multifocal cytotoxic edema. Moreover, DWI has been presented as a potential instrument for prognostic assessment in patients with suspected cerebral fat embolism (6). A systematic review from the United States described different phases according to MRI findings. In the acute phase, scattered cytotoxic edema was observed, whereas the subacute phase was marked by either confluent cytotoxic or vasogenic edema. In the chronic phase, neuroimaging demonstrated cerebral atrophy and loss of myelin. Small, confluent petechial hemorrhages were present at each stage of the condition (17).

As illustrated earlier by the case of the 42-year-old woman, in whom CFE was initially misdiagnosed as an acute stroke, caution is warranted regarding the potential of FES to mimic other conditions. This is particularly important when neurological symptoms occur in isolation, as their broad and nonspecific nature can lead to a misdiagnosis. Presentations dominated by behavioral changes may be wrongly attributed to psychiatric disorders, further complicating the timely recognition and diagnosis of FES (14).

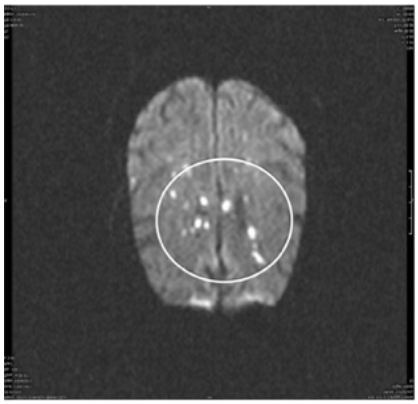

Figure 2. *Diffusion-weighted imaging reveals a ‘starfield’ pattern, defined by numerous small, bright hyperintense foci scattered across a dark background, symmetrically affecting both white matter and deep gray matter, as highlighted by a white circle (14).*

Dermatological manifestations, particularly petechial rashes (Figure 3, 4), typically appear within 24 to 36 hours and are reported in up to 50% of FES cases (11,18). Unlike petechiae seen in sepsis or disseminated intravascular coagulation (DIC), which also can occur in dependent areas such as the back, the rash in FES is found exclusively on gravity-independent, anterior regions like the head, neck, anterior thorax, and axillae (11,19). This distinct distribution is explained by Tachakra's hypothesis, which suggests that fat droplets, due to their floating tendency, accumulate in the aortic arch and embolize selectively to these areas via the carotid and subclavian arteries (13,19). Additional contributing factors include stasis, thrombocytopenia, depletion of clotting factors, and endothelial damage caused by free fatty acids (FFA) (13). In most cases, the rash resolves spontaneously within a week (11).

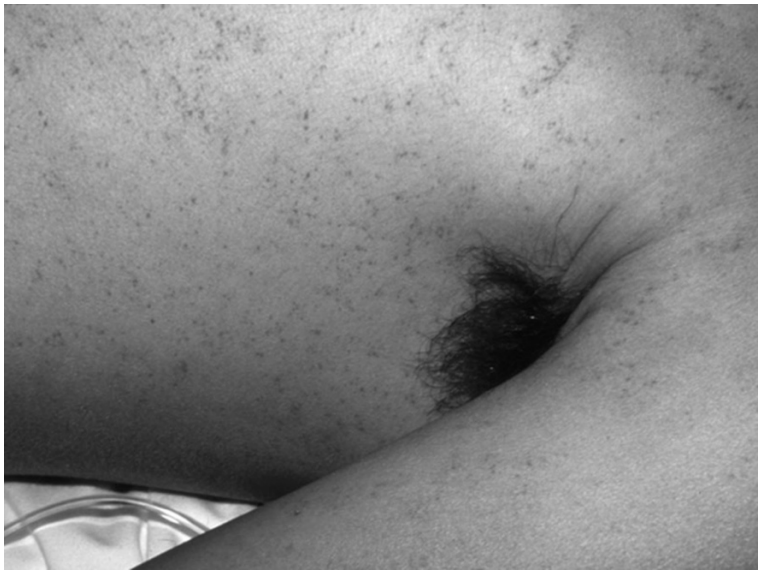

Figure 3. *Typical petechiae observed in the axillary region of a patient diagnosed with fat embolism syndrome (10).*

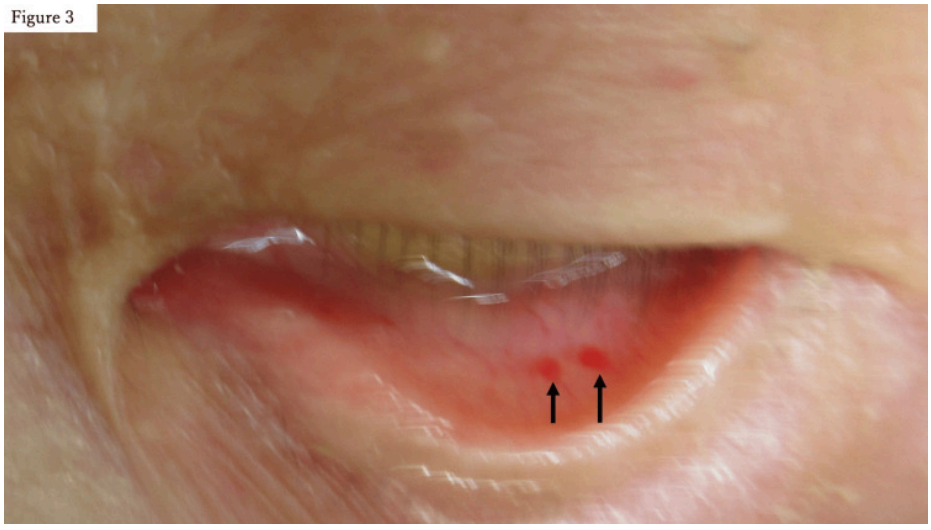

Figure 4. *Petechial hemorrhage of the conjunctiva of the eyelid (20).*

In addition to the previously mentioned clinical manifestations, retinal symptoms occur in approximately 50% of individuals with FES. These may include visual field defects, vision loss, or blurred vision (21). Fat emboli may cause retinal ischemic events by traveling through the bloodstream to the eye, where they obstruct small blood vessels. This, then, is called ocular FES. Retinopathy, which may manifest as cotton wool spots or other retinal abnormalities like macular edema and hemorrhage, is also noted as a symptom in FES cases. It underscores the systemic nature and its potential to cause widespread microvascular damage (8). While these retinal symptoms are not the most prevalent indicators of FES, their presence can aid in the clinical suspicion and diagnosis of the syndrome, especially when considered alongside other systemic signs and symptoms. This is why a fundoscopic examination can be a valuable tool in supporting the diagnosis (12).

Laboratory findings have been utilized in the assessment of FES, but they lack specificity and reliability, as they frequently develop alongside multiple traumas or medical conditions that themselves can cause similar laboratory abnormalities, such as elevated inflammatory markers, anemia, or thrombocytopenia (13,14). Nevertheless, some laboratory abnormalities are considered minor criteria in Gurd's diagnostic framework (Figure 5). Common laboratory findings in FES include anemia without reticulocytosis, thrombocytopenia, and a leukoerythroblastic picture, which includes immature white cells and nucleated red blood cells (12,22). Additionally, there may be a significant increase in serum ferritin levels, sometimes up to 100-fold from baseline, particularly in cases associated with sickle cell disease. Elevated lactate dehydrogenase (LDH) and, occasionally, increased creatinine levels could also be observed (22,23). The arterial blood gas analysis is an important tool to use because an imbalance between ventilation and perfusion represents a key feature of FES. Due to the obstruction of pulmonary blood vessels, the blood is unable to adequately absorb oxygen despite preserved ventilation of the lungs. This results in hypoxemia (12). Biomarkers and invasive diagnostic methods have proven to be unreliable in the assessment of FES. Among inflammatory markers, interleukin-6 (IL-6) has been studied as a potential biomarker, with elevated levels approximately 12 hours after trauma showing statistical correlation with later FES development. However, due to its lack of specificity in distinguishing FES from other systemic inflammatory responses, its diagnostic value remains limited (21). Although bronchoalveolar lavage (BAL) has shown macrophages with intracellular lipid inclusions, these finding lacks specificity and as already discussed in the context of laboratory abnormalities and multiple traumas, can also be seen in other conditions frequently accompanying FES. Similarly, biomarkers such as lipase, phospholipase A2, and FFAs may be elevated but are not unique to FES, as they are also seen in

various pulmonary diseases. Even the detection of fat globules in blood, sputum, or urine is not specific enough to confirm the diagnosis (12).

The first clinical diagnosis of the syndrome of FE was made in 1873 by von Bergmann (14). Diagnosing FES remains a challenge due to its nonspecific signs and symptoms, which can affect multiple organ systems. It is often a diagnosis of exclusion and elimination, as there are no definitive laboratory tests or radiological findings specific to it, and the absence of universally accepted diagnostic criteria (5,12). Physicians should remain alert in settings with known risk factors like long bone fractures or surgical trauma, integrating lab and imaging diagnostics to differentiate FES from other conditions. As a structured diagnostic aid in these high-risk scenarios, Gurd and Wilson's criteria (Table 1) are the most extensively utilized of the three proposed diagnostic systems for FES. According to these criteria, a diagnosis is suggested when the diagnostic threshold of either two major criteria or one major criterion combined with four minor criteria is fulfilled. Major criteria consist of respiratory compromise with corresponding imaging findings and cerebral manifestations not attributable to head trauma (12). Minor criteria include tachycardia, fever, and retinal changes, among others (13,19). Schonfeld's criteria (Table 1) provide an alternative, point-based scoring system. A diagnosis of FES is suggested when the total score exceeds 5 points. Lindeque et al. suggested that respiratory findings alone may be adequate for diagnosing FES (Table 1). However, it is not as widely accepted as Gurd and Wilson's criteria and Schoenfeld’s criteria (12).

Given the wide variability in clinical presentation and the absence of specific biomarkers, the most reliable approach to diagnosing FES lies in the integration of clinical context with targeted imaging findings. Cerebral MRI, especially DWI, which may reveal the characteristic “starfield” pattern, combined with chest imaging findings suggestive of pulmonary involvement, provides the highest diagnostic yield. These tools are especially valuable when interpreted within the appropriate clinical setting, such as the presence of long bone fractures, respiratory symptoms, and neurological deterioration. Thus, while diagnostic criteria such as those proposed by Gurd, Schonfeld, or Lindeque offer valuable frameworks, it is the combination of clinical suspicion, organ system involvement, and supportive imaging that currently represents the most effective strategy for identifying the syndrome.

Table 1. *Criteria for the Diagnosis of Fat Embolism Syndrome (19).*

Criteria	Findings	Points
Gurd criteria[a]	Major	
	Respiratory insufficiency	—
	Cerebral involvement	—
	Petechial rash	—
	Minor	—
	Fever	—
	Tachycardia	—
	Retinal changes	—
	Jaundice	—
	Renal changes	—
	Anemia	—
	Thrombocytopenia	—
	Elevated ESR	—
	Fat macroglobulinemia	—
Schonfeld criteria[b]	Petechia	5
	Chest radiograph changes	4
	Hypoxemia (PaO2 < 9.3 kPA)	3
	Fever (>38C)	1
	Tachycardia (>120 bpm)	1
	Tachypnea (>30 bpm)	1
Lindeque criteria[c]	Sustained Pao_2 < 8 kPa	—
	Sustained PCo_2 > 7.3 kPa or pH < 7.3	—
	Sustained respiratory rate > 35 bpm	—
	Increased work of breathing (dyspnea, accessory muscles, tachycardia, anxiety)	—

ESR = erythrocyte sedimentation rate, FES = fat embolism syndrome

ESR = erythrocyte sedimentation rate, FES = fat embolism syndrome

Diagnosis of fat embolism syndrome requires at least one major criterion and four minor criteria. A cumulative score of <5 supports the diagnosis. The presence of any single criterion may already suggest FES.

5.2. Disease mechanisms and pathology

5.2.1. Etiopathogenesis of Fat Embolism Syndrome

5.2.1.1. Etiology of FES

FES is primarily associated with trauma-related events, occurring more frequently due to major injuries than non-traumatic causes (12,24). Although FE can develop following severe soft tissue trauma without an associated bone fracture (24), it most frequently occurs after blunt force trauma involving long bone fractures, particularly of the femur (Figure 5) and pelvis (12), making it the primary cause of FES (24).

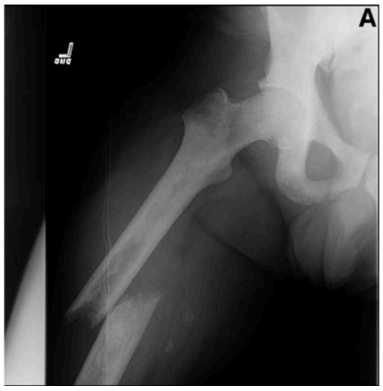

Figure 5. *Initial radiographic evaluation of the left lower limb reveals a closed, oblique fracture of the femur, with displacement of the distal fragment (10).*

Other trauma-related causes include burns (4) or lung transplants (8) as well as surgical interventions, such as orthopedic procedures involving manipulation of intramedullary contents (19). Certain technical factors during the insertion of intramedullary nails may further increase this risk, including high-velocity reaming, excessive force applied during nail insertion, and a widened gap between the nail and the cortical bone (12). FES has also been observed after cardiopulmonary resuscitation (CPR), likely due to marrow fat entering the circulation from rib fractures or sternum injury (13). Also, non-orthopedic-related trauma could be the cause of FES, including Liposuction, cardiopulmonary bypass procedures, burns, or fat translocation during cosmetic augmentation (4,8,24,25).

Besides traumatic causes, several non-traumatic conditions have been associated with FE. Diabetes mellitus, pancreatitis, osteomyelitis, decompression sickness, corticosteroid use, and parenteral lipid infusion have all been identified as potential contributors (24). FES has also been documented in conditions such as sickle cell disease and hemorrhagic pancreatitis. Additionally, cases have been reported following carbon tetrachloride poisoning. In sickle cell disorders, bone marrow necrosis is considered a key factor in the development of FE. Similarly, in pancreatitis, fat necrosis plays a significant role. Furthermore, FE has been associated with massive hepatic necrosis in the presence of fatty liver, while carbon tetrachloride poisoning is also known to contribute to liver fat accumulation (4). Understanding the multifactorial nature of FES is crucial, as it highlights the importance of managing underlying conditions and mitigating risk factors to prevent its occurrence in vulnerable patients.

5.2.1.2. Pathophysiology of Fat Embolism Syndrome

FES is a complex clinical condition that arises when lipid droplets enter the systemic circulation, leading to a cascade of pathophysiological events affecting multiple organ systems. The underlying pathophysiology of FES is still not fully clarified (13,21,24), but two main hypotheses are widely proposed to explain it: the mechanical theory and the biochemical theory, with the coagulation theory increasingly discussed as a complementary component of both (13,24) (Figure 6).

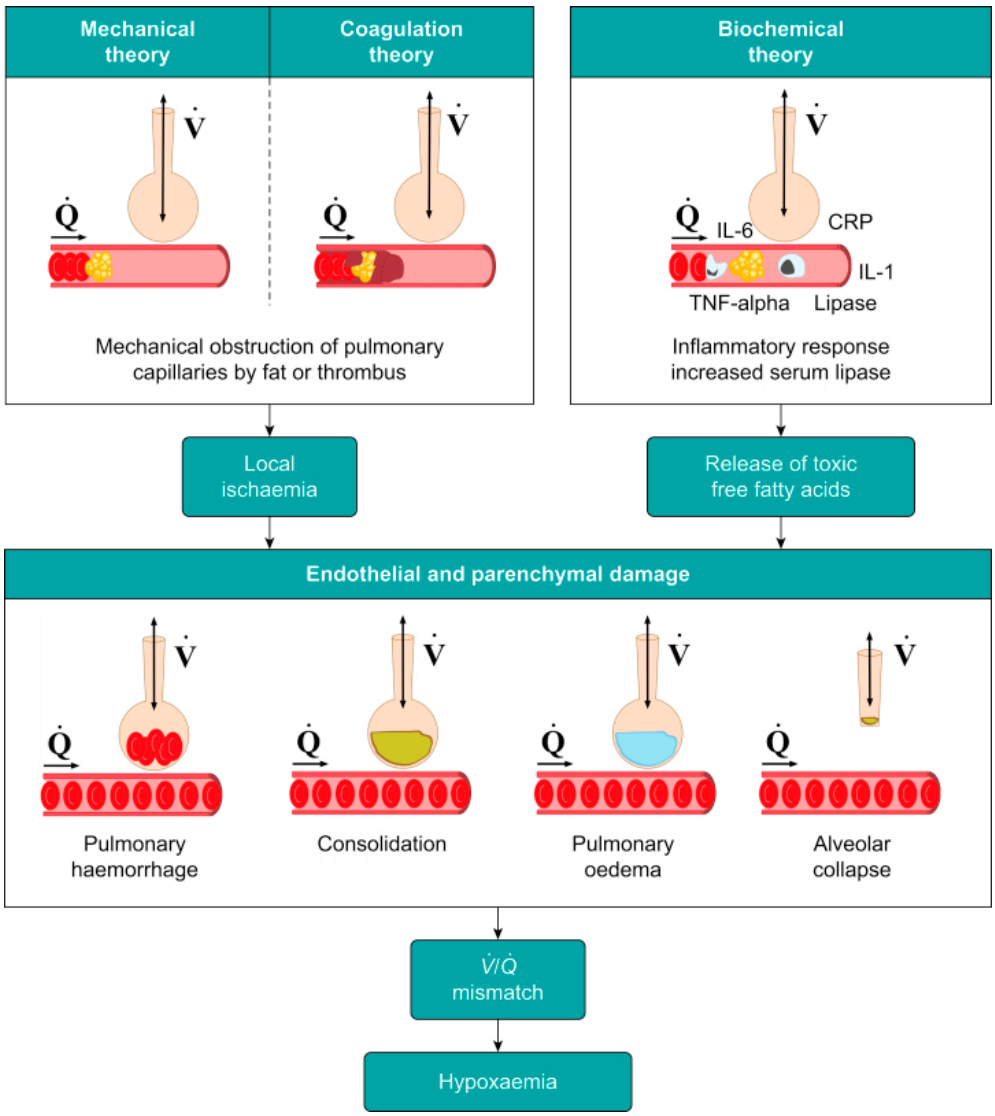

Figure 6. *Three primary models have been suggested to explain the development of fat embolism: mechanical, coagulative, and biochemical pathways (24).*

These theories offer complementary perspectives on how FE develops, with the mechanical theory focusing on the physical entry of fat globules into the bloodstream and the biochemical theory emphasizing systemic inflammatory and molecular responses. In addition, the coagulation theory suggests that this inflammation, in combination with hypovolemia and endothelial injury after trauma, promotes a hypercoagulable state. Activation of the clotting cascade may lead to further enlargement of fat emboli and increased vascular obstruction. This mechanism could explain the thrombocytopenia and DIC seen in some severe cases (24). Both theories, mechanical and biochemical, are backed by clinical and animal studies (21), indicating that they are not mutually exclusive but rather act in parallel or together, with each mechanism participating in the development of FES (Figure 7). This interplay is reflected in the fact that FES affects both the arterial and venous circulation, contributing to its diverse clinical manifestations (10).

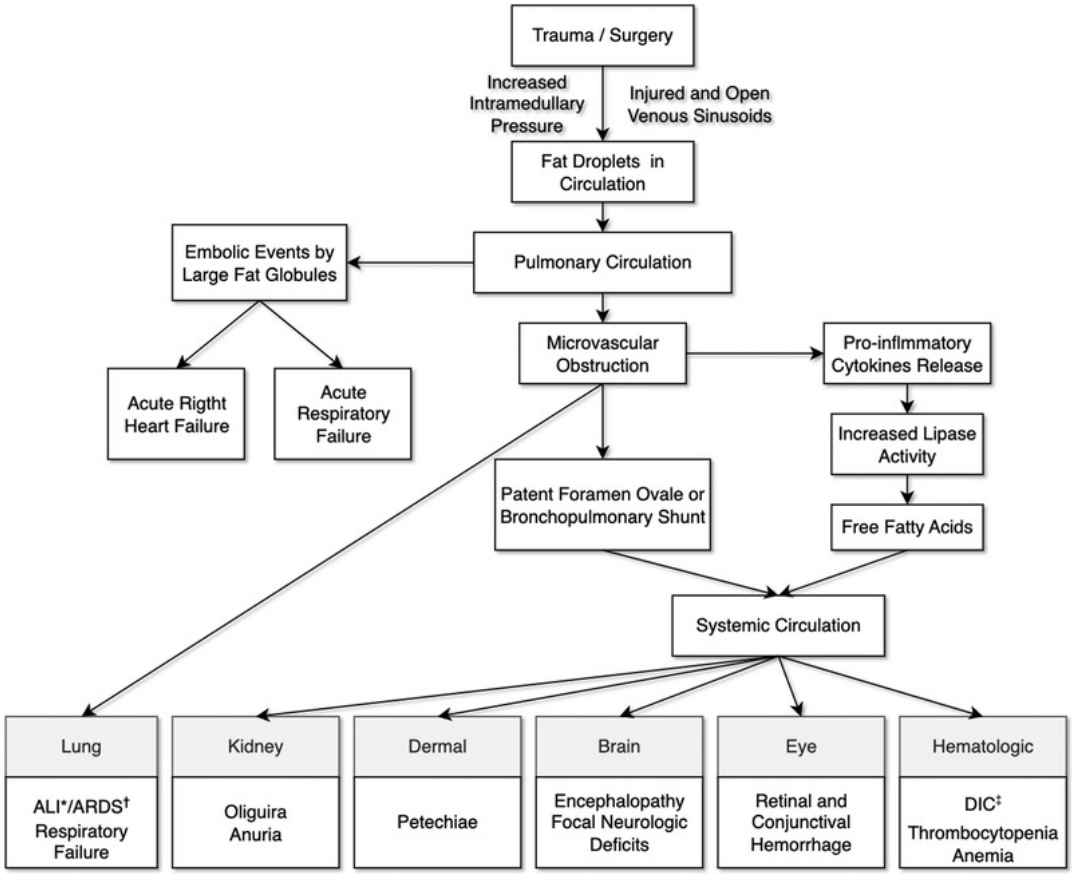

Figure 7. *Schematic representation of fat embolism syndrome pathophysiology. Abbreviations: ALI - acute lung injury; DIC - disseminated intravascular coagulation; ARDS - acute respiratory distress syndrome (21).*

The classical mechanical model first presented by Gauss in 1924 (19) includes trauma, e.g., long bone or pelvic bone fractures, that disrupts the bone marrow and surrounding tissues. The resulting increase in intramedullary pressure forces fat droplets through lower-pressure, open-ended venous channels directly into the bloodstream (19,21,26).

The process can be exacerbated by arthroplasty or intramedullary manipulation, such as reaming during orthopedic surgery, which further increases intramedullary pressure (19). The released fat droplets, varying in size, then travel through the circulation, potentially reaching various organs, including the lungs, brain, and kidneys (4). During this migration of Fat emboli through the venous circulation, small pulmonary arterioles up to 20 μm get occluded, causing ischemic necrosis and localized tissue damage (21). Fat emboli trapped in the pulmonary capillaries trigger a strong proinflammatory response, leading to increased platelet adhesion and fibrin production, contributing to a thrombus formation, which leads to interstitial hemorrhage and alveolar collapse. Additionally, larger fat droplets can block vessels directly, possibly causing right heart failure and shock (21).

The occurrence of FES, although rare, after procedures like liposuction (27,28) further supports the role of mechanical disruption in triggering the syndrome, even in the absence of long bone fractures.

However, the mechanical hypothesis does not adequately clarify how larger fat emboli evade pulmonary filtration and access systemic circulation and distal organs (21)**.** Approaches here were that fat emboli may bypass the pulmonary circulation through a Patent Foramen Ovale (PFO), which is overserved in 20-30% of the population. PFOs can be congenital or reopen due to elevated pulmonary artery pressure, allowing fat to pass from the right to the left atrium (19). However, neurologic symptoms and skin lesions also occur in patients free of PFOs or right-to-left cardiac shunts, as confirmed by transesophageal echocardiography (21), challenging the assumption that a PFO is necessary for systemic fat embolization. Alternative pathways for fat emboli to enter the systemic circulation include pulmonary-bronchial shunts, which could allow them to bypass the lungs, and/or elevated right atrial pressure, which could push fat globules from the pulmonary capillary system into the pulmonary venous circulation (4,19,21).

Although this mechanical theory is supported by clinical and experimental data, it does not explain why the presence of large fat globules detectable via echocardiography does not consistently lead to FES (21), nor why the syndrome typically manifests with a delay of 2–3 days post-injury (29). This suggests additional factors are involved in the pathogenesis of FES, necessitating further theoretical exploration.

Beyond the mechanical aspect, the biochemical theory, first described by Lehman and Moore in 1927 (19), aims to explain cases of atraumatic FES and is also supported by biochemical studies on animal models (13). Once in circulation, fat globules can undergo lipolysis, releasing glycerol and toxic FFAs, such as chylomicrons (4,13,28). Lipase activity has been identified near fat emboli obstructing pulmonary vessels, promoting the hydrolysis of fat into FFAs (21).

These can directly damage and inflame alveolar epithelial cells and pulmonary endothelium (13,30), triggering an inflammatory cytokine response characterized by increased concentrations of tumor necrosis factor α, IL-1, and IL-6 (13,21). These cytokines further increase inflammation and vascular permeability, leading to vasogenic and cytotoxic edema and hemorrhage (10,28). They promote the clustering of blood lipids into macromolecular structures, enhancing the risk of thrombogenesis and exacerbating vascular injury (21).

This cascade contributes to pathophysiological changes similar to ARDS (13), including interstitial edema, increased vascular permeability, surfactant deactivation, and alveolar collapse. These shared features make distinguishing FES-induced ARDS from ARDS caused by other conditions challenging (21). Further studies suggest that FFA toxicity may also play a role in a “second hit” phenomenon: animal models have shown that prior exposure to FES exacerbates lung injury following a secondary insult, leading to more severe pulmonary damage (13). This may suggest that the biochemical effects of FFAs extend beyond the acute phase of FES, leading to persistent changes in endothelial function, capillary permeability, and immune response. These alterations

may sensitize the lung to future insults, amplifying inflammatory damage and aligning with the biochemical theory.

5.2.1.3. Risk factors

Several factors contribute to the development of FES, with trauma and patient-related aspects playing a central role. In the literature, a distinction is made between trauma-related and patient-related risk factors. A wide range of risk factors have been identified, ranging from closed or multiple fractures to metabolic conditions such as diabetes, or even simply gender. The following section outlines the key risk factors identified in the literature.

Among the trauma-related risk factors, closed fractures, where the skin remains intact, have been associated with an increased risk of developing FES (12,31). The absence of an open wound may allow intramedullary fat to enter the bloodstream more readily, leading to embolization and subsequent systemic complications.

Additionally, a sustained hypovolemic state following trauma has been recognized as an independent predictor for FES. Hypovolemia disrupts the microcirculation, initiating a systemic inflammation and stimulating platelet activity, thereby promoting the attachment of fat emboli to the endothelium (21). This mechanism highlights the role of hemodynamic stability in preventing FES-related complications.

The presence of multiple fractures, especially involving long bones, significantly elevates the risk of developing FES. A study conducted data analysis from the Trauma Quality Improvement Program (TQIP) and reported that patients with multiple long bone fractures had an increased incidence of FES (31). This is further supported by a systematic review analyzing data from 15 studies encompassing 3,095 patients, which found that the incidence of FES was higher in cases of bilateral high-energy femur fractures (4.6%) than in unilateral high-energy fractures (2.9%) (3). This indicates that the cumulative effect of multiple fractures contributes to an increased risk of FES, which may be related to a greater volume of fat emboli entering the circulation.

Also crucial in minimizing the risk of FES is the early operative fixation of fractures, ideally within $\leq$ 48 h (32). Delaying operative intervention has been associated with an increased incidence of FES. Therefore, timely fracture stabilization is advised to lower the risk of this complication. This contrasts with earlier perspectives from the 1950s and 1960s, when prompt fracture stabilization was thought to be a contributing factor to the syndrome (3).

However, surgical technique also influences the risk of FES. Intramedullary reaming during the fixation of long bone fractures has been identified as a significant risk factor, as it increases intramedullary pressure and facilitates the release of fat emboli into the circulation. In contrast,

unreamed nailing has been suggested as a possibly safer alternative, as demonstrated in experimental studies (21).

Beyond trauma-related factors, patient characteristics also play a significant role in the development and outcome of FES. This condition tends to occur more frequently in younger individuals, especially those in their twenties, who have sustained multiple fractures of the lower extremities (26). This increased incidence in younger populations is likely related to the higher prevalence of high-energy trauma, such as motor vehicle accidents, in this demographic. However, while FES is more frequently diagnosed in younger individuals, the associated mortality rate rises significantly with age. A study analyzing patient outcomes found that individuals aged 65 and older diagnosed with FES had an in-hospital mortality rate of 17.6%, compared to only 8.3% in patients younger than 40 years. Further statistical modeling identified age over 65 as an independent factor associated with increased mortality (33).

Gender differences have also been reported in FES incidence, with males being more frequently affected than females (31). Similar to the increased incidence of FES in individuals under 30 years of age, this disparity may be explained by the increased exposure of males to high-energy trauma, including motor vehicle collisions and motorcycle collisions, which often results in long bone fractures, one of the most significant risk factors for FES.

Additionally, metabolic conditions, including obesity and diabetes mellitus, have been recognized as independent contributors to the development of the syndrome. A study focusing on patients with isolated lower extremity long bone fractures found an association between obesity, diabetes mellitus, and an increased risk of developing the condition, suggesting a potential pathophysiological link between metabolic dysfunction and fat embolization (32). These findings underscore the importance of considering both trauma-related and patient-related factors when assessing the risk of FES in clinical settings.

5.3. Treatment/management methods

The clinical management of FES involves a broad spectrum of interventions targeting respiratory, hemodynamic, and neurological complications. An overview of these management strategies is illustrated in Figure 8.

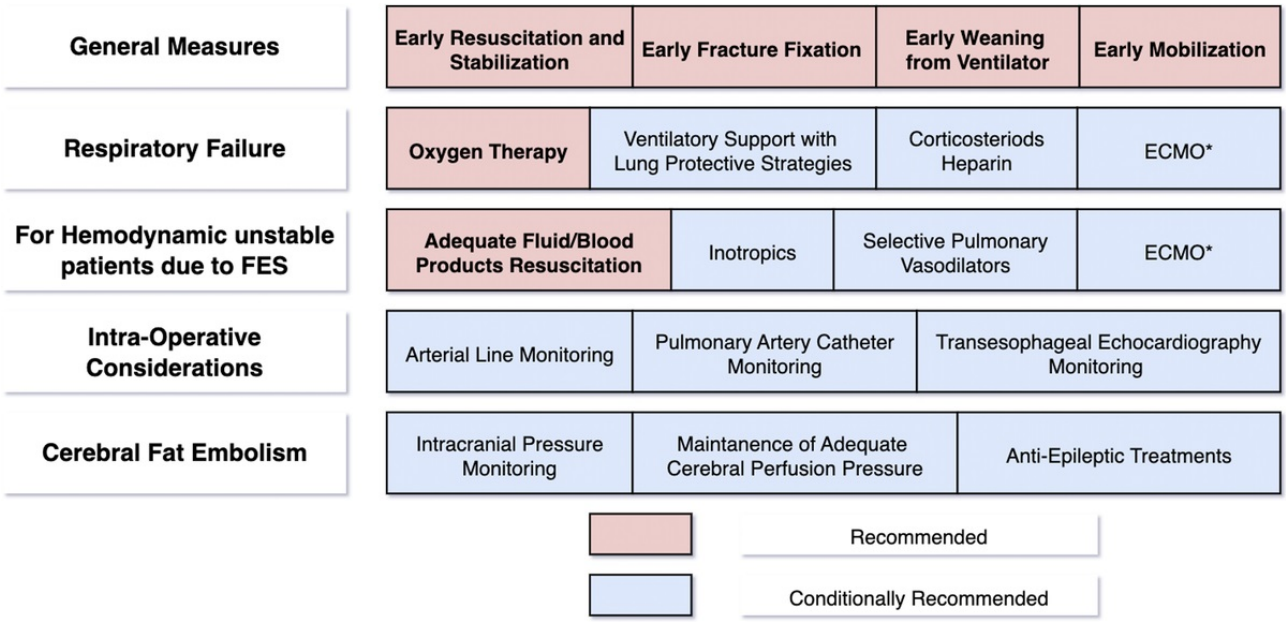

Figure 8. *Approaches to managing patients vulnerable to developing fat embolism syndrome, including extracorporeal membrane oxygenation (21).*

If FES is suspected, the patient requires admission to the intensive care unit (ICU). Particular attention should be paid to signs of right heart failure or pulmonary hypertension. To guide therapy, central venous pressure (CVP) should be monitored (34). The management of FES is primarily supportive and focuses on ensuring adequate oxygenation and maintaining sufficient intravascular volume through appropriate fluid resuscitation, as hypotension and shock can worsen pulmonary injury (5). To restore circulating volume, albumin is often preferred due to its volume-expanding properties and additional lipophilic effects. Hypovolemia should be corrected using isotonic crystalloids such as normal saline or Ringer's lactate, and colloids like dextran may also be considered. In the presence of circulatory shock, plasma expanders are indicated. For hemodynamic support, dobutamine is favored over norepinephrine due to its stronger inotropic effects (5,34). Nevertheless, various therapeutic approaches have been investigated to improve clinical outcomes. These include the administration of corticosteroids, the use of blood purification techniques, and the application of advanced supportive measures such as extracorporeal membrane oxygenation (ECMO). Heparin was trialed as a therapeutic option in the mid-20th century but failed to demonstrate a clear benefit in reducing morbidity or mortality. Its routine use is discouraged, particularly in polytrauma patients, due to the elevated risk of bleeding, although it may be cautiously considered for thromboembolic prophylaxis in selected cases (13,34). High-dose corticosteroids like methylprednisolone have been reported to improve hemodynamic stability in patients with FES. For instance, a 74-year-old woman demonstrated significant clinical improvement following a single 250 mg dose of methylprednisolone, suggesting potential efficacy

in symptom control (35). In terms of blood purification, red cell exchange (RCE) and therapeutic plasma exchange (TPE) have shown promise, particularly in patients with sickle cell disease. RCE can be lifesaving by reducing sickled hemoglobin levels and clearing fat emboli from circulation. The combination of RCE and TPE appears even more effective, as it targets the inflammatory milieu of FES and has been associated with reduced mortality and improved neurological outcomes compared to RCE alone (36). In fulminant cases, veno-arterial ECMO has been used successfully to provide temporary cardiopulmonary support, as documented in a case where the patient was stabilized and later weaned off ECMO (20,37). When initiated early, noninvasive ventilation (NIV) may reduce the risk of requiring invasive mechanical ventilation and, together with supportive therapies such as corticosteroids, albumin, diuretics, and anticoagulants, has been used in FES cases following cosmetic procedures like liposuction (38). Occasionally, surgical interventions are also necessary, particularly in cases with cerebral involvement. Decompressive hemicraniectomy (DHC) has been used to manage elevated intracranial pressure, with some reports indicating favorable neurological recovery (39). In pediatric patients, emergent external fixation (Figure 9) after orthopedic trauma has facilitated rapid recovery by stabilizing fractures and reducing the risk of ongoing fat embolization (40).

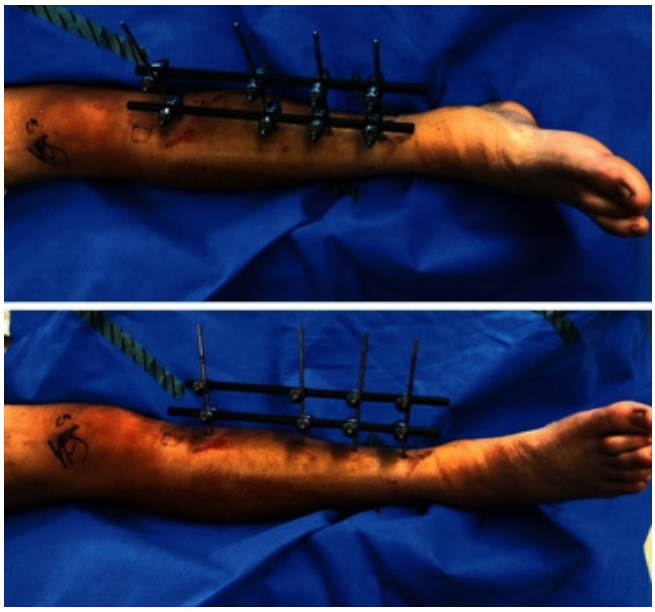

Figure 9. *Clinical images of the patient's external fixator setup captured on the fourth postoperative day during definitive fixation (40).*

Despite these promising interventions, the treatment of FES remains largely supportive. Patient stabilization and targeted management of complications are central, and the diversity of therapeutic approaches underscores the need for individualized treatment strategies. Further research is essential to establish standardized treatment protocols and improve outcomes in this complex and potentially life-threatening syndrome.

5.3.1. Evidence-based Prevention and Management Strategies

5.3.1.1. Surgical Prevention Strategies in Trauma Patients

The prevention of FES consists mainly of the identification of at-risk patients, a treatment strategy adapted to the patient's physiological condition and the nature of the injury, as well as consistent monitoring and supportive care (41).

Among the various components of prevention, the timing of surgical intervention in long bone fractures, particularly in polytrauma patients, has been identified as a significant factor in managing the risk of FES. The degree of fracture displacement and the techniques used for reduction may have a greater influence on the development of the condition than previously recognized (42). The management of fractures in polytraumatized patients has evolved significantly over the years, with two primary strategies emerging: ETC and DCO.

The rationale for distinguishing between those two is based on the 'first hit-second hit' theory. According to this concept, the initial trauma (first hit) triggers a systemic inflammatory response, which then may be exacerbated by early definitive surgical intervention (second hit), particularly in physiologically unstable patients. This mechanism is considered a potential contributor to the development or aggravation of FES (41).

While ETC is associated with decreased mortality, lower infection rates, and a reduced risk of venous thromboembolism (43), it may also exacerbate systemic inflammation in polytraumatized patients, leading to Systemic Inflammatory Response Syndrome (SIRS), which can progress to ARDS or Multiple Organ Failure (MOF) (44). In hemodynamically stable patients who had isolated fractures of the femoral shaft, early internal fixation within 10 hours of injury was shown to reduce the risk of FES occurrence in a population of young adults. The rate of FES was 10.1% when fixation was performed after 10 hours, compared to 0% in those operated on earlier. Also, delayed fixation (>48 h) was associated with a 27% complication rate in the form of respiratory complications, compared to only 2% with early fixation (9).

In contrast, DCO follows a staged approach with initial external fixation (Figure 9), aiming to prevent intensified surgical load in the acute phase, before proceeding with definitive surgical intervention. This strategy has been particularly beneficial for hemodynamically unstable patients (45). The rationale behind this approach is to avoid intramedullary pressurization with the intention of minimizing fat embolus showering and therefore the risk of FES and other complications (40,43). By avoiding prolonged surgery and minimizing blood loss, DCO helps prevent the lethal triad of hypothermia, acidosis, and coagulopathy (46). However, delayed definitive fixation is associated

with prolonged immobilization, increased risk of malunion and nonunion, and a higher burden on healthcare resources (47).

In recent years, the concept of Safe Definitive Surgery (SDS) (Figure 10) has emerged as a middle ground between ETC and DCO. This approach tailors the timing of definitive fixation based on the patient's physiological status rather than sticking to a fixed protocol (44). The goal of SDS is to avoid premature fixation in unstable patients while preventing unnecessary delays in fracture healing (48). It provides a structured but flexible framework for decision-making in severely injured trauma patients, ensuring that surgical interventions are performed at the most appropriate time. The process begins with a primary assessment in the emergency room (ER), where patients are categorized according to their physiological stability as borderline, unstable, or in extremis. While borderline patients may be candidates for early definitive fixation, unstable or in-extremis patients require immediate resuscitation using multiple endpoints or the Early Appropriate Care (EAC) protocol. This includes aggressive fluid resuscitation, vasopressor support, and, if necessary, surgical hemorrhage control. Patients in extremis undergo urgent damage control interventions, such as traction or temporary stabilization, to address life-threatening injuries. Following resuscitation, a secondary assessment is conducted to determine the patient's suitability for definitive surgery. At this stage, stable patients can proceed directly to SDS, while borderline patients are typically managed with DCO to allow for further stabilization. Unstable patients remain in the damage control phase, with only temporary fixation techniques employed to maintain alignment and reduce complications.

On Day 1 post-trauma, a tertiary assessment is performed to reassess the patient's coagulation status, fluid balance, vasopressor requirements, and lung function. Depending on their condition, patients are reclassified as stable, borderline, or unstable, leading to the next step in their surgical management. SDS emphasizes continuous reassessment because physiological stability is a dynamic process that can change permanently. Stable patients proceed directly to definitive surgery, whereas borderline patients undergo repeated reevaluations to determine the optimal timing for definitive fixation. Unstable patients remain in a damage control state until they reach an adequate level of physiological stability. Studies indicate that SDS can reduce morbidity and mortality by balancing the benefits of both strategies (44). By adapting surgical timing to the patient's physiological state, SDS prevents the complications associated with both ETC (excessive early surgical stress) and DCO (prolonged immobilization and delayed recovery). The approach ensures that definitive fixation occurs at the optimal physiological window, reducing both systemic inflammatory complications and musculoskeletal morbidity.

In clinical practice, the decision between ETC, DCO, and SDS should be chosen according to the patient's physiological stability and individual risk factors, which could also include genetic predispositions to excessive inflammatory or procoagulant responses (41).

While early fixation can reduce complications such as FES and infection, it may also exacerbate systemic inflammation in unstable patients. SDS offers a balanced approach, integrating the benefits of both strategies while minimizing risks.

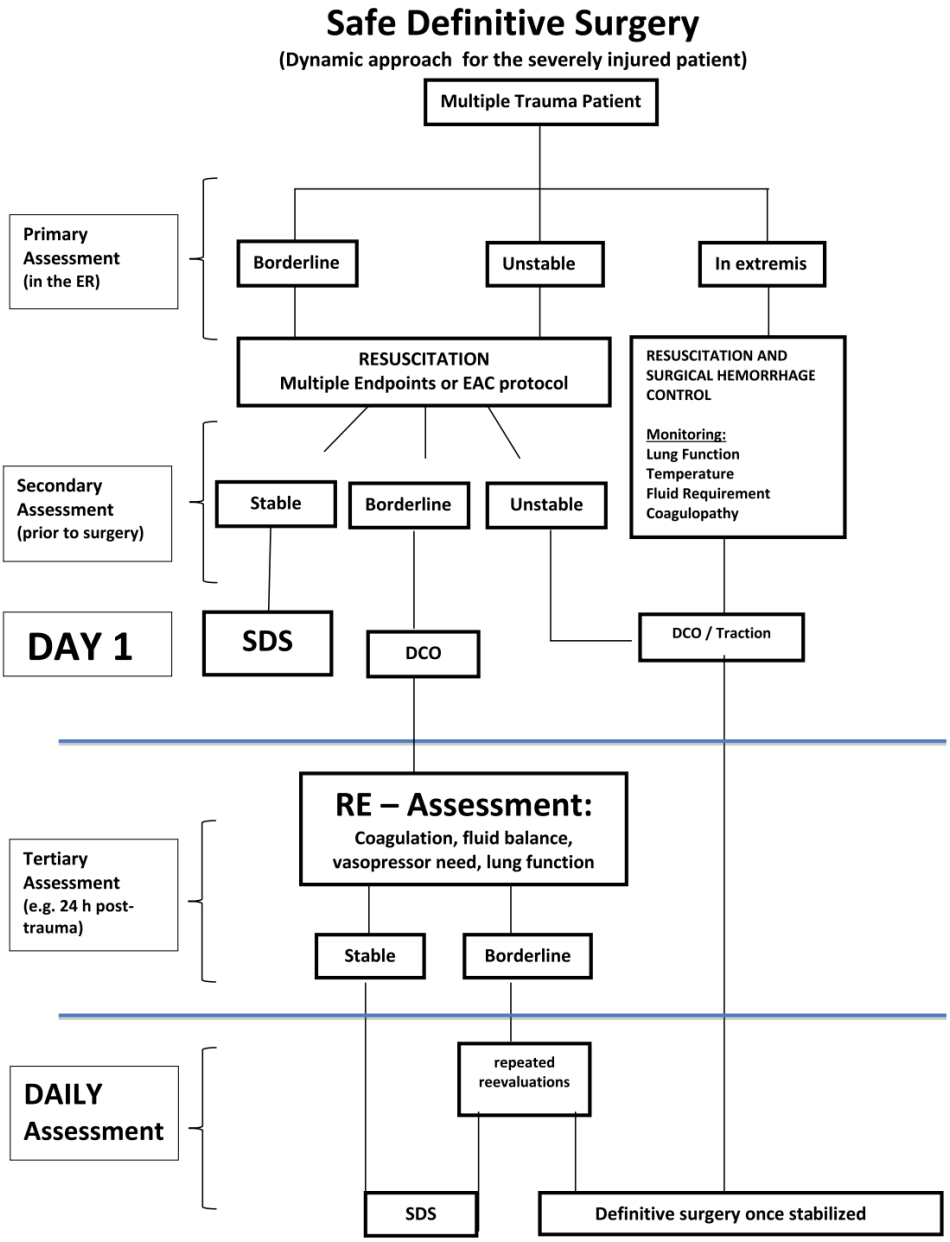

Figure 10. *Four steps to fulfill the Safe definitive surgery concept (48).*

Not only does the timing of surgical fixation play an important role in preventing FES, but also the technique used during the procedure significantly impacts patient outcomes. Intramedullary nailing (IMN) is widely regarded as the preferred method for managing long bone fractures due to its minimally invasive nature and biomechanical advantages. Compared to plating techniques, IMN offers several clinical benefits, including limited surgical exposure at the fracture site, early mobilization, and the potential for early weight-bearing (49). However, despite its widespread use, the choice of surgical technique, especially between reamed (RIN) and unreamed intramedullary nailing (URIN), remains a subject of ongoing debate, as both approaches carry risks and advantages that can significantly influence the outcome for the patient.

The choice between RIN and URIN must therefore be carefully considered based on the patient's condition and fracture characteristics. There are two surgical approaches used to stabilize long bone fractures (50). Both methods involve inserting a metal rod, using controlled mechanical force with a sliding hammer device, into the medullary cavity, which provides structural support and facilitates bone healing. The procedure is typically performed under X-ray guidance to ensure correct alignment, implant positioning, and to monitor for possible complications. The primary difference between these techniques lies in how the medullary canal is prepared before nail insertion (51). In RIN, a reamer is used to enlarge the canal, allowing for the placement of a larger diameter nail. This permits the use of thicker locking screws, which increases the overall stability and durability of the fixation. Reamed nailing became the standard approach after studies demonstrated improved union rates compared to unreamed techniques, particularly in long bone fractures (49). To facilitate nail insertion, the canal is typically reamed approximately 1.5 mm wider than the intended nail diameter. However, this process can temporarily disrupt the intramedullary blood supply and cause localized necrosis of the diaphyseal bone (Figure 11). Reaming has also been shown to generate temperatures exceeding 50 °C, which may result in osteocyte damage and thermal necrosis. The extent of thermal injury is determined by reamer size, design, rotational speed, viscosity, and other physical properties of the reamed canal contents (49). Over time, several reamer designs have been developed to reduce these effects. These include various design modifications such as reamers with a small core that allow proximal channeling of medullary contents, reducing intramedullary pressure compared to cylindrical geometries. Additionally, reamers with deep flutes, which are the spiral-shaped longitudinal grooves along the cutting surface, as well as smaller or hollow shafts and reduced drive diameters, have been shown to lower pressure peaks and decrease the incidence of FE (49).

In contrast, URIN maintains the natural diameter of the medullary canal, thereby preserving the bone's internal vascular network. This technique is often preferred in cases where maintaining bone

perfusion is a priority, such as in open fractures (51). Both methods have distinct advantages and drawbacks, and the choice of technique depends on various clinical factors, including the patient's individual anatomy and the expected mechanical stress on the implant.

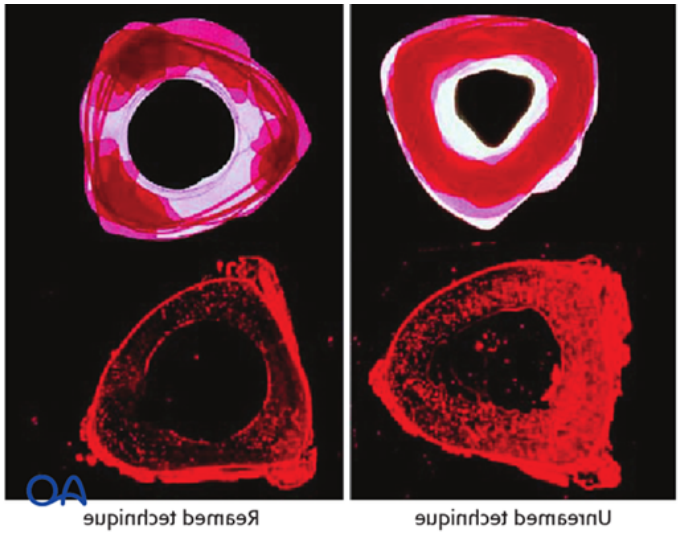

Figure 11. *Cross-sections of the tibia after unreamed (left) and reamed (right) intramedullary nailing, likely using histological or fluorescence microscopy imaging (51).*

Although acute fat embolization during reaming has been observed in 88% of patients using intraoperative transesophageal echocardiography (3), clinical studies suggest that the overall incidence of FES remains low. Akoh et al. (2014) reported a low incidence of FES of only 0.5% in patients undergoing reamed intramedullary nailing, indicating that while intraoperative embolization occurs frequently, it does not necessarily lead to clinically significant FES (52). Nevertheless, the intramedullary pressure generated during reaming, which often reaches values of over 1,000 mmHg, can lead to the release of fat and bone marrow particles, which can cause pulmonary complications in susceptible patients (49).
However, RIN has not been associated with increased intraoperative blood loss, higher incidence of ARDS, implant failure, or mortality when compared to unreamed techniques (50).
Some animal studies even showed that URIN was associated with an increase in intramedullary pressure and greater embolism formation due to larger fat droplets, which calls into question the assumption that unreamed techniques are fundamentally safer (49).

Even though the possibility of an increased risk of FES exists, it remains uncertain. RIN is often favored due to its biomechanical advantages, including faster fracture healing and lower rates of nonunion or delayed union and subsequent reoperation (50). This is further supported by a meta-analysis of 1,229 tibial fractures, which demonstrated that RIN significantly reduces the risk of nonunion and implant failure, without increasing complications such as infection or compartment

syndrome (53). Also, the reaming process allows for the insertion of larger nails, which can provide an appropriate intramedullary fit and better stability for the fracture (54). While reaming may release fat during the procedure, the overall benefits often outweigh the risks. This is particularly relevant when considering economic factors, as secondary procedures are highly expensive and associated with increased complications and mortality rates. Given that the likelihood of requiring reoperation is higher in the URIN group, reamed intramedullary nailing is recommended (50). Although design improvements in reaming instruments, such as fluted reamers, thinner shafts, and intramedullary lavage tubing, have been introduced, none have significantly reduced the risk of developing FES (54). Reamed nailing has still been associated with clinically relevant FES in rare cases, such as a reported bilateral femur fracture treated with reamed nailing that resulted in FE (52).

Therefore, it is crucial to implement techniques that actively reduce the embolic load associated with reaming. In contrast to the previously mentioned design improvements, the combined suction-reamer systems, such as the rinsing-suction reamer (RSR) and the RIA system, have been suggested as an effective method to minimize this risk. Studies demonstrated that RSR, which integrates intramedullary lavage and aspiration into reaming, significantly decreases pressure and FE formation compared to conventional reamers, while preserving thermal parameters (49). In comparison, Husebye et al. found that both RSR and RIA systems achieve similar reductions in intramedullary pressure. However, the RIA system may offer additional clinical advantages, as it requires fewer reaming steps and is associated with lower osteonecrosis in the reamed region (49).

Furthermore, RIA significantly reduces the volume of embolic load and is associated with fewer large-sized (>200 μm) emboli compared to the unreamed and sequentially reamed groups. Additionally, irrigating the canal during reaming helps lower overall temperature and decreases the viscosity of its contents, while aspiration facilitates the removal of reamed debris (54). Given the potential risk of FES during reaming, these advantages make the RIA system a valuable advancement in fracture fixation. Furthermore, studies have shown that extensive saline lavage of the intramedullary canal before cemented hip arthroplasty can reduce the number and size of emboli. Patients who received thorough lavage also exhibited more stable oxygen saturation and carbon dioxide levels, indicating better overall pulmonary function (9). Another intraoperative strategy, especially during total hip arthroplasty, involves suction along the linea aspera. This method creates a vacuum effect in the proximal femoral canal, preventing sudden pressure increases when inserting a cemented stem. Compared to standard techniques, patients treated with this approach showed fewer signs of cardiopulmonary impairment, such as hypotension and

desaturation. Additionally, the method was associated with a reduced risk of postoperative deep vein thrombosis, suggesting potential benefits beyond FE prevention (9).

Apart from the RIA system or suction techniques, additional experimental approaches have been explored. These include the use of cell-saver systems to process autologous blood before retransfusion and mechanical venous filters, which have shown efficacy in reducing FE in animal models (41). However, the clinical applicability of those filters remains uncertain (41).

Ultimately, optimizing the timing and method of surgical intervention plays a crucial role in minimizing the risk of FES. While strategies such as DCO and SDS help guide fracture management to the patient's physiological status, intraoperative modifications, including intramedullary lavage, suction techniques, and pressure-limiting methods, further reduce embolic burden. The continuous refinement of orthopedic techniques, combined with an individualized patient-centered treatment strategy, remains essential in mitigating complications associated with long bone fractures and major orthopedic procedures.

5.3.1.2. Lung-Protective Ventilation and Advanced Mechanical Ventilation Techniques in Preventing ARDS

Given the pathophysiological complexity of FES and its potential progression to ARDS, the implementation of evidence-based preventive strategies is crucial. While surgical considerations, such as the choice of intramedullary nailing technique and the timing of surgery, play a significant role in reducing the risk of FES, respiratory management may also contribute to improved outcomes, particularly in patients at risk of pulmonary complications.

Lung-protective ventilation (LPV) and advanced mechanical ventilation techniques, such as permissive hypoxemia, have emerged as critical strategies in preventing ARDS in patients at risk of FES. These approaches aim to minimize ventilator-induced lung injury (VILI) while maintaining adequate gas exchange. The integration of reduced tidal volumes and optimized positive end-expiratory pressure (PEEP) settings, and adjunctive therapies has been extensively studied in the context of ARDS prevention and management. These strategies aim to minimize VILI while preserving effective pulmonary gas transfer (55–57).

This section synthesizes evidence from recent studies to explore how these strategies contribute to ARDS prevention in patients at risk of FES.

Low tidal volume ventilation forms the basis of LPV (4–8 mL/kg of predicted body weight) and lower positive inspiratory pressure (plateau pressure < 30 cm H2O), as recommended by clinical guidelines (55,58). These parameters are designed to avoid overdistension of alveoli and reduce the

risk of barotrauma. In patients with FES, who are prone to pulmonary complications, such as FE obstructing microvasculature, these settings are particularly beneficial.

The application of PEEP is critical to prevent alveolar collapse and improve oxygenation, with individualized PEEP settings recommended to optimize lung recruitment and minimize lung stress (57,59). Based on the extent of hypoxemia, the Berlin definition proposed 3 categories of ARDS (Table 2). For all of them, literature proposes a PEEP ≥ 5 cm H2O (58).

Table 2. *A comparative analysis of the American-European Consensus Conference and Berlin criteria for defining acute respiratory distress syndrome (58).*

	AECC		Current Berlin Definition[10]	
	Definition[8]	Limitations	How AECC Limitations Were Addressed	Definition
Timing	Acute onset	No definition of acute	Acute time frame specified	Within 1 week of a known clinical insult or new or worsening respiratory symptoms
ALI category	All patients with Pao_2/Fio_2 ≤300 mm Hg	ALI often misinterpreted as only referring to patients with Pao_2/Fio_2 = 201-300 mm Hg, leading to confusing "ALI/ARDS" term	3 mutually exclusive subgroups of ARDS by severity; ALI term removed	Mild: 200 mm Hg < Pao_2/Fio_2 ≤ 300 mm Hg with PEEP or CPAP ≥5 cm H_2O; moderate: 100 mm Hg < Pao_2/Fio_2 ≤ 200 mm Hg; severe: Pao_2/Fio_2 ≤ 100 mm Hg
Oxygenation	Pao_2/Fio_2 ≤300 mm Hg (regardless of PEEP)	Inconsistency of Pao_2/Fio_2 ratio due to the effect of PEEP and Fio_2	Minimal PEEP level added across subgroups; Fio_2 effect less relevant in severe ARDS subgroup	Mild: PEEP or CPAP ≥5 cm H_2O; moderate or severe: PEEP ≥5 cm H_2O
Chest radiograph	Bilateral infiltrates observed on frontal chest radiograph	Poor inter-observer reliability of chest radiograph interpretation	Chest radiograph criteria clarified; example radiographs created[8]	Bilateral opacities—not fully explained by effusions, lobar or lung collapse, or nodules
PAWP	PAWP ≤18 mm Hg when measured or no clinical evidence of left atrial hypertension	High PAWP and ARDS may coexist; poor interobserver reliability of PAWP and clinical assessments of left atrial hypertension	PAWP requirement removed; hydrostatic edema not the primary cause of respiratory failure; clinical vignettes created to help exclude hydrostatic edema[8]	Respiratory failure not fully explained by cardiac failure or fluid overload
Risk factor	None	Not formally included in definition	Included (eg, pneumonia, trauma, sepsis, pancreatitis); when none identified, need to objectively rule out hydrostatic edema	Need objective assessment (eg, echocardiography) to exclude hydrostatic edema if no risk factor present

Abbreviations: AECC, American-European Consensus Conference; ALI, acute lung injury; ARDS, acute respiratory distress syndrome; CPAP, continuous positive airway pressure; FiO_2, fraction of inspired oxygen; Pao_2, partial pressure of arterial oxygen; PAWP, pulmonary artery wedge pressure; PEEP, positive end-expiratory pressure.

Permissive hypoxemia, allowing arterial oxygen levels to remain lower than normal (e.g., SpO2 88–92%), is also a key component of LPV, as it avoids excessive oxygen toxicity and reduces the risk of hyperoxic lung injury (60).

Advanced mechanical ventilation techniques, such as prone positioning and ECMO, have shown promise in severe ARDS cases. Prone positioning redistributes lung stress and strain, improving gas exchange and reducing pulmonary vascular resistance, particularly in patients with severe hypoxemia (61). ECMO, when combined with ultra-lung-protective ventilation strategies, may further reduce lung injury by allowing gas exchange to be partially offloaded from the injured lungs, thereby reducing the need for high tidal volumes and inspiratory pressures (62,63).

Since oxygen saturation is mostly routinely monitored in trauma patients at risk of FES, continuous pulse oximetry may further aid in the early detection of desaturation, enabling prompt initiation of oxygen and adjunctive therapies to prevent systemic complications (41).

Despite the growing evidence supporting LPV, the application of these strategies in patients at risk of FES requires careful consideration of individual patient factors, such as pre-existing lung disease, obesity, and hemodynamic instability. Obesity, for instance, poses unique challenges due to restricted lung mechanics and increased risk of atelectasis, necessitating higher PEEP levels and recruitment maneuvers to maintain adequate lung recruitment (64).
In conclusion, the prevention of ARDS in patients at risk of FES requires a multifaceted approach that incorporates LPV, permissive hypoxemia, and advanced mechanical ventilation techniques. While significant progress has been made in understanding the pathophysiology of ARDS and the role of mechanical ventilation in its prevention, further research is needed to tailor these strategies specifically to patients at risk of FES and to address the unique challenges posed by this patient population.

5.3.1.3. Pharmacological Prevention

Over the past 50 years, various pharmacological approaches have been explored for the prevention and treatment of FES, among them heparin, steroidal anti-inflammatories, hypertonic glucose, aspirin, N-acetylcysteine, and aliskiren (24,65). So far, pharmacologic prevention strategies have struggled to match the clinical impact achieved by surgical techniques in preventing FES.

Glucocorticoids represent the best-investigated pharmacological approach for preventing FES. A meta-analysis of seven randomized controlled trials (RCTs) revealed a mitigation of the relative risk of approximately 77–78% for FES in patients with long bone fractures, indicating a protective effect (12,24). Another meta-analysis of six trials involving 389 patients by Bederman et al. revealed a 43–92% decrease in FES risk through the use of prophylactic corticosteroids. Another review by Sen et al. showed the same tendency: FES developed in just 4% of corticosteroid-treated patients versus 23% of the untreated patients (9). Despite these promising results, the use of corticosteroids remains controversial, as they do not reduce mortality and show no significant differences in infection rates or the risk of avascular necrosis between treatment and control groups (12,13). Furthermore, methodological heterogeneity, non-standardized outcome definitions, and the overall low incidence of FES make it challenging to establish strong evidence-based recommendations (24). Concerns regarding delayed wound healing, increased infection risk, and potential long-term complications, such as osteonecrosis, are major arguments against the routine use of corticosteroids in FES prophylaxis (12,24). Although inhaled steroids have been explored to reduce systemic adverse effects, ciclesonide, unlike most other inhaled corticosteroids, effectively reaches the lung parenchyma and has minimal systemic absorption, lowering the risk of cortisol

suppression and other systemic side effects (9). However, a study evaluating its use found no significant benefit in preventing FES (24).

While corticosteroids have demonstrated positive effects on cardiopulmonary recovery in critical pulmonary conditions such as ARDS and COVID-19 pneumonitis, there is no clear evidence of their efficacy in established FES treatment (24). Additionally, the evolving surgical strategies for long bone fracture management, including the shift toward EAC, may limit the applicability of previous randomized controlled trial (RCT) findings to modern trauma populations (13). Given these limitations, a large-scale, well-designed RCT will be necessary to determine the role of corticosteroids in evidence-based FES prophylaxis and treatment (13).

Heparin was initially proposed as a potential therapy for FES over 60 years ago due to its ability to enhance lipase activity, thereby clearing lipemic plasma. However, this mechanism also results in increased concentrations of FFA, which may contribute to local tissue damage (24). Although animal models suggested some benefits, no clear clinical advantage has been demonstrated, and its use has largely been abandoned due to the significant risk of bleeding (12). The lack of mortality benefit observed in experimental studies, coupled with concerns regarding anticoagulation in trauma patients who are already at risk for systemic hemorrhage, has led to the general avoidance of therapeutic-dose heparin in FES management (24).

Similarly, aspirin has been considered for FES treatment due to its antiplatelet properties, which might reduce embolic events. While small-scale clinical trials have suggested some benefits, aspirin is not routinely recommended for FES due to insufficient evidence and the associated bleeding risks (24). In trauma patients, the decision to use aspirin must also account for its potential to exacerbate intraoperative bleeding or hematoma formation, particularly when early fracture fixation is required. Given the lack of clear efficacy in FES, exposing patients to aspirin's risks, such as increased bleeding and gastrointestinal ulceration, is generally not justified.

In addition to these clinically tested agents, others have been investigated in preclinical models, including sildenafil and N-acetylcysteine, which showed beneficial effects on pulmonary hemodynamics and inflammatory lung injury. However, their applicability to clinical FES prevention remains unproven (41).

In addition to these agents targeting pulmonary hemodynamics and oxidative stress, another experimental line of investigation has focused on modulating systemic inflammatory pathways, particularly the renin-angiotensin system. Angiotensin II not only has vasoconstrictive effects but also proinflammatory and profibrotic effects (66), potentially exacerbating pulmonary damage

following fat embolization. In a preclinical rat model, fat uptake by alveolar macrophages was shown to induce local renin release, which subsequently elevated angiotensin I and II levels within the pulmonary circulation. To interrupt this cascade, Aliskiren, a direct renin inhibitor, was administered one hour after triolein-induced FE. Treated animals demonstrated larger vessel diameters, reduced perivascular fibrosis, and lower fat content in pulmonary vessels in comparison to untreated controls, suggesting a potential vascular-protective and anti-inflammatory effect (13,65).

Although these results are limited to animal studies, they highlight a possible molecular pathway contributing to FES and could complement surgical prevention strategies by addressing systemic inflammatory mechanisms at the molecular level.

5.4. Prognosis

The clinical course of FES varies depending on the severity of the condition, the promptness of diagnosis, and the effectiveness of treatment (13). The patient's overall health status also represents a critical factor that may adversely influence the prognosis (5). While early diagnosis and open reduction and internal fixation (ORIF) of fractures are considered essential, improvements in patient outcomes have also been attributed, at least in part, to advances in supportive intensive care (10,12,13,34). Although the estimated mortality rate of FES in the general population ranges between 7% and 10%, the lack of long-term follow-up studies limits the ability to assess long-term functional outcomes (12,21). Up to 44% of patients may require mechanical ventilatory support, and some develop focal neurological deficits or seizures, however, current data suggest that these complications are largely reversible. Respiratory function typically recovers within one week, and 90.5% of patients experiencing neurological symptoms eventually achieve favorable outcomes (21). Nevertheless, respiratory failure remains the most common cause of death in FES. Moreover, although neurological symptoms, e.g., Cerebral edema, are typically reversible, their presence is associated with a worse overall prognosis (12,67).

6. SUMMARY OF RESULTS AND FUTURE RESEARCH

Fat Embolism Syndrome remains a clinically significant complication, particularly in the context of long bone fractures and orthopedic trauma surgery. Although its incidence has declined in recent decades, it continues to pose diagnostic and therapeutic challenges due to its variable presentation and lack of specific biomarkers.

The pathogenesis is multifactorial, involving mechanical, biochemical, and coagulation mechanisms. These theories likely act in parallel and may reinforce one another, contributing to both pulmonary and systemic manifestations. Clinical symptoms most commonly include respiratory distress, neurological deficits, and petechial rash, though not all features occur simultaneously.

Prevention of Fat Embolism Syndrome has shifted toward individualized surgical strategies that balance early intervention with physiological tolerance. Stabilization of fractures, preferably within 48 hours, and the use of surgical approaches, such as Damage Control Orthopedics and Safe Definitive Surgery, play a central role in reducing the incidence. Although intramedullary reaming is associated with intraoperative embolic events, it remains the biomechanically superior technique for long bone fixation. Recent advances, particularly the use of the Reamer-Irrigator-Aspirator system, have significantly reduced embolic risk, thereby re-establishing reamed nailing as a safe and effective option in many cases. Adjunctive techniques such as intramedullary lavage and suction along the linea aspera further support intraoperative prevention.

Lung-protective ventilation strategies are essential in reducing pulmonary complications and improving oxygenation in affected patients. Pharmacologic interventions, particularly corticosteroids, show promise in prophylaxis but remain controversial and are not used in clinical routine, due to limited evidence on long-term efficacy and safety.

Despite these advances, several gaps in knowledge persist. There is a lack of standardized diagnostic criteria, and no reliable biomarkers currently exist for early detection. Furthermore, there is a lack of long-term outcomes, hindering the assessment of lasting neurological or pulmonary impairment. The role of genetic or metabolic predispositions, as well as molecular pathways like the renin-angiotensin system, deserves closer investigation.

Future research should focus on high-quality prospective studies to validate existing prevention strategies, explore novel therapeutic targets, and establish standardized diagnostic and prognostic

tools. Multicenter collaborations and registries may help generate clinical data, ultimately improving patient outcomes in fat embolism syndrome.

Working on this thesis has highlighted for me how much is still unknown about fat embolism syndrome, and how important it is to bridge the gap between surgical technique and systemic response in trauma patients.

7. CONCLUSIONS AND RECOMMENDATIONS

Fat Embolism Syndrome is an uncommon, potentially fatal complication, usually occurring in the setting of orthopedic trauma due to a long bone fracture. Its multifactorial pathophysiology, involving mechanical, biochemical, and coagulative mechanisms, reflects the complexity of both diagnosis and management. In spite of an overall good outcome when diagnosed in time and treated properly, the syndrome remains a challenging entity because of its nonspecific presentation and lack of specific diagnostic equipment.

Preventive strategies have been found to be the most effective approach in reducing the risk of fat embolism syndrome. These include fracture stabilization at an early stage, individually timed surgery according to patient physiologic status, and intramedullary approaches minimizing embolic burden, e.g., Reamer-Irrigator-Aspirator system and lavage. Supportive intensive care, particularly lung-protective ventilation and appropriate fluid therapy, plays an essential role in managing acute complications and improving patient outcomes.

Nevertheless, substantial knowledge gaps remain. The lack of standardized diagnostic criteria and reliable biomarkers continues to hinder early identification. Furthermore, there is a clear need for long-term follow-up studies to evaluate functional recovery and potential long-term complications better. Emerging experimental strategies, such as modulation of the renin-angiotensin system, may offer promising avenues for future therapy but require further clinical validation.

Considering the existing evidence, clinicians should exercise caution in risky situations, make treatment decisions based on physiological data, and employ intraoperative and intensive care strategies to minimize embolic and inflammatory load. In the future, integrating clinical practice with experimental research will optimize prevention and care for fat embolism syndrome and enhance patient outcomes.

LIST OF REFERENCES

1. Cantu CA, Pavlisko EN. Liposuction-Induced Fat Embolism Syndrome: A Brief Review and Postmortem Diagnostic Approach. Arch Pathol Lab Med. 2018 Jul;142(7):871–5.

2. Aggarwal R, Banerjee A, Soni K dev, Kumar A, Trikha A. Clinical characteristics and management of patients with fat embolism syndrome in level I Apex Trauma Centre. Chin J Traumatol. 2019 Jun;22(3):172–6.

3. Lempert M, Halvachizadeh S, Ellanti P, Pfeifer R, Hax J, Jensen KO, et al. Incidence of Fat Embolism Syndrome in Femur Fractures and Its Associated Risk Factors over Time-A Systematic Review. J Clin Med. 2021 Jun 21;10(12):2733.

4. Milroy CM, Parai JL. Fat Embolism, Fat Embolism Syndrome and the Autopsy. Acad Forensic Pathol. 2019 Sep;9(3–4):136–54.

5. Martens S, De Wit M, De Grim L. Dyspnea after endomedullary nailing: Fat embolism. Clin Case Rep. 2022 Dec 26;10(12):e6788.

6. Stump B, Weinhouse G. Fat Embolism Syndrome: Fact or Myth? Curr Trauma Rep. 2016 Jun 1;2(2):66–72.

7. Morales-Vidal SG. Neurologic Complications of Fat Embolism Syndrome. Curr Neurol Neurosci Rep. 2019 Feb 20;19(3):14.

8. Bentaleb M, Abdulrahman M, Ribeiro-Junior MAF. Fat embolism: the hidden murder for trauma patients! Rev Colégio Bras Cir. 2024 Apr 17;51:e20243690.

9. Fukumoto LE, Fukumoto KD. Fat Embolism Syndrome. Nurs Clin North Am. 2018 Sep;53(3):335–47.

10. Kosova E, Bergmark B, Piazza G. Fat embolism syndrome. Circulation. 2015 Jan 20;131(3):317–20.

11. Uransilp N, Muengtaweepongsa S, Chanalithichai N, Tammachote N. Fat Embolism Syndrome: A Case Report and Review Literature. Case Rep Med. 2018 Apr 29;2018:1479850.

12. Adeyinka A, Pierre L. Fat Embolism. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [cited 2024 Sep 8]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK499885/

13. Timon C, Keady C, Murphy CG. Fat Embolism Syndrome – A Qualitative Review of its Incidence, Presentation, Pathogenesis and Management. Malays Orthop J. 2021 Mar;15(1):1.

14. Scarpino M, Lanzo G, Lolli F, Grippo A. From the diagnosis to the therapeutic management: cerebral fat embolism, a clinical challenge. Int J Gen Med. 2019 Jan 4;12:39–48.

15. 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):E515–21.

16. Fernández-Torre JL, Burgueño P, Ballesteros MA, Hernández-Hernández MA, Villagrá-Terán N, de Lucas EM. Super-refractory nonconvulsive status epilepticus secondary to fat embolism: A clinical, electrophysiological, and pathological study. Epilepsy Behav EB. 2015 Aug;49:184–8.

17. 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 Jun;35(6):1052–7.

18. Godoy DA, Di Napoli M, Rabinstein AA. Cerebral Fat Embolism: Recognition, Complications, and Prognosis. Neurocrit Care. 2018 Dec;29(3):358–65.

19. Rothberg DL, Makarewich CA. Fat Embolism and Fat Embolism Syndrome. J Am Acad Orthop Surg. 2019 Apr 15;27(8):e346–55.

20. Egashira T, Nakamura T, Setoguchi A, Takeno M, Akiyama D, Miyoshi H, et al. A Case of Fatal Fat Embolism Syndrome During Osteosynthesis Saved by Veno-Arterial Extracorporeal Membrane Oxygenation. Cureus. 16(10):e72326.

21. Kwon J, Coimbra R. Fat embolism syndrome after trauma: What you need to know. J Trauma Acute Care Surg. 2024 Oct;97(4):505.

22. Gangaraju R, Reddy VVB, Marques MB. Fat Embolism Syndrome Secondary to Bone Marrow Necrosis in Patients with Hemoglobinopathies. South Med J. 2016 Sep;109(9):549–53.

23. Tsitsikas DA, Bristowe J, Abukar J. Fat Embolism Syndrome in Sickle Cell Disease. J Clin Med. 2020 Nov 8;9(11):3601.

24. Luff D, Hewson DW. Fat embolism syndrome. BJA Educ. 2021 Sep;21(9):322–8.

25. Cárdenas-Camarena L, Bayter JE, Aguirre-Serrano H, Cuenca-Pardo J. Deaths Caused by Gluteal Lipoinjection: What Are We Doing Wrong? Plast Reconstr Surg. 2015 Jul;136(1):58–66.

26. Vetrugno L, Bignami E, Deana C, Bassi F, Vargas M, Orsaria M, et al. Cerebral fat embolism after traumatic bone fractures: a structured literature review and analysis of published case reports. Scand J Trauma Resusc Emerg Med. 2021 Mar 12;29(1):47.

27. Ansari Y, Ansari SA, Hussain M, Kazimuddin N, Khan TMA, Ansari Y, et al. Fat Pulmonary Embolism With Crazy-Paving Pattern Opacities and Pneumothorax: A Rare Complication of Liposuction. Cureus [Internet]. 2023 Jun 18 [cited 2025 Jan 13];15(6). Available from: https://www.cureus.com/articles/155422-fat-pulmonary-embolism-with-crazy-paving-pattern-opacities-and-pneumothorax-a-rare-complication-of-liposuction

28. Recinos S, Barillas S, Rodas A, Ardebol J. A rare case of fat embolism syndrome secondary to abdominal liposuction and gluteal fat infiltration. J Surg Case Rep. 2020 Dec 1;2020(12):rjaa441.

29. Rahman SA, Valliani A, Chanda A, Rahman SA, Valliani A, Chanda A. Fat Embolism Syndrome. In: Intensive Care [Internet]. IntechOpen; 2017 [cited 2025 Feb 22]. Available from: https://www.intechopen.com/chapters/56283

30. Nathan CL, Aamodt WW, Yalamarti T, Dogon C, Kinniry P. Cerebral fat embolism syndrome in sickle cell disease without evidence of shunt. eNeurologicalSci. 2019 Mar 1;14:19–20.

31. Alpert M, Grigorian A, Scolaro J, Learned J, Dolich M, Kuza CM, et al. Fat embolism syndrome in blunt trauma patients with extremity fractures. J Orthop. 2020;21:475–80.

32. Owattanapanich N, Lewis M, Biswas S, Benjamin ER, Demetriades D. Epidemiology and risk factors for fat embolism in isolated lower extremity long bone fractures. Eur J Trauma Emerg Surg Off Publ Eur Trauma Soc. 2024 Aug;50(4):1775–81.

33. Tsai SHL, Chen CH, Tischler EH, Kurian SJ, Lin TY, Su CY, et al. Fat Embolism Syndrome and in-Hospital Mortality Rates According to Patient Age: A Large Nationwide Retrospective Study. Clin Epidemiol. 2022;14:985–96.

34. Semita IN, Fatmawati H, Raharjo AM, Gandi P, Juliasih NN. Successful management of respiratory distress in fat embolism syndrome: A case report and literature review. Int J Surg Case Rep. 2024 Nov 26;126:110646.

35. Baba D, Yamashita Y, Fukuda Y, Yamaji K, Shiomi H, Horie T, et al. A Case of Fat Embolism Syndrome Treated with Methylprednisolone. Intern Med Tokyo Jpn. 2024 Dec 26;

36. Tsitsikas DA, Rowe S, Bosch A, Hui C, Sadasivam N, Palaskas NJ, et al. Addition of plasma exchange to red cell exchange improves outcomes of fat embolism syndrome in sickle cell disease. Br J Haematol. 2023;200(6):e50–2.

37. Ota T, Sawada T, Shimoura H, Terao Y, Ito T, Okajima K, et al. Fat embolism syndrome: A severe case diagnosed early using dual-energy CT and saved with VA-ECMO and inhaled nitric oxide. Clin Case Rep. 2024 Mar 29;12(4):e8681.

38. Ding YJ, Zhang L, Sun XW, Lin YN, Li QY. Rapid recovery of fat embolism syndrome with acute respiratory failure due to liposuction. Respirol Case Rep. 2022 Oct 3;10(11):e01047.

39. Sokol Z, Gonzalez GAA, Lopez A, Harrop J, Jabbour P. Decompressive Hemicraniectomy After Cerebral Fat Embolism. Cureus. 16(5):e61338.

40. O'Neill DC, Dekeyser GJ, Mortensen AJ, Makarewich CA. Adolescent Fat Embolism Syndrome after Closed Tibial Shaft Fracture: Treatment with Emergent External Fixation. Case Rep Orthop. 2021 Apr 24;2021:5585085.

41. Tzioupis CC, Giannoudis PV. Fat embolism syndrome: What have we learned over the years? 2017 May 8; Available from: https://journals.sagepub.com/doi/10.1177/1460408610396026

42. Kalbas Y, Seaver T, Kumabe Y, Halvachizadeh S, Lempert M, Pfeifer R, et al. Fat embolism syndrome in patients with bilateral femur fractures: a systematic review and case comparison. OTA Int. 2022 Apr 18;5(2 Suppl):e187.

43. Blokhuis TJ, Pape HC, Frölke JP. Timing of definitive fixation of major long bone fractures: Can fat embolism syndrome be prevented? Injury. 2017 Jun;48 Suppl 1:S3–6.

44. Volpin G, Pfeifer R, Saveski J, Hasani I, Cohen M, Pape HC. Damage control orthopaedics in polytraumatized patients- current concepts. J Clin Orthop Trauma. 2021 Jan;12(1):72–82.

45. Cimbanassi S, O'Toole R, Maegele M, Henry S, Scalea TM, Bove F, et al. Orthopedic injuries in patients with multiple injuries: Results of the 11th trauma update international consensus conference Milan, December 11, 2017. J Trauma Acute Care Surg. 2020 Feb;88(2):e53.

46. Kalinterakis G, Koutras A, Syllaios A, Michalakeas N, Lytras D, Tsilikis I. The evolution and impact of the “damage control orthopedics” paradigm in combat surgery: a review. Eur J Orthop Surg Traumatol. 2019 Apr 1;29(3):501–8.

47. Guerado E, Bertrand ML, Cano JR, Cerván AM, Galán A. Damage control orthopaedics: State of the art. World J Orthop. 2019 Jan 18;10(1):1–13.

48. Pape HC, Pfeifer R. Safe definitive orthopaedic surgery (SDS): repeated assessment for tapered application of Early Definitive Care and Damage Control?: an inclusive view of recent advances in polytrauma management. Injury. 2015 Jan;46(1):1–3.

49. Hildebrand F, Andruszkow H, Barkatali BM, Pfeifer R, Lichte P, Kobbe P, et al. Animal models to assess the local and systemic effects of nailing: review of the literature and considerations for future studies. J Trauma Acute Care Surg. 2014 Jun;76(6):1495–506.

50. Li AB, Zhang WJ, Guo WJ, Wang XH, Jin HM, Zhao YM. Reamed versus unreamed intramedullary nailing for the treatment of femoral fractures. Medicine (Baltimore). 2016 Jul 22;95(29):e4248.

51. Whitee R, Camuso M. AO surgery reference. [cited 2025 Feb 25]. Intramedullary nailing for Simple fracture. Available from: https://surgeryreference.aofoundation.org/orthopedic-trauma/adult-trauma/tibial-shaft/simple-fracture-spiral/intramedullary-nailing

52. Akoh CC, Schick C, Otero J, Karam M. Fat Embolism Syndrome After Femur Fracture Fixation: a Case Report. Iowa Orthop J. 2014;34:55–62.

53. Xia L, Zhou J, Zhang Y, Mei G, Jin D. A meta-analysis of reamed versus unreamed intramedullary nailing for the treatment of closed tibial fractures. Orthopedics. 2014 Apr;37(4):e332-338.

54. Jacobson E, Schieve BC, Klahs KJ, Macias RA, Abdelgawad A, Thabet AM. Reamer irrigator aspirator (RIA) reduces risk of fat embolism in bilateral pediatric femur shaft fractures: a case report. J Surg Case Rep. 2024 Feb 9;2024(2):rjae042.

55. Fan E, Del Sorbo L, Goligher EC, Hodgson CL, Munshi L, Walkey AJ, et al. An Official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine Clinical Practice Guideline: Mechanical Ventilation in Adult Patients with Acute Respiratory Distress Syndrome. Am J Respir Crit Care Med. 2017 May;195(9):1253–63.

56. Brochard L, Slutsky A, Pesenti A. Mechanical Ventilation to Minimize Progression of Lung Injury in Acute Respiratory Failure. Am J Respir Crit Care Med. 2017 Feb 15;195(4):438–42.

57. Young CC, Harris EM, Vacchiano C, Bodnar S, Bukowy B, Elliott RRD, et al. Lung-protective ventilation for the surgical patient: international expert panel-based consensus recommendations. Br J Anaesth. 2019 Dec 1;123(6):898–913.

58. Fan E, Brodie D, Slutsky AS. Acute Respiratory Distress Syndrome: Advances in Diagnosis and Treatment. JAMA. 2018 Feb 20;319(7):698–710.

59. Yang D, Grant MC, Stone A, Wu CL, Wick EC. A Meta-analysis of Intraoperative Ventilation Strategies to Prevent Pulmonary Complications: Is Low Tidal Volume Alone Sufficient to Protect Healthy Lungs? Ann Surg. 2016 May;263(5):881–7.

60. Chiumello D, Brioni M. Severe hypoxemia: which strategy to choose. Crit Care. 2016;20:132.

61. Koulouras V, Papathanakos G, Papathanasiou A, Nakos G. Efficacy of prone position in acute respiratory distress syndrome patients: A pathophysiology-based review. World J Crit Care Med. 2016 May 4;5(2):121–36.

62. Abrams D, Lorusso R, Vincent JL, Brodie D. ECMO during the COVID-19 pandemic: when is it unjustified? Crit Care. 2020 Aug 17;24:507.

63. Chiu LC, Kao KC. Mechanical Ventilation during Extracorporeal Membrane Oxygenation in Acute Respiratory Distress Syndrome: A Narrative Review. J Clin Med. 2021 Oct 26;10(21):4953.

64. Fernandez-Bustamante A, Hashimoto S, Serpa Neto A, Moine P, Vidal Melo MF, Repine JE. Perioperative lung protective ventilation in obese patients. BMC Anesthesiol. 2015 May 6;15:56.

65. 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 Feb;82(2):338–44.

66. Xu Z, Li W, Han J, Zou C, Huang W, Yu W, et al. Angiotensin II induces kidney inflammatory injury and fibrosis through binding to myeloid differentiation protein-2 (MD2). Sci Rep. 2017 Mar 21;7:44911.

67. 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 Apr;113:93–100.