Introduction

Fat embolism syndrome (FES) resulted in 10–20% mortality rates in the 1960s and early 1970s [1]. Since then, with early diagnostic aids and aggressive pulmonary therapy, the prognosis has improved somewhat [1]. However, morbidity from posttraumatic FES remains high.

In attempting to prevent the development of FES, the treating surgeon is faced with a number of conceptual difficulties. There is no universally accepted definition of what constitutes the condition; FES and associated conditions causing respiratory insufficiency arise from pathophysiological processes that are poorly understood, and which are themselves largely diagnoses of exclusion. There is very little high-quality evidence on which to base recommendations regarding treatment, which still remains largely empirical and supportive. In this section we aim to define the condition and the patients who are at risk of developing it. We then aim to review the available evidence for the optimal management of the patient, from resuscitation, through surgery, and into the recovery period in order to minimize the risk of FES. Finally, we aim to review adjuvant and experimental strategies that may be of benefit in the future.

Defining FES

Intravasation of fat and medullary contents can be demonstrated following over 95% of fractures [3, 4] and even bone contusion without fracture [5]. Although most of this material becomes embolized in the pulmonary bed, it seems likely that at least some of this material gains access to the systemic circulation via pulmonary shunts. It is therefore remarkable that the clinical features of FES itself are so rare, occurring in only 3–4% of patients with long-bone fractures. FES involves multiple organ systems...
and can cause a devastating clinical deterioration within a few hours. Gurd and Wilson [6] attempted to define the condition on the basis of major and minor criteria (Table 1), to which several other authors have subsequently proposed adaptations and modifications [7–9]. Although Gurd’s “cerebral signs” and the presence of a skin rash are apparently relatively trivial after major injury, one should not underestimate the long-term importance of the disabling cognitive defects that may result [10], nor the likely internal organ endothelial disruption that is the correlate of the skin rash. However, respiratory insufficiency is clearly the most clinically crucial component of the syndrome in the acute phase. This insufficiency has been recognized under many names: FES, neurogenic pulmonary edema, shock lung, pulmonary failure septic state, and acute lung injury. More recently, the term acute respiratory distress Syndrome (ARDS) has allowed several of these disparate concepts to be united, and to be defined according to consensus criteria [11].

We now recognize that the stress response to trauma represents a broad spectrum of systemic and pulmonary pathophysiology, of which respiratory insufficiency is just one component, and of which FES in turn is merely one manifestation. We propose that except in rare circumstances where a rash occurs in isolation from respiratory insufficiency, FES should be viewed as being ARDS due to bone trauma, with additional features. In this section, we will review the historical literature that refers to FES and to more contemporary studies that have centered on ARDS.

### Who is at risk—predicting susceptibility

The likelihood of a patient developing respiratory insufficiency after trauma is a function of the severity of the initial trauma, its anatomical location, the patient’s genetic predisposition to an exaggerated inflammatory or coagulative response, and the medical and surgical management of the patient.

Most cases of respiratory insufficiency can be predicted from the severity or “dose” of trauma. An injury severity score (ISS) of over 16, the presence of a femoral fracture, a combined abdominal and extremity injury, or abnormal vital signs at admission are each independently predictive of the later development of ARDS [12]. It is rare to encounter ARDS in a patient with an ISS below 9 [12]. However, these criteria have low positive predictive value, and also fail to identify those occasional patients who develop respiratory insufficiency after apparently innocuous injury.

There has been substantial interest in the possibility of improving this discrimination using hematological markers or scores of vascular fat embolism. Interleukin 6 (IL-6) has shown the most promise as a marker for later complications. Normal levels are less than 10 pg/ml, and do not rise significantly after minor injuries such as an ankle fracture [13]. However, Pape and others have shown that after trauma these levels rise significantly and proportionally to the extent of injury [16]. He has also shown that patients with high IL-6 levels have a higher risk of requiring prolonged intubation, with a level of over 500 pg/ml being associated with multiple organ dysfunction [14]; a finding that has been confirmed by other investigators [15]. However, these markers correlate most closely with injury severity, and it has not yet been demonstrated that such markers offer any additional independent discriminative ability or correlate with clinically important outcomes.

Thoracic injury, in particular pulmonary contusion, is associated with respiratory insufficiency. There is, however, debate over whether an additional concomitant long-bone injury causes an increased level of risk above that associated with the thoracic injury alone.

Pathological deposits in bone have a greater propensity to cause embolism than traumatic fractures, and instrumentation of an intact long bone for prophylactic stabilization of a tumor in particular

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**Table 1: Gurd and Wilson’s diagnostic criteria for fat embolism syndrome [49].**

<table>
<thead>
<tr>
<th>Major</th>
<th>Minor</th>
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<tr>
<td>Respiratory symptoms, signs, and radiographic changes</td>
<td>Tachycardia over 110 beats per minute</td>
</tr>
<tr>
<td>Cerebral signs unrelated to head injury or other conditions</td>
<td>Pyrexia &gt;38.5°C</td>
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<tr>
<td>Petechial rash</td>
<td>Retinal changes of fat or petechiae</td>
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<td>Renal changes</td>
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<td>Jaundice</td>
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<td>(Laboratory):</td>
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<td></td>
<td>Acute fall in hemoglobin</td>
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<td></td>
<td>Sudden throbocytopenia</td>
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<td>High ESR</td>
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<td>Fat macroglobulinemia</td>
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FES: One major and four minor criteria and fat macroglobulinemia are required for diagnosis.
carries a high risk of causing excessive trans-cardiac embolism, and is associated with an increased risk of ARDS and death [17].

Initial management—role of resuscitation and damage control orthopedics

Numerous simultaneous improvements in the management of trauma patients have resulted in a marked fall in the incidence of respiratory insufficiency from up to 22% of trauma admissions in the 1960s and 1970s, when much of the published work on FES was produced [18], to below 5% in recent studies. More recently, a significant decrease in the prevalence of ARDS after major trauma has also been shown when comparing the 1980s with the late 1990s [19]. Many factors are likely to be of importance in this falling incidence, including better pre-hospital care, more rapid and (aggressive) resuscitation protocols, and improved intensive medical supportive therapy.

It is important when resuscitating a polytrauma patient to be able to recognize the severity of injury and subsequent level of aggressiveness of resuscitation required. In a recent review of outcomes in polytrauma patients, Pape et al delineated four broad types of patient presenting at the trauma suite [20]. The four proposed groups were: the stable patient, the borderline patient, the unstable patient, and the patient in extremis. From the available literature, they discerned four main factors that play a role in deciding which group to place the patient into on presentation. These factors were the presence of hemorrhagic shock, hypothermia, a hypercoagulable state, and the presence of soft-tissue injuries. The hallmark clinical parameters that constitute an unstable patient compared to a stable or borderline patient include, blood pressure (BP) < 90 mm Hg, temperature < 33 °C, platelets < 90,000 and significant soft-tissue injuries (lung injury with an abbreviated injury severity score > 2, major pelvic trauma, or crush injuries) [20]. These parameters constitute the upper limits of the unstable patient and, with worsening scores, the patient falls further into the category of the patient in extremis [20]. These groupings may help to guide the management and resuscitation in general and also the specific orthopedic management of the polytraumatized patient. Based on retrospective and basic science studies [19], these authors recommended that patients who are unstable or in extremis receive damage control surgery (that is, rapid long-bone stabilization with an external fixator) and have subsequent definitive stabilization performed at a later date, typically within 5–7 days. In those patients who are borderline or where there is continued uncertainty as to their physiological state, damage control surgery was also recommended as a safe management option [20]. However, there is no prospective clinical evidence for this approach in these unstable patients, and indeed the concept has recently been challenged [21].

Research evidence is, however, available regarding the effect of DCO techniques on hemodynamically and physiologically stable trauma patients with femoral fractures. In one study, patients were randomized to receive either early total care or damage control orthopedic care (early external fixator stabilization followed by intramedullary fixation). In this study, proinflammatory markers were used as a surrogate outcome measure for estimating the physiological burden of surgery on the polytraumatized patient. Those patients treated with primary intramedullary fixation were shown to have higher levels of proinflammatory interleukins (interleukins 6 and 9) than those treated with an external fixator [32]. It was suggested that damage control orthopedic surgery minimized the additional physiological impact caused by the acute intramedullary stabilization of the femur [32]. Interestingly, this elevation of proinflammatory response proteins was also higher than the elevation seen after the delayed (definitive) intramedullary stabilization [32]. However, no patients with borderline, unstable or in extremis physiology were included and there were no clinical complications seen in the group with the higher elevation of cytokines [32]. Thus it remains to be seen whether the difference in the proinflammatory response correlates with an increase in clinical morbidity in relevant patients.

When to operate—early versus late fixation

Orthopedic fracture management has developed considerably over the past four decades. Until the 1970s, the accepted treatment for long-bone fractures was conservative, with the use of plaster of Paris and traction. Prolonged immobilization was attended by the recognized complications of recumbency: muscular wasting, peptic stress ulceration, decubitus ulceration, infections of the respiratory and urinary tracts, and psychological depression [18, 22]. In addition, conservative management was associated with a reported incidence of FES of up to 22% [18].

Movement of the fracture ends has been shown to result in the release of “showers” of fat emboli into the circulation [23] and early surgical immobilization of lower extremity fractures is advocated. Rigid fracture fixation soon after injury has been indirectly
supported by three observations by Tackakra et al: 1) development of hypoxemia in nonsurgically treated patients with long-bone fractures; 2) occurrence of two separate episodes of FES in the same patient with multiple fractures; and 3) appearance of skin petechiae in "crops" suggesting repeated episodes of embolization [23].

During prolonged treatment without surgical stabilization, fat embolism is also exacerbated by the formation, disruption, and release of thrombi from the injured limb [24], which also results in recurrent transient hypoxia [25]. Moreover, delayed stabilization of fractures also results in prolonged activation of the components of the systemic physiological stress response. It has been shown that inflammatory markers remain persistently elevated in those patients treated with skeletal traction until delayed stabilization is performed, after which they return promptly to normal [26]. In addition, the immobile, supine patient is prone to atelectasis, pneumonia, and a reduced functional residual capacity, which causes shunting and impairs oxygenation. The introduction of internal fixation techniques was shown by Riska in 1977 to be accompanied by a marked reduction in incidence of FES to under 5% [27]. Subsequently, several other studies have been published, each confirming this reduction in the risk of respiratory complications by a ratio of 5:1 [27–29].

Amongst a number of retrospective studies, Johnson and coworkers reported on the occurrence of the ARDS in 132 multiply injured patients who had undergone operative fracture stabilization at different intervals from the time of injury [30]. The overall incidence of ARDS was increased more than five fold in the group in whom pelvic and major long-bone fracture stabilization was delayed more than 24 hours after injury, increasing from 7% in the group receiving early fixation to 39% in the delayed fixation group. In patients with an ISS of less than 30, no ARDS was seen in the group that underwent early stabilization as compared with an 8% incidence when orthopedic surgery was delayed more than 24 hours. In patients with an ISS exceeding 30, ARDS was found in 17% of those who underwent early fracture stabilization and in 75% of those who had a delay in operative fracture fixation ($p<.05$). In a subsequent key paper, these investigators reported the results of a randomized controlled trial in which the effects of early (within 24 hours, n=88) and delayed (after 48 hours, n=90) stabilization of femoral shaft fractures in multiply injured patients were compared. They reported a trend towards increased risk of FES and ARDS in multiply injured patients. One patient in the early group (n=46) developed ARDS in comparison to six patients in the delayed treatment group (n=37). Although no patients in the early group developed clinically detectable FES, two patients in the delayed group did. The lack of statistical significance was likely to have been a consequence of beta-error (insufficient sample size) [31].

Thus although the selection of which surgical treatment to offer remains somewhat controversial, it is now accepted that some form of operative skeletal stabilization is required within 24 hours of a major long-bone fracture.

The effect of reaming technique

Instrumentation of the femoral canal prior to the insertion of an intramedullary nail is known to generate increased intramedullary pressure and to cause intravasation of fat emboli [33]. Several studies, both animal and clinical have assessed the effect of inserting an intramedullary nail with and without reaming [34–39]. While reaming was shown to increase the medullary canal pressure, it has been shown that femoral nail insertion without reaming also results in an increase in canal pressure [39]. Indeed, the very act of opening the canal with an awl results in some emboli being introduced to the lungs [39]. Coles et al assessed the emboli during femoral nailing comparing a reamed and unreamed technique with the aid of transesophageal echocardiography [39]. They found that both techniques resulted in the presence of similar emboli and that unreamed nails did not protect patients from pulmonary embolization [39]. A further randomized controlled trial of reaming found no significant statistical difference in the rate of pulmonary physiological responses between the group that had femoral nailing done with reaming compared to those that had an unreamed nail [34]. However, this study was underpowered and larger randomized trials may be needed to be able to differentiate between the two groups.

Several studies have examined the effect of reamed intramedullary nailing in terms of neurological outcomes in patients with head injuries [40–43]. McKee and colleagues used a prospective database to identify 46 multiply injured patients whose head injury was treated with early reamed intramedullary nailing [40]. They further identified control patients matched for age, gender, Glasgow coma scale score (within 1 point), and mechanism of injury. They reported that early (within 24 hours) reamed intramedullary nailing did not significantly alter mortality, Glasgow outcome scores, and neurological outcomes in patients with a closed head injury.

A similar database study compared reamed femoral nails and femoral plates in multiply injured patients with a concomitant head injury. The au-
thors concluded that reamed intramedullary nails in addition to not increasing the risk of central nervous system complications, also resulted in fewer overall complications and demonstrated equivalent functional outcomes to plate fixation at one year [44]. The current literature supports the belief that head injury is not a contraindication to early reamed intramedullary nailing; however, randomized trials will best resolve this issue.

With respect to the act of reaming, several factors are thought to potentiate or alleviate the increase in pressure seen and they are broadly classified into two main categories, that of reamer design and adjunctive techniques during the act of reaming.

Reamer design has evolved over the past few years, progressing from large bore reamers and shafts to thinner bore reamers with wide reaming flutes and thinner shafts. This evolution has been thought to allow debris to flow past the reaming hole decreasing the plunger-like effect of older designs, theoretically decreasing the intramedullary pressure [45]. Indeed, experimental studies have shown a decrease in pressure associated with a decrease in the shaft of the reamer by as much as 50% [45]. Another design change has been the advent of a reaming system with a built-in suction aspirator [46–48]. Experimental work has shown the efficacy of this system and found a significant decrease in intramedullary pressure with a reamer aspirator in both a porcine and sheep model [46, 47]. This finding also correlated with a decrease in pulmonary artery pressure within the experimental animals [46].

Adjunctive techniques to the act of reaming have been described and include aspiration of the canal prior to reaming and venting the femur. Experimental data suggests that distal venting of the femur during reaming may reduce the intramedullary pressures by 50–90% [49]. However, the efficacy of this technique has not been documented in prospective randomized clinical trials and, in addition, it is unclear whether this in itself will correlate with a decreased incidence of FES.

Adjuvant techniques

Early approaches to treating posttraumatic respiratory insufficiency reflected the limited understanding of the underlying pathophysiology of the condition. A number of early trials of methylprednisolone as a "membrane stabilizer" claimed a reduced incidence of FES in the treatment group [50, 51] (although sepsis was reported to be a significant complication [46]) but subsequent modern studies have not supported its use [53, 54]. A recent meta-analysis of randomized trials of corticosteroids used to prevent FES in patients with long-bone fractures identified 84 studies of which only six were considered adequate for analysis. The pooled analysis found that corticosteroids reduced the risk of FES by 77% (95% CI: 40–91%) and that only 7.4 patients needed to be treated to prevent one case of FES (95% CI: 5–14 patients), although it should be noted that the quality of these studies, most of which were performed in the 1970s, does not reflect contemporary standards. Investigators did not find any significant difference in the rates of mortality, infection, or delayed union [54].

Pretreatment with heparin in experimental models has been shown to reduce the degree of pulmonary compromise [55] and intravascular coagulation [56], and heparin transiently enjoyed widespread clinical use, despite the dangers of hemorrhage and rapid lipolysis [5, 56]. However, its use has not shown consistent benefits in reducing lung injury and a recent review of anticoagulant therapies concluded that its current role remains to be defined [53]. Ethanol (which decreases lipolysis) and dextrose (which decreases free fatty acid mobilization) have also been used empirically, but little evidence is available to support the use of these treatments [29, 51, 58, 59].

Experimental techniques

Current treatments for FES are therefore largely prophylactic or supportive only, and no evidence-based therapeutic strategies are available. However, recent advances in many fields, particularly the closely related immunological field of sepsis management, have suggested more focused possible treatments for trauma patients in the future. Specific anti-cytokine therapies such as the administration of receptor antagonists to IL-1 have been shown to reduce death from sepsis in experimental animal models [60]. Antibodies to adhesion proteins CD 11 and ICAM significantly reduced pulmonary endothelial injury in animal models of sepsis [61] and cyclo-oxygenase inhibitors by reducing thromboxane synthesis and neutrophil adherence. They have been shown to decrease lung injury [62] if given early [63]. Specific blockade of tissue factor and factor VII reduces coagulation activation and prevents lung dysfunction and pulmonary fibrin deposition in animal models of sepsis [64], and administration of tPA [65] and AT III reduces lung injury in animal models of ARDS [52, 66]. However, it is becoming increasingly clear that there are numerous significant differences between species in the activity of the inflammatory...
and coagulation systems [60] and overall, studies in humans have been less encouraging so far [58, 67].

In contrast, one molecular medical treatment for sepsis has been approved for use in human patients. Activated protein C (APC) has been shown to reduce mortality in septic human patients, an effect that may be due to its promotion of fibrinolysis, or its direct inhibition of Il-1, Il-6, and TNF-alpha expression [68]. Although APC increased the risk of significant hemorrhage (a feature which therefore limits its applicability in trauma), the success of this immunological therapy raises the prospect of more specific drug treatments for trauma patients in the future.

Some patients develop a stress response to trauma that is seemingly out of proportion to their injury, with complications arising after apparently innocuous trauma. Genetic polymorphisms for many of the components of the inflammatory and coagulation system have recently been identified, and some, such as those for plasminogen activation inhibitor (PAI) and Il-6, are now known to be associated with an increased risk of complications and mortality [69, 70]. There is now the exciting prospect of being able to screen patients at the time of admission with gene array techniques to identify susceptible individuals and tailor their treatment accordingly.

<table>
<thead>
<tr>
<th>Technique</th>
<th>Description</th>
<th>Level of evidence/notes</th>
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<tbody>
<tr>
<td>Prediction of susceptibility</td>
<td>Trauma scores</td>
<td>Level 1</td>
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<tr>
<td></td>
<td></td>
<td>Poor positive predictive value.</td>
</tr>
<tr>
<td>Thoracic injury</td>
<td>Level 1</td>
<td>An isolated thoracic injury carries greater risk than isolated femoral fractures, but combined injuries do not raise risk further.</td>
</tr>
<tr>
<td>Pathological fracture</td>
<td>Level 1</td>
<td>Higher risk</td>
</tr>
<tr>
<td>Inflammatory markers</td>
<td>Il-6 level correlates with outcome, but it is not yet clear whether this is independently predictive.</td>
<td></td>
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<tr>
<td>Genetic predisposition</td>
<td>Certain polymorphisms correlate with outcome, may allow targeted therapy in future</td>
<td></td>
</tr>
<tr>
<td>Resuscitation</td>
<td>BP &lt; 90</td>
<td>Observational studies suggest a correlation between BP &lt;90mm Hg on admission and adverse outcome.</td>
</tr>
<tr>
<td>Transfusion requirements</td>
<td>Observational studies have found massive transfusion requirements to be associated with adverse outcomes (eg, multiple organ dysfunction)—however, definitions of massive transfusion remains controversial.</td>
<td></td>
</tr>
<tr>
<td>Timing of surgery</td>
<td>Long-bone surgical stabilization within 24 hours</td>
<td>Level 1 Surgical stabilization reduces ARDS rate by factor 5:1 compared with late.</td>
</tr>
<tr>
<td>Type of surgery</td>
<td>DCO</td>
<td>Observational and retrospective studies may suggest that damage control orthopedics reduces the insult of initial operative long bone stabilization but level 1 evidence is awaited.</td>
</tr>
<tr>
<td>Adjuvants</td>
<td>Prednisolone</td>
<td>Early papers suggest reduction in incidence of respiratory insufficiency but at expense of increased infection rate.</td>
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<tr>
<td></td>
<td>Heparin</td>
<td>Empirical</td>
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<td>Ethanol</td>
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<td></td>
<td>Dextrose</td>
<td>Empirical</td>
</tr>
<tr>
<td>Experimental</td>
<td>Specific antibody treatments</td>
<td>Not currently available. Some animal studies exciting and success of APC in sepsis raises possibility of therapeutic options in future.</td>
</tr>
<tr>
<td>Filters</td>
<td>Experimental studies suggest that inferior vena cava filters decrease the embolic load to the heart during femoral nail insertion</td>
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</table>

Table 2: Summary of recommendations.
Mechanical techniques

Another theoretical technique in the prevention of fat embolism is that of placing a venous filter [71]. Experimental work in an animal model has shown that proximal venous blockade with a filter reduced both the size and quantity of the embolic load seen by the lungs [71]. Whether this technique is effective in reducing the clinical syndrome of fat embolism yet remains to be seen. Further clinical trials are necessary to both determine its feasibility as well as its clinical utility.

Conclusion

Many factors play a role in the prevention of FES and ARDS. These factors range from identifying those at risk, timing of long-bone stabilization and possibly the type of initial fixation, to preventive mechanical and medical management. While there is an increasing amount of prospective randomized data available to help guide treatment (Table 2) more such studies are needed to evaluate further those measures that may in the future allow prevention of FES.

Bibliography

24. Winquist RA. 2003. personal communication,


Prevention of fat embolism syndrome


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