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Early Risk Factors for Postinjury Multiple Organ Failure

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Abstract. Epidemiologic studies, based on retrospective data from heterogeneous populations with poor control of confounders, led early investigators to conclude that infection was the overriding risk factor for multiple organ failure (MOF). More recent studies have convincingly shown that MOF frequently occurs in the absence of infection. Consequently, we have shifted our research focus away from the traditional infectious models of MOF to the newer "one-hit" and "two-hit" inflammatory models. Clinically, we have chosen to study trauma patients because they are a relatively homogeneous group with a low incidence of common confounders. Trauma also permits a clear distinction between the first insult and the outcome, both temporally and with respect to the definition criteria. In this review we discuss the background, rationale, and our initial attempts to use indicators of the first insult (i.e., tissue injury quantification and clinical signs of shock) and indicators of the host response (i.e., systemic inflammatory response syndrome) to predict MOF early after injury.

There is occasions and causes, why and wherefore in all things.

William Shakespeare: *Henry V*, v;1599

During the early 1980s, based on compelling epidemiologic association, multiple organ failure (MOF) was believed to be the "fatal expression of uncontrolled infection" [1, 2]. However, by the mid-1980s other studies had demonstrated that MOF could occur in the absence of infection, particularly in blunt trauma patients [3, 4]. The term "sepsis syndrome" was introduced [5], and bacterial translocation was suggested to be the driving mechanism of postinjury MOF [6–8]. Animal models of bacterial translocation are logical and consistent, but clinically it has been difficult to show that significant bacterial translocation occurs early after injury [9]. Also, the repeated failure of selective gut decontamination to reduce mortality has challenged the notion that gut-derived infection is the predominant cause for MOF [10, 11]. Thus our research focus has shifted to determining how the initial traumatic insult sets the stage for the development of MOF without infection or bacteria [3, 12–16]. Our hypothesis is that a dysfunctional inflammatory response is the pivotal risk factor for MOF (Fig. 1). After major trauma patients are resuscitated into a hyperinflammation state, now referred to as the systemic inflammatory response syndrome (SIRS) [17]. The amplitude and duration of early SIRS depends on the initial insult. Negative feedback mechanisms down-regulate early SIRS to limit unnecessary and potentially autodestructive inflammation, resulting in a delayed immunosuppression state. Our research interest has focused on early SIRS. In our concept framework (Fig. 2), massive trauma can precipitate severe SIRS, which can evolve into MOF ("one-hit" model). The alternative is multiple sequential insults. With this "two-hit" model, less severely injured patients enter a moderate state of SIRS; certain patients appear to be vulnerable (i.e., primed) such that an otherwise innocuous second inflammatory insult amplifies (i.e., activates) SIRS to produce MOF [12, 15, 18].

Over the past 5 years, our Trauma Research Center has been testing this concept in basic models and clinically. A primary goal of our clinical project is to develop early predictive models of MOF. They focus on observational studies and ultimately will allow early identification of high risk patients for interventional trials. We hypothesize that: (1) the severity of the first insult, quantified by tissue injury and shock indicators, predicts postinjury MOF; and (2) the severity of SIRS predicts postinjury MOF. This review provides background information and our preliminary data supporting these hypotheses. Specifically, we (1) examine unique aspects of our trauma population, (2) define outcome, (3) examine indicators of severity of the first insult, (4) examine indicators of SIRS, and (5) discuss potential confounders and effect modifiers.

Trauma Population

Previous attempts to characterize patients at risk for MOF have included heterogeneous populations subjected to a variety of inciting events [1, 2, 7, 19]. These investigations provided the useful concept that diverse insults cause a similar host response (i.e., SIRS) [17]. Also, quantification of this host response [e.g., the acute physiology, age, chronic health evaluation (APACHE) scoring system] predicts adverse outcomes. The latter efforts have minimized the value of the first insult as a predictor of MOF. Trauma offers the unique possibility of establishing the time of the first insult and characterizing it independently of outcome and MOF [20]. Also, trauma patients are usually young, healthy individuals, and so common confounders or effect modifiers (e.g.,

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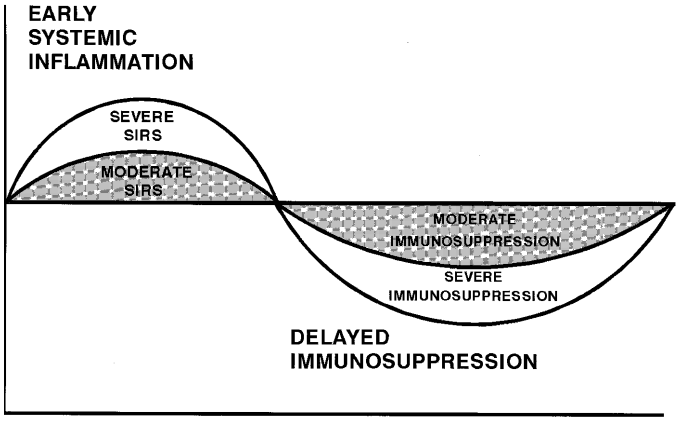

Fig. 1. Dysfunctional inflammatory response. SIRS: systemic inflammatory response syndrome.

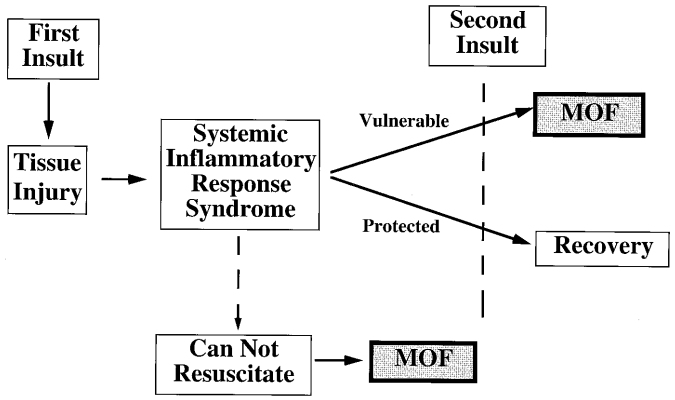

Fig. 2. Pathogenesis of postinjury multiple organ failure.

age and comorbid conditions) are less important [15, 21, 22]. Moreover, injured patients are rapidly triaged to regional trauma centers where standardized treatment minimizes the confounding effect of therapy.

Defining the Outcome

Multiple Organ Failure

When we initiated our National Institutes of Health (NIH) research center on adult respiratory distress syndrome (ARDS) in 1987, we recognized MOF to be an important endpoint and developed a MOF score based on the available literature. Eight organ dysfunctions were graded from 0 to 3, and MOF was scored daily to evaluate temporal trends and the intensity of derangement. Scores obtained during the first 48 hours were not used to diagnose MOF because these abnormalities might have been due to the primary injury or incomplete resuscitation [9]. After experience with this score in a multicenter trial, gastrointestinal, hematologic, neurologic, and metabolic failure were deleted because their definitions were subjective, and more importantly they did not contribute to the diagnosis of MOF. Based on discussions with other investigators we revised the criteria for pulmonary, renal, hepatic, and cardiac failure [15, 18]. In brief,

Table 1. Postinjury multiple organ failure scoring.

	Grade 1	Grade 2	Grade 3
Pulmonary dysfunction (ARDS score)*	>5	>9	>13
Renal dysfunction (Creatinine level)	>1.8 mg/dl	>2.5 mg/dl	>5.0 mg/dl
Hepatic dysfunction (Bilirubin level)**	>2.0 mg/dl	>4.0 mg/dl	>8.0 mg/dl
Cardiac dysfunction (Inotrope level)***	Minimal	Moderate	High

ARDS: adult respiratory distress syndrome.

*ARDS score = A + B + C + D + E:

A. Pulmonary findings by plain chest radiography: 0 = normal; 1 = diffuse, mild interstitial marking/opacities; 2 = diffuse, marked interstitial/mild air-space opacities; 3 = diffuse, moderate air-space consolidation; 4 = diffuse, severe air-space consolidation.

B. Hypoxemia (PaO_2/FiO_2): 0 = >250; 1 = 175–250; 2 = 125–174; 3 = 80–124; 4 = <80.

C. Minute ventilation (l/min): 0 = <11; 1 = 11–13; 2 = 14–16; 3 = 17–20; 4 = >20.

D. Positive end expiratory pressure (cmH_2O): 0 = <6; 1 = 6–9; 2 = 10–13; 3 = 14–17; 4 = >17.

E. Static compliance (ml/cmH_2O): 0 = >50; 1 = 40–50; 2 = 30–39; 3 = 20–29; 4 = <20.

**Biliary obstruction and resolving hematoma not involved.

***Cardiac index <3.0 l/min. M^2 requiring inotropic support: Minimal dose = Dopamine or Dobutamine <5 μg/kg/min; Moderate dose = Dopamine or Dobutamine 5–15 μg/kg/min; High dose = Greater than moderate doses of above agents.

individual organ failure is defined as a dysfunction grade of ≥ 2, and MOF is defined as the sum of simultaneously obtained organ grades ≥ 4 (Table 1). Other MOF scores that have been developed for trauma [3, 12, 16] and mixed ICU populations [2, 4, 7, 19, 23, 24] are predictably similar.

Nevertheless, the question remains: How do we validate these definitions? In the absence of a gold standard, an alternative is to relate the various scores to mortality. With the exception of Fry et al. [2], whose criteria for lung dysfunction only captured severely ill patients, the scores yielded a relatively narrow range: 38% to 59%. Figure 3 shows that the 95% confidence intervals of MOF case-fatality rates, according to several definitions, present a reasonable overlap. In fact, the four studies confined to trauma patients performed during the last 8 years [9, 12, 15, 25] had essentially the same center (i.e., roughly 50%). We are currently collecting data to calculate the incidence and case-fatality rates of postinjury MOF in our population according to two other widely employed scores [4, 7] as well as by our own definition. If comparable, these results will considerably improve our predictive models.

Surrogates for MOF

It is difficult to elucidate risk factors for postinjury MOF because of the paucity of published work. Thus we have also analyzed studies addressing ARDS and intensive care unit (ICU) deaths. These alternatives appear to correlate strongly with MOF.

ARDS. It is now believed that ARDS is a systemic disease [14, 26]. Pulmonary failure presents first either because the lungs are more vulnerable or our clinical tools are more sensitive to detect this organ dysfunction [14, 26]. Regardless, it is generally believed

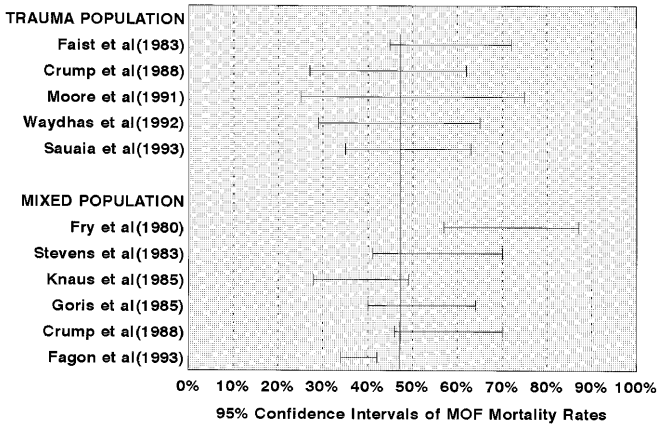

Fig. 3. Ninety-five percent confidence intervals of multiple organ failure case-fatality rates according to different definitions.

that simultaneous multiple organ injury is occurring via similar mechanisms. This belief is supported by animal models in which a variety of inciting events (burns, gut ischemia/reperfusion, shock, sterile peritonitis) have been shown to cause synchronous multiple end-organ dysfunction [27, 28].

ICU Death. Over the past decade considerable effort has been expended in developing predictive models for death of patients admitted to an ICU (Tables 2, 3). Because MOF carries a high case-fatality rate, these models offer a source of potential variables associated with MOF. Their disadvantage, however, is that it is impossible to distinguish between risk of MOF (i.e., potentially causative exposures) and prognostic factors for MOF (i.e., variables that worsen the clinical course of established disease).

Indicators of Severity of the First Insult

Tissue Injury Indicators

In a mixed population a variety of insults (e.g., pancreatitis, aspiration, sepsis, hypertransfusion, abdominal trauma, pulmonary contusion, pelvic fractures, and multiple long bone fractures) are risk factors for ARDS and MOF [20, 29, 38]. In our experience, abdominal trauma (defined as an Abdominal Trauma Index of > 15) is associated with an 18% incidence of ARDS, hypertransfusion is implicated in 21% of the ARDS cases, pulmonary contusion is associated with a 25% incidence, and multiple fractures are associated with 48% ARDS rates [38]. Problems with using individual injuries as predictors include a reduction in the number of cases in each injury category and disregard of the combined effect of multiple injuries. Thus in our more recent predictive models for MOF, we have used the Injury Severity Score (ISS) and the Anatomic Profile, which take into account the synergistic effect of multiple injuries.

The ISS, devised by Baker et al. in 1974 [47], is based on the Abbreviated Injury Scale (AIS). This index correlates moderately well with ICU mortality after blunt trauma [16, 22, 36]. Shortcomings of the ISS include (1) failure to account for multiple injuries in a single body region, which represents a substantial problem when scoring penetrating injuries; (2) underweighting of head injuries; and (3) relative overvaluing of orthopedic and facial trauma [52]. Although the fifth (1985) and sixth (1990) revisions of the AIS have attempted to alleviate these deficits, recent evaluations of the ISS continue to suggest problems [48–50].

The Anatomic Profile (AP) was developed in response to the acknowledged limitations of the ISS [51]. In brief, the AP also uses the AIS and summarizes all serious injuries (AIS > 2) to the head and spinal cord (component A), injuries to the thorax and front of the neck (component B), all remaining serious injuries (component C), and all nonserious injuries (component D). The outcome prediction performances of the ISS and AP alone have not been compared, but some inferences can be made from comparisons between the probability of survival equations that rely on these two scores. The ISS is part of the Trauma Severity Injury Scale (TRISS) methodology, whereas the first three components of the AP are included in the ASCOT (A New Severity Characterization Of Trauma) [51]. In the first comparison, the ASCOT performance was better than that of TRISS for penetrating injuries. Subsequently, Markle et al. observed that ASCOT performed better in patients with multiple blunt injuries in a single body region [52]. In a more recent study, the Major Trauma Outcome Study group used the AIS-90 and concluded that ASCOT was a better overall predictor of outcome than TRISS [53]. In contrast, Osler used the AIS-90 version and found no significant differences between ASCOT and TRISS [54]. The American Association for the Surgery of Trauma is currently leading an international group in developing an improved ISS.

Acknowledging its limitations, we and others have found the ISS to be a good predictor of postinjury MOF [15, 16]. Additionally, investigators have consistently found the ISS to be associated with ARDS [20, 22, 31]. In fact, Roumen et al. found the association between ISS and ARDS stronger than the association between standard physiologic severity scores (e.g., Trauma Score and APACHE II) and ARDS [22].

For convenience purposes the Glasgow Coma Scale (GCS) is discussed under the heading of tissue injury indicators, but in fact this index measures functional impairment of the central nervous system [55]. It is not surprising that the GCS is a strong predictor of postinjury death, as 50% of the traumatic deaths are due to brain injury [21, 56, 57]. In the Vassar et al. study in ICU trauma patients, the GCS explained 75% of the predictive power of the APACHE II and of their 24-ICU point system, using death as the endpoint [21]. As expected, both systems performed considerably better in patients with isolated brain injury than in those without brain injury. Siegel et al. found the GCS to be one of the most powerful predictors of death for patients with major hepatic blunt injuries in whom associated brain injury was one of the most important determinants of death [58]. It is of interest that Genarelli and coworkers recently found that the GCS predicts mortality for extracranially injured patients as well as for the head-injured population (T.A. Genarelli, personal communication).

Although the GCS appears to be a powerful independent predictor of brain injury fatalities, most investigators have found no association between head injury and ARDS [20, 29] or MOF [2, 15]. Hebert et al., however, found a GCS score of < 8 to be an independent predictor of postinjury MOF [24]. It should be noted that these authors used the worst MOF score during admission as an endpoint, which in fact may represent an elaborate description of death. In contrast, in our experience, a GCS score of < 8 was not associated with MOF, either univariately or after adjustment for confounders [15]. Potential drawbacks of the GCS include the

Table 2. Predictors of multiple- and single organ failure (MOF, OF), ARDS, and intensive care unit (ICU) mortality in trauma patients.

Reference	Population	Outcome	Predictors	Comments
[29]	399 critically ill patients (~70% trauma, 7% blunt)	ARDS	Univariate: age, sepsis, shock, massive fluid therapy, multiple trauma, chest injury; Stratified: sepsis	Power <50% to test sepsis independent effect of shock/massive fluid therapy.
[30]	78 mechanically ventilated patients (100% trauma, 7% blunt)	ARDS	Early ARDS: shock, chest injury; Late ARDS: sepsis	First description of one- and two-hit models
[31]	136 patients at risk for ARDS (65% trauma, 7% blunt)	ARDS	Trauma patients: ISS, no. of risk factors present	Major risk factors: sepsis, aspiration, lung contusion, blood transfusions
[3]	433 critically ill patients (100% trauma, ~100% blunt)	MOF	Shock indicators, sepsis, errors in treatment	Mean age of MOF > whole group
[32]	132 critically ill patients (100% trauma, 100% blunt)	ARDS	ISS, early fracture stabilization, nervous system injury (the Hospital Trauma Index)	Predictors derived by MLR. Early fracture stabilization = lower risk for ARDS
[33]	191 ICU patients (100% trauma, 79% blunt)	Death	ISS, age, shock (presence and length)	No adjustment for confounders
[34]	51 trauma patients with ISS>=20 (100% trauma, 7% blunt)	Death, infection	Death: %LD50 of the ISS (adjusted for age), high degree of wound contamination	No difference in ISS, but ISS adjusted for age was a predictor of death
[25]	195 ICU patients (68% trauma, 62% blunt)	OF	Trauma: ventilator days, blood products/day	MOF mortality and incidence: Nontrauma > trauma
[35]	39 ICU patients (100% trauma, 83% blunt)	MOF	Univariate = 0, 12, 24hs VO_2; 12h lactate, Multivariate = 12h VO_2, 12h lactate	Potential predictors chosen by clinical judgement and tested by MLR
[12]	100 critically ill patients (100% trauma, 100% blunt)	Death; OF	OF: elastase, neopterin, C-reactive protein, lactate, antithrombin III, phospholipase A	Infection preceded/concided with OF in late OF, followed in early OF
[21]	1000 ICU patients (100% trauma, 77% blunt)	Death	GCS, PaO_2 FiO_2, 24 h ICU fluid balance	Predictors chosen by MLR in a pilot study. Better performance in brain injury
[16]	206 ICU patients (100% trauma, 60% blunt)	MOF, Death	MOF: age, comorbid conditions, malnutrition, ISS, admission GCS <8, H2-blockers/antacids, number U blood, IAA; Death: Age, comorbid conditions, ISS, H2-blocker/antacid, MOF score	Predictors derived by stepwise multiple linear regression for MOF (worst score during admission), and MLR for death
[22]	56 ICU patients (100% trauma, 100% blunt)	ARDS, MOF	ARDS = ISS MOF = lactate at day 3; SSS	Predictors derived by MLR. SSS is actually a description of MOF
[36]	428 ICU patients (100% trauma, 7% blunt)	Death	Univariate: Trauma Score, ISS, APACHE II Discriminant analysis: APACHE II	None of de models explained >50% of the total variance
[15]	394 ICU patients (100% trauma, 77% blunt)	MOF	Age >55 yrs, ISS >=25, shock indicators (>6 U RBC/12 hrs, base deficit, lactate)	Predictors derived by MLR
[20]	695 ICU patients (39% trauma, 7% blunt)	ARDS	Trauma: age>=70 yrs, female gender, APACHE II >=20, ISS>=20, sepsis	Predictors derived by Cox proportional hazards model, significance level <0.10
[37]	56 ICU patients (100% trauma, 100% blunt)	MOF	Complement activation and elastase were early predictors	Predictors not adjusted for confounders
[38]	351 patients at risk for ARDS (50% trauma, 59% blunt)	ARDS	Trauma: APACHE II >=16 (calculated upon meeting an at risk diagnosis)	Predictor derived by MLR

RBC, red blood cells; U, units; MLR, multiple logistic regression; VO_2, oxygen consumption index; GCS, Glasgow Coma Scale; ISS, Injury Severity Score; IAA, intra-abdominal abscess; SSS, Sepsis Severity Score.

confounding effect of shock, which causes both coma and MOF, and its unreliability in the presence of substance abuse, sedation, intubation, and paralyzing agents. Moreover, studies that include head injury patients may be contaminated by the inadvertent inclusion of neurogenic lung edema.

Clinical Signs of Shock

Shock has been consistently associated with ARDS, MOF, and ICU death (Tables 2, 3) [58, 59]. The best physiologic definition of shock is oxygen consumption (VO_2) inadequate to meet peripheral tissue oxygen demands. Several studies have shown that low VO_2 early after injury (trauma and nontrauma) predicts both organ failure and ICU death [35, 60, 61]. It appears that a low VO_2 is the result of not being able to achieve an early hyperdynamic state (cardiac index > 4.5 $L/min \cdot m^2$); thus patients destined for MOF have an early unrecognized peripheral perfusion deficit [35, 62]. This finding is supported by studies using gastric tonometry, which have consistently shown that an uncorrected low gastric intramucosal pH (reflecting splanchnic hypoperfusion), despite otherwise normal hemodynamic variables, predicts MOF and ICU death [63, 64].

These indicators of shock perform well in predicting adverse outcome but are not practical because they require advanced monitoring techniques, which are not available or feasible in all patients. Unfortunately, routinely monitored clinical variables

Table 3. Predictive models for mortality in intensive care unit populations, which quantify the systemic inflammatory response syndrome (SIRS).

Reference	Study	Population	Outcome	Predictors	Comments
Knaus et al, (Crit Care Med, 1981) [39]	APACHE	805 mixed ICU patients	Death	APS: 34 variables (1st 24hrs in ICU) + age, sex, operative status, pre-admission status, principal physiologic system	Predictors chosen by panel of experts; APS validated in mixed populations with good results
Knaus et al (Crit Care med, 1985) [40]	APACHE II	5815 mixed ICU patients; 785 CABG	Death	12 variables from original APS (first 24 hrs in ICU) + age + chronic health status + operative status + disease category	Predictors chosen based on clinical judgement + maintenance of good prediction. Validations in trauma patients with mixed results
Knaus et al (Chest, 1991) [41]	APACHE III	17,440 mixed ICU patients	Death	APS with 17 variables + age + comorbid conditions + operative status + disease category + location prior to ICU	Predictors chosen based on clinical judgement. Used a validation sample, where the APS performed well. Trauma patients = 8% of sample (9% mortality, of which 85% were head injuries)
LeGall et al (Crit Care Med, 1984) [42]	SAPS	679 ICU mixed patients, 40% surgical	Death	13 variables from APS (first 24 hrs in ICU) + age	Predictors chosen by discriminant analysis and availability
LeGall et al (JAMA, 1993) [43]	SAPS II	13,152 mixed ICU patients	Death	Age + 12 physiologic variables + chronic diseases + type of admission	Predictors/weights chosen by univariate. LOWESS, MLR
Lemeshow et al (Crit Care Med, 1985) [44]	MPMs	743 mixed ICU patients 1988:	Death	Level of consciousness, type of admission, cancer, number OF on admission, age, SBP (ICU admission) + Infection, FIO_2, shock (first 24 hrs in ICU)	Predictors chosen by stepwise linear discriminant function, weights derived by MLR. Two models: admission and first 24 hrs. Validated with good results
Lemeshow et al (Crit Care Med, 1988) [45]	MPMs	2,644 mixed ICU patients	Death	Level of consciousness, type of admission, CPR prior to ICU, cancer, chronic renal failure, infection, age, prior ICU admission, heart rate on ICU admission, surgical procedure at ICU admission. SBP (ICU admission) + shock, 5 physiologic variables, hours on ventilator, number of "lines" (first 24 hrs in ICU)	Predictors chosen by discriminant function and MLR analysis. Three models: admission, first 24 hrs (shown), first 48 hrs (not shown). Modification of original MPM.
Lemeshow et al (Yearbook of Intensive Care and Emergency Medicine, 1994) [46]	MPM II	19,124 mixed ICU patients	Death	Age, level of consciousness, chronic diagnoses, acute diagnoses, CPR prior to ICU, MV, type of admission (surgical vs non) + 4 physiologic variables, infection, IV vasoactive drug (first 24 hours)	Predictors chosen by discriminant function and MLR analysis. Modification of original MPMs. Four models: admission, first 24 hours (shown), first 48 hours, first 72 hours (not shown)

ICU, intensive care unit; APS, Acute Physiology Score; CABG, coronary artery bypass graft; LOWESS, locally weighted least squares; MPM, mortality prediction model; MLR, multiple logistic regression; OF, organ failure; SBP, systolic blood pressure; MV, mechanical ventilation.

(e.g., systolic blood pressure, pulse rate, urine output, and respiratory rate) have poor discriminatory power [60]. The common laboratory measurements of base deficit and lactate concentration appear to be good indicators of shock. Both correlate well with death and MOF [12, 15, 22, 35, 58, 59, 65]. In our predictive models, after adjustment for other shock indicators, injury severity, and other covariates, we have found that early base deficit (0–12 hours after emergency room admission) predicted postinjury MOF, but the later base deficit (13–24 hours) did not. The reverse was true for lactate levels (i.e., the 13- to 24-hour lactate levels were associated with MOF, but earlier levels were not) [15]. It may be due to selection bias, as lactate determination is generally reserved for more severely injured patients [15], or it may be due to the sodium bicarbonate administered during later phases of resuscitation of patients with severe shock.

Another potential indicator of shock is early blood transfusion requirement, which has been consistently shown to be an important risk factor for ARDS [38] and MOF (Table 2). In our experience, after adjustment for other indicators of shock, blood transfusions were independently associated with MOF [15]. The requirement of > 6 units within the first 12 hours of admission was associated with a ninefold increase in the likelihood of developing MOF (95% CI: 4.2–17.7). This variable retained a high predictive power in subsets analysis, reinforcing the case for causation [66]. Tran et al., studying a similar population, found comparable results [16].

Blood transfusion requirement appears to be a good predictor of ARDS and MOF, but its role as an indicator of shock imposes some difficulties: (1) indications for transfusions vary across trauma services; (2) allogenic blood products have been impli-

cated as a direct cause of ARDS; and (3) blood transfusions have potentially immunosuppressive effects predisposing to infections, which are a recognized risk factor for MOF [67–69].

Systemic Inflammatory Response Syndrome

Systemic inflammatory response syndrome (SIRS) is a term coined to describe a "generic" inflammatory response triggered by a variety of infectious and noninfectious events [17]. SIRS is defined by the presence of two or more of the following signs: (1) body temperature $> 38°C$ or $< 36°C$; (2) heart rate > 90 bpm; (3) respiratory rate > 20 rpm or $PaCO_2 < 32$ mmHg; and (4) WBC $> 12{,}000/mm^3$ or $< 4000/mm^3$ or "bands" $> 10\%$. We believe this term is a step forward; however, SIRS, as defined, appears to be too sensitive to function as a predictor of MOF. For example, in the first article by Bone et al., reporting on 519 ICU admissions with a primary diagnosis of sepsis, 503 (97%) fit the criteria for SIRS [17]. SIRS did not discriminate between high and low mortality risk as estimated by the APACHE III method [70]. Rangel-Frausto et al. found that 68% of all ICU and general ward admissions fit the definition of SIRS [71]. The incidence of ARDS in these patients was low, varying according to the number of SIRS criteria. Later, Bone divided SIRS into "severe" versus "nonsevere," where "severe" was defined as SIRS associated with organ dysfunction, hypoperfusion abnormality (lactic acidosis, oliguria, or an acute alteration in mental status), or inflammation-induced hypotension [72]. These criteria clearly overlap with the current definitions of MOF, thereby invalidating use of this classification as a predictor for this outcome.

A variety of predictive models quantify the early host response and are alternative ways to quantitate SIRS. Some were developed specifically for trauma patients (Table 2), whereas others were based on mixed ICU populations (Table 3). The APACHE system is most commonly employed. In brief, the APACHE system, described in 1981, included the Acute Physiology Score (APS: worst value obtained during the first 24 hours of the ICU admission based on 34 physiologic variables), host factors (age, preadmission health status, sex), and factors related to the principal diagnosis (operative status, principal physiologic system) [39]. In a revision (APACHE II), the authors reduced the number of the APS variables to 12, restricted comorbid conditions to those related to the most severe chronic organ insufficiencies or immunocompromised state, and derived coefficients for specific disease categories [40]. APACHE II performed reasonably well in mixed ICU populations but had limited success as a predictor of ICU death or MOF in trauma patients [21, 22, 36, 59, 73]. APACHE II has several potential limitations for trauma patients. First, the GCS, a powerful predictive component of the APS, was not intended for extracranial injuries. Second, comorbid conditions are less frequent in trauma patients [15, 21, 22]. A third potential drawback is the lead time or pretreatment bias. By using only ICU data and not acknowledging prior treatment, APACHE II underestimates mortality in patients transferred to the ICU after relative stabilization [74], which is often the case with trauma patients. Finally, trauma constituted only 8% of the APACHE database, with a 9% case-fatality rate of which 85% were due to head trauma.

A third version (APACHE III), published in 1991, has addressed these issues [41]. The most important changes include (1) modification of the APS to include 17 variables; (2) comorbid conditions limited to those that affect immune function; (3) specific equations for 78 major disease categories, including operative and nonoperative head and multiple trauma; (4) a refinement of the distinction between head and nonhead trauma; and (5) prior location of the patient to minimize lead-time bias. So far, the APACHE III has not been independently validated in trauma patients. We are currently collecting ICU data to test the predictability of APACHE III in trauma patients, and we are obtaining the APS data prior to ICU admission to determine if it can improve APACHE III performance. Zimmerman et al. review their use of APACHE III in this issue of *World Journal of Surgery*.

Other models have been developed. The Simplified Acute Physiology Score (SAPS) and the Mortality Prediction Model (MPM) appear to be the most competitive [42–46]. The SAPS and MPM systems have been customized for use in patients with early, severe sepsis; but neither has been tested in trauma patients [75].

Finally, as we better understand the deleterious components of SIRS that cause MOF, we may be able to develop specific laboratory assays to predict MOF early after injury. For example, evidence of neutrophil priming and activation (e.g., elastase levels, in vitro neutrophil superoxide release), complement activation indicators (terminal complement complex, C4a and C3a), cytokine elaboration (e.g., interleukins 6 and 8), arachidonic acid breakdown (thromboxane B_2, platelet-activating factor), and endothelial cell activation (soluble ICAM) were early predictors of ARDS and MOF in small groups of selected trauma patients [12, 14, 37, 76]. High levels of these mediators, however, may simply represent an epiphenomenon due to massive trauma. Thus assessment of causation is difficult. Also, there is controversy about the methodology to measure these variables [77]. Currently, these investigations provide valuable insight into the potential deleterious mechanisms of SIRS that induce MOF. Testing in large groups of patients, with adjustment for injury severity and shock, is needed to improve predictive capabilities.

Potential Confounders and Effect Modifiers

Controlling for confounding factors and detecting effect modification are two major concerns when developing epidemiologic studies. A *confounding variable* is a factor causally related to the outcome and associated with the exposure; it is not a consequence of the exposure. Confounding variables distort the association between the variables of interest, forging an apparent, but false, causal relation (i.e., the confounding triangle). For example, in the relation of injury severity and MOF, comorbid or preexisting conditions can confound that association; that is, comorbid conditions may potentially influence injury severity and affect physiologic reserve, placing the patient at risk for MOF. Avoiding or removing confounding is therefore desirable and can be achieved in the study design by matching, restricting (e.g., excluding individuals with comorbid conditions), or randomizing. Confounding can also be controlled *a posteriori*, during the analysis by restriction, stratification, or multivariate methods [66, 78]. Confounding can then be inferred by comparing the discrepancy between the crude estimate of effect and the estimate obtained after the confounding factor was removed. The extent of confounding can be evaluated based on investigator judgment and previous research but not on statistical significance. It is important to note the difference between statistical significance and clinical

significance. Statistical significance (p value) serves to control random error (chance), not systematic error (confounding, systematic bias). In other words, a clinically irrelevant small difference may become statistically significant ($p < 0.05$) simply because of a large sample size, whereas a clinically relevant association may turn out to be statistically nonsignificant because of a small sample size. Thus the sole use of statistical significance to assess confounding, although commonly done, is inappropriate [78, 79].

Effect modification (epidemiologic term) or *interaction* (statistical term) refers to a change in the magnitude of the association between the causal agent and the outcome according to the level(s) of a third variable. It does not represent a distortion of the causal association; rather, it represents an elaborate description of the effect itself. Therefore it should be evaluated and described, not controlled or removed [78]. For example, Henao et al. reported that there was an apparent interaction between shock and sepsis in the risk analysis for MOF; that is, the odds ratio changed from 84 when both shock and sepsis were present to 7.2 and 4.4 when only shock or sepsis, respectively, was present [80].

Age

Virtually every model used to predict death in the ICU (Tables 1, 2) is adjusted for age. Likewise, for ARDS and MOF most investigators have found age to be an important confounder, particularly among trauma patients [15, 16, 20, 80]. In addition to its effect as a confounder, age may play a role in modifying the effect of injury severity on the incidence of MOF. Goris et al., comparing nontrauma surgical patients and trauma patients, showed that the mean number of organ failures was directly proportional to age in the surgical patients [4]. Among trauma patients, however, this relation was U-shaped owing to the distribution of the ISS over age groups; that is, older patients, despite lower ISSs, had a higher mean number of organ failures than the young patients. The mortality analysis for these patients exhibited a similar quadratic (U-shape) function.

Comorbid Conditions

For a detailed description of the role of premorbid conditions, readers are referred to the excellent overview by Milzman et al. [81]. In our experience with trauma patients, we did not find comorbid disease to be independently associated with MOF after controlling for the effect of age [15]. However, the prevalence of those conditions among our trauma patients was low (7%), and a type II error was likely. Preexisting diseases seem to exert their influence in selective populations as a function of the incidence or the impact of the disease that caused the ICU admission. For example, the APACHE analysis found that comorbid conditions did not increase the explanatory power for elective postoperative patients [40, 41]. Trauma patients, in general, have a low prevalence of preexisting conditions (ranging from 7% to 19%) [15, 81, 82]; but among older trauma victims (> 70 years) the incidence can be as high as 50% [83]. This situation could confound the association between advanced age and mortality, although premorbid conditions have been shown to increase trauma mortality independent of age and injury severity [81]. This association seems to be stronger among young and less severely injured patients, suggesting an interaction between these variables [81].

An interesting, often ignored aspect of comorbid conditions is substance abuse. Studies on the effects of acute alcoholism on mortality have been inconsistent [81], although Herve et al. [84] and Jurkovich et al. [85] both found chronic alcohol abuse to be associated with higher mortality among trauma patients. We and others have found no independent effect of chronic alcohol abuse on postinjury ARDS, and we have not been able to establish an independent effect on postinjury MOF [38].

Injury Mechanism and Pattern of Injury

The injury mechanism (i.e., blunt versus penetrating) is another potential confounder, having an important role in injury severity [86], limitation of the physiologic response (e.g., pulmonary and myocardial contusion by blunt trauma), and infections (e.g., penetrating trauma with bowel perforation and secondary intraabdominal infection), which are highly related to the development of MOF [87]. There are also differences in the clinical course of head versus torso injuries with respect to MOF, infections, and death [15, 21]. The analysis of the Major Trauma Outcome Study demonstrated that head injuries increase morbidity (as quantified by the percentage of patients who are discharged home) and mortality than do extracranial injuries, regardless of the mechanism [88].

Future Plans

Based on our global hypothesis (Fig. 1) and the conceptual framework of early SIRS-related MOF (Fig. 2) our trauma center is investigating potential mediators of SIRS responsible for end-organ dysfunction as well as methods to modulate them favorably. Clinically, our first goal is to develop early predictive models for MOF [15]. To date, these models have permitted more focused observational studies [9, 35, 76], and in the future it should allow early stratification of high risk patients for inclusion in new interventional trials. We will also evaluate the severity of SIRS and better characterize its priming stage to define the earliest predictive model. We have chosen trauma patients because they exhibit a low incidence of common confounders, such as age and comorbid conditions. Moreover, use of this population permits clearer distinction between the first insult and the outcome MOF, both temporally and in regard to the definition criteria. Currently, our database contains more than 500 patients who were followed prospectively, of whom 13% developed MOF. With an additional 100 patients, the sample size should be appropriate to derive and validate predictive models to be employed at admission and at 12 hours and 24 hours after injury. These models can be used to clarify the best window for interventions aimed at modulating dysfunctional inflammation. As Baue thoughtfully pointed out when our group presented a study on early predictors for postinjury MOF in 1993, "predictors are useful only if they suggest therapeutic intervention."

Résumé

Au début de notre expérience, des études épidémiologiques, basées sur des populations hétérogènes combinées avec des contrôles insuffisants, ont amené les investigateurs à l'époque à conclure que l'infection était le facteur principal de la survenue du syndrome de défaillance polyviscérale (multiple organ failure = MOF). Des études plus récentes ont démontré que le MOF peut

survenir en l'absence d'infection. Par conséquent, notre modèle d'étude expérimental traditionnel, infectieux, s'est peu à peu transformé en un modèle plus moderne, « inflammatoire », dit en « un » ou en « deux » coups. En clinique, nous étudions les patients atteints d'un traumatisme, car il s'agit là d'un groupe de patients relativement homogène avec une incidence assez faible de facteurs de risque. Le modèle traumatique permet également de bien définir le moment exact de l'agression initiale et le délai entre cet événement et la survenue du MOF ainsi que son évolution. Dans cette revue, nous envisageons le pourquoi du problème, les résultats et les raisons de l'utilisation pour prédire la survenue du MOF post-traumatique précoce de facteurs prédictifs d'une part de l'agression initiale (c'est-à-dire la quantification des lésions tissulaires et des signes cliniques de choc) et d'autre part, les indicateurs de la réponse de l'hôte, c'est-à-dire le syndrome de réponse inflammatoire systémique, ou le « SIRS ».

Resumen

Estudios epidemiològicos basados en informaciòn retrospectiva y controles inadecuados de poblaciones heterogèneas, llevaron a la conclusiòn de que la infecciòn era el factor de riesgo preponderante en la falla orgànica mùltiple. Estudios recientes han de mostrado convincentemente que el sìndrome frecuentemente ocurre en ausencia de infecciòn. Por consiguiente, hemos modificado el enfoque de nuestra investigaciòn apartàndonos de los tradicionales modelos infecciosos del sìndrome hacia los nuevos modelos in flamatorios. Desde el punto de vista clìnico, hemos escogido el estudio de los pacientes traumatizados, por cuanto ellos representan un grupo relativamente homogèneo con una baja incidencia de factores comunes. El trauma tambièn permite una clara distinci òn entre la injuria primariay el resultado final, tanto temporalmente como en relaciòn con los criterios de definiciòn. En la presente revisiòn discutimos los antecedentes, la racionalizaciòn y nuestros intentos iniciales para usar indicadores de la primera injuria (o sea cuantificaciòn de la lesiòn tisular y signos clìnicos de shock) e indicadores de la respuesta de huèsped, o sea el sìndrome de respuesta inflamatoria sistèmica para predecir falla orgànica mùltiple en la fase postraumàtica temprana.

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