A 12-Year Prospective Study of Postinjury Multiple Organ Failure

Has Anything Changed?

David J. Ciesla, MD; Ernest E. Moore, MD; Jeffrey L. Johnson, MD; Jon M. Burch, MD; Clay C. Cothren, MD; Angela Sauaia, MD, PhD

Hypothesis: The incidence and severity of postinjury multiple organ failure (MOF) has decreased over the last decade.


Setting: Regional academic level I trauma center.

Patients: One thousand three hundred forty-four trauma patients at risk for postinjury MOF. Inclusion criteria were aged older than 15 years, admission to the trauma intensive care unit, an Injury Severity Score higher than 15, and survival for more than 48 hours after injury. Isolated head injuries were excluded from this study. Previously identified risk factors for postinjury MOF were age, Injury Severity Score, and receiving a blood transfusion within 12 hours of injury.

Main Outcome Measures: Multiple organ failure was defined by a Denver MOF score of 4 or more for longer than 48 hours after injury. Multiple organ failure severity was defined by the maximum daily MOF score and the number of MOF free days within the first 28 postinjury days.

Results: Multiple organ failure was diagnosed in 339 (25%) of 1244 patients. The mean age and Injury Severity Scores increased and the use of blood transfusion during resuscitation decreased over the 12-year study period. After adjusting for age, injury severity, and amount of blood transfused during resuscitation, there was a decreased incidence of MOF over the study period. Of the patients who developed MOF, there was a decrease in disease severity and duration as measured by the maximum daily MOF score and the MOF free days. Although the overall mortality rate remained constant, the MOF-specific mortality decreased.

Conclusions: The incidence, severity, and attendant mortality of postinjury MOF decreased over the last 12 years despite an increased MOF risk. Improvements in MOF outcomes can be attributed to improvements in trauma and critical care and are associated with decreased use of blood transfusion during resuscitation.

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MULTIPLE ORGAN FAILURE (MOF) remains a major source of postinjury morbidity and the leading cause of in-hospital mortality despite more than 25 years of intense investigation.1,2 The current pathophysiologic model of MOF focuses on uncontrolled systemic hyperinflammation as a unifying concept following a variety of insults.3-5 Thus, therapeutic strategies aimed at decreasing postinjury morbidity have targeted systemic hyperinflammation as a means to control associated organ dysfunction and progression to organ failure. Examples include damage control surgery, recognition of abdominal compartment syndrome, lung protective ventilation strategies, and tight glucose level control.6-9 The incidence of postinjury MOF has been reported to be between 7% and 66% with an associated mortality rate between 31% and 80%.10-14 It has been suggested that MOF is disappearing owing to advances in trauma and critical care;15 however, recent reports have not demonstrated a consistent change in either the incidence or the mortality rate associated with postinjury MOF. Some groups have reported no change in the incidence but a decreased mortality13 while others have reported both decreased incidence and mortality compared with historical control subjects.16,17 The disparity reported in the literature is in part owing to different populations studied in relatively short study intervals. Consequently, an accurate estimation of the current risk of postinjury MOF and a description of clinical outcome remains to be established.
In 1987, we developed an MOF scale as a descriptive end point for clinical studies. Since 1992, we have prospectively collected clinical data on patients at risk for postinjury MOF for the first 28 postinjury days. We designed this study to characterize the changes in postinjury MOF presentation, risk factors, and clinical outcome in a homogeneous trauma population over time. We hypothesized that the incidence and severity of postinjury MOF has decreased over the last decade as a result of advances in trauma and critical care.

### METHODS

Trauma patients admitted to the Rocky Mountain Regional Trauma Center’s surgical intensive care unit (ICU), Denver Health Medical Center, Denver, Colo, were studied prospectively from May 10, 1992, until December 31, 2003. The Denver Health Medical Center is a state-designated level I trauma center verified by the American College of Surgeons’ Committee on Trauma. Inclusion criteria were an Injury Severity Score exceeded 15, survival for longer than 48 hours after injury, admission to the surgical ICU within 24 hours of injury, and aged 15 years or older. Patients with isolated head injuries and head injuries with an external or extremity Abbreviated Injury Score exceeding 15, survival for longer than 48 hours after injury, or transfer to a non-ICU acute care facility. Multiple organ failure-related mortality was defined as the number of patients with MOF who died while MOF-specific mortality was defined as those whose cause of death was attributable to MOF. Cause of death was determined from the patient’s medical record and death certificate.

Statistical analyses were performed using SAS for Windows (SAS Institute, Cary, NC). Categorical variables were analyzed using a chi-square test with the Yates correction for continuity or the Fisher exact test when expected cell values were less than 5. For continuous variables with normal distribution, analysis of variance, or t-tests (with the appropriate Welch modification when the assumption of equal variances did not hold) were used. Multivariate analyses were performed using logistic regression for categorical outcome variables and standard linear regression for continuous numeric variables. Study year was used as an independent variable to examine the changes in outcome variables over time with 1992 defined as year 1. Continuous data are reported as mean±SD unless otherwise noted. P<.05 was considered statistically significant.

### RESULTS

Data were collected on 1344 severely injured patients over a 12-year period ending December 31, 2003. The distribution of patients with and without MOF according to study year is shown in Figure 1. Most (975 [73%]) were male, and the mean age was 37.5±16.3 years (Figure 2). Blunt, penetrating, and mixed mechanisms accounted for 1013 (75%), 235 (17%), and 96 (7%) injuries, respectively, with an overall mean Injury Severity Score (ISS) of 29.3±11.2 (Figure 3). Multiple organ failure developed in 339 patients (25%), 112 (8%) died. Ninety (26%)
of 342 patients in whom MOF developed died. The unadjusted incidence of MOF and mortality did not change over the study period ($P = .32$ and $P = .45$, respectively) (Figure 4).

Changes in previously identified MOF risk factors (age $>55$ years, ISS $>24$, and $>6$ U of red blood cells transfused within 12 hours of injury) were examined over the study period.\(^{19,22,23}\) There was a significant increase in both the annual mean age ($\beta = .33, P = .01$) and the proportion of at-risk patients older than 55 years (odds ratio [OR], 1.06; 95% confidence interval [CI], 1.01-1.11; $P = .01$) during the study period (Figure 5). Similarly, there was a significant increase in the annual mean ISS ($\beta = .58, P < .001$) and the proportion of patients with an ISS higher than 24 (OR, 1.11; 95% CI, 1.07-1.14; $P < .001$; Figure 6). In contrast, the annual mean number of 12-hour blood
transfusions decreased ($\beta = -0.14; P = 0.049$) as did the proportion of patients who received more than 6 U of blood within 12 hours of injury (OR, 0.96; 95% CI, 0.92-0.99; $P = 0.04$; **Figure 7**). The decrease in blood use over time remained statistically significant after adjusting for age and ISS (mean number of units 12-hour red blood cells; $\beta = -0.20; P = 0.006$, >6 U of red blood cells in 12 hours: OR, 0.94; 95% CI, 0.90-0.98; $P = 0.003$). Indeed, after adjusting for age and ISS, the patients admitted in 1992 were 1.5 times more likely to receive more than 6 U of red blood cells within the first 12 hours after injury than the patients admitted in 2002.

After adjusting for these risk factors, we found there was a significant decrease in the incidence of MOF. The results of the multiple logistic regression adjusting MOF incidence for age, ISS, and 12-hour blood transfusion after injury (as continuous or categorical values) is given in **Table 2**. Regardless of the confounding variable formats, MOF incidence in 1992 was almost twice (OR per 10 years = 1.8) the rate observed after 2002. The goodness-of-fit of the models using continuous and categorical formats was similar with a slight advantage for the continuous variables model. Although the interaction between SS and time was not significant ($P = 0.12$), the time reduction seemed to be more pronounced among patients with an ISS higher than 40 after adjusting for patient age and blood transfusion received during resuscitation (**Figure 8**).

Next we compared the ORs associated with the risk factors we previously identified for postinjury MOF in the first 12 hours after injury in the first 5 years with the association observed in the second half of the study period (**Table 3**). All factors remained highly predictive of MOF, but the association between an ISS greater than 24 and MOF became less strong in the second half, further suggesting that the effect of injury severity on the development of MOF decreased over time.

The degree of postinjury MOF was assessed by examining the maximum daily MOF score and the number of MOF free days in the first 28 days after injury. Among the patients with MOF, there was a significant decrease in the annual maximum daily MOF score ($\beta = -1.5$, $P < 0.001$) after adjusting for patient age, ISS, and amount of red blood transfused during resuscitation (**Figure 9**). There was also a significant increase in the annual MOF free days ($\beta = -0.04$, $P = 0.006$) after adjusting for age, ISS, and 12-hour RBC transfusion (**Figure 10**). The surgical ICU length of stay among patients with MOF did not change over time after adjusting for age, ISS, death, and the presence of a head injury ($\beta = 0.49$, $P = 0.08$).

Finally, MOF as a cause of death was examined over the study period. Overall, 112 of 1244 patients died (mortality rate 8%) and 90 of 339 MOF patients died (MOF-related mortality rate, 27%). Of the 112 patients who died, 57 patients (31%) died of MOF, 26 (23%) died of severe head injury, 25 (22%) had care withdrawn, and 4 (4%) died of other causes (2 of pulmonary embolus, 1 of acute myocardial hemorrhage, and 1 of a bleeding gastric ulcer). The overall and MOF-related mortality rates did not

**Figure 6.** Injury Severity Score (ISS) and proportion of patients with an ISS exceeding 24. A, The mean ISS (mean±SEM) of patients at risk for postinjury multiple organ failure. B, Proportion of patients with an ISS exceeding 24. A, The mean ISS (mean±SEM) of patients at risk for postinjury multiple organ failure. B, Proportion of patients with an ISS exceeding 24.

**Figure 7.** Mean age and proportion of patients older than 55 years increased over the study period. A, Total number (mean±SEM) of red blood cells transfused within 12 hours (RBC12) of injury in patients at risk for postinjury multiple organ failure. B, Proportion of patients who received more than 6 U of RBC12.
change over the study period even after adjusting for patient age, ISS, 12-hour red blood cell transfusion after injury, mechanism, and the presence of head injury. However, the annual proportion of patients who died of MOF decreased significantly (Figure 11) after adjusting for age, ISS, 12-hour red blood cell transfusion after injury, mechanism of injury, and the presence of head injury (OR, 0.90; 95% CI, 0.83-0.97; P = .001).

Disparities in study design have made interpretation of the postinjury MOF literature difficult with respect to changes in MOF presentation and outcome over time. In 1987, we developed an MOF scale to characterize organ dysfunction following injury.17 This scale was used consistently throughout this study period and has been used to identify risk factors and develop predictive models of postinjury MOF.18,19,24 We enrolled patients at risk for postinjury MOF into this prospective study since 1992. In concert with other studies, we found that most patients in this population were male (73%) victims of blunt trauma (83%). Our study population limited to those patients with an ISS exceeding 15 demonstrated an overall MOF incidence (25%), mortality rate (8%), and MOF-related mortality rate (26%).

The present study has confirmed that age, injury severity, and the use of blood transfusion during resuscitation are significant risk factors for postinjury MOF. Over the 12-year study period, we found an increase in both patient age and injury severity. The increase in age is expected considering the aging of the US population and projected change in the general surgery patient population.25,26 The increase in injury severity may be explained by our ongoing efforts to serve as the Rocky Mountain Regional Trauma Center. As a result, our hospital has experienced an increased number of trauma admissions over the past several years.27 Increases in both age and injury severity would be expected to be associated

### Table 2. Multiple Logistic Regression of Multiple Organ Failure Incidence for Age, Injury Severity Score, and 12-Hour Red Blood Cell Transfusion

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Parameter Estimate</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>-3.8108</td>
<td>NA</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Year</td>
<td>-0.057</td>
<td>0.945 (0.907 to 0.984)</td>
<td>.006</td>
</tr>
<tr>
<td>Age</td>
<td>0.0323</td>
<td>1.033 (1.025 to 1.041)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ISS</td>
<td>0.0495</td>
<td>1.051 (1.038 to 1.064)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>12-h RBC transfusion</td>
<td>0.0667</td>
<td>1.069 (1.053 to 1.086)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

### Table 3. Risk Factors for Postinjury Multiple Organ Failure (MOF) in the First 12 Hours After Injury in Each 5 Years of the Study

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Parameter Estimate</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1992-1996</td>
<td>-2.387</td>
<td>0.085 (0.047 to 0.159)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age &gt;55 y</td>
<td>1.128</td>
<td>3.09 (1.63 to 5.852)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ISS ≥25</td>
<td>1.015</td>
<td>2.76 (1.69 to 4.50)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>12-h RBC transfusion &gt;6 U</td>
<td>1.285</td>
<td>3.62 (2.28 to 5.72)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>1997-2003</td>
<td>-1.895</td>
<td>0.156 (0.085 to 0.326)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age &gt;55 y</td>
<td>1.059</td>
<td>2.88 (1.93 to 4.31)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ISS ≥25</td>
<td>0.506</td>
<td>1.46 (1.13 to 1.94)</td>
<td>.02</td>
</tr>
<tr>
<td>12-h RBC transfusion &gt;6 U</td>
<td>1.385</td>
<td>4.00 (2.73 to 5.85)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: AIC, Akaike Information Criterion; CI, confidence interval; ISS, Injury Severity Score; NA, not applicable; OR, odds ratio; RBC, red blood cell.
with an increase in the incidence of MOF. In contrast, the use of blood transfusion during resuscitation decreased during the study period. Blood transfusion was recognized as a consistent early risk factor for postinjury MOF independent of other indices of shock in 1997 and has since been reported to be a major contributing factor to worse outcomes in trauma and critical illness. These findings have prompted more judicious use of blood transfusion during resuscitation and in the postresuscitation surgical ICU setting. In this study we found a decrease in both the number of units of blood transfused and the proportion of patients receiving more than 6 U of packed red blood cells during resuscitation. The changes in the risk factor distribution among the at-risk patient population also had an effect on our previously developed predictive model of postinjury MOF. Both age and injury severity had less influence on the conditional probability of developing MOF in the patients admitted in the first half of the study period compared with those admitted during the second. In contrast, the influence of blood transfusion during resuscitation was greater during the second half of the study. These findings further support a change in the presentation of MOF over the last decade and warrant a reevaluation of MOF risk factors in the context of current trauma and surgical ICU care.

The purpose of this study was to characterize the changes in MOF incidence and its risk factors over 12 years using an accepted MOF definition uniformly applied to a homogeneous trauma population. The primary end points of this study were MOF incidence and measures of MOF severity. Although the incidence of MOF in the population as a whole did not change, there was a decreased incidence among the more severely injured after adjusting for age and for receiving a blood transfusion. These findings are encouraging because there appears to be progress in preventing progression of MOF in the population at highest risk. Moreover, indices of MOF severity improved over the study period with a decrease in the maximum daily MOF score and an increase in the number of MOF free days. The overall surgical ICU length of stay and mortality rate did not change which may be reflective of the underlying severity of injury. However, death due to MOF decreased with a commensurate increase in death due to severe head injury or following withdrawal of care. We believe that this represents an improved ability to support patients who would have otherwise succumbed to MOF only to realize the full potential of the underlying injury. Alternatively, this may represent earlier recognition of futile care by both the patient’s representative and the critical care team.

CONCLUSIONS

We have found a decrease in the incidence of postinjury MOF among the most severely injured and an overall improvement in the indices of MOF severity over the last 12 years. Of the risk factors studied, only reduction in blood transfusion during the resuscitation period correlated with improvement in outcome. Several other major advances in trauma and critical care also occurred over the last decade that may have influenced our results. The concept of damage control surgery, which appeared in the late 1980s and matured during the 1990s, is widely accepted and applied in a variety of situations including...
thoracic, abdominal, and vascular injuries, as well as for orthopedic and neurologic trauma. Recognition of abdominal compartment syndrome and decompressive laparotomy also emerged during the 1990s. Improvements in respiratory support such as lung protective ventilation decreased ventilator-induced lung injury and improved outcome following adult respiratory distress syndrome. The use of intensive insulin therapy, described in 2001, was shown to reduce morbidity and mortality in the critically ill including patients with postinjury MOF. More recently, cortisol replacement therapy for acute adrenal insufficiency has been shown to improve the outcome in the critically ill. Each of these advances has influenced our approach to trauma and critical care although the relative effect of any one advance on postinjury MOF outcome awaits further study. Nevertheless, our prospectively collected patient data indicate a substantial reduction in the incidence and severity of MOF following severe injury over the last decade.

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Correspondence: David J. Ciesla, MD, Department Surgery, Denver Health Medical Center, 777 Bannock St, Denver, CO 80204 (David.ciesla@dhha.org).

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DISCUSSION

David Hoyt, MD, San Diego, Calif: Eiseman coined the term multiple organ failure in 1976. It became a household word after Baker and Trunkey’s 1980 paper describing MOF as the third peak in mortality following injury and after Fry’s 1980 description of its relation to sepsis. Over the last 30 years pursuing its cause and pathogenesis has driven surgeons into academic careers and defined our essential role in the critical care of surgical patients.

Many hypotheses have been put forth. Our evolving understanding of the inflammatory response and its association with this lethal complication has dominated the surgical literature, caused the formation of unique surgical organizations and journals, and dominated the target of the NIH [National Institutes of Health] surgical funding at the basic science level.

Moore’s decision to collect a prospective database on patients sustaining MOF was visionary. This commitment has allowed many observations essential to our study of MOF and scores of publications associated with it. From this we have learned that the importance of risk factors as emphasized again today, the differing types of MOF, both early and late, the role of the gut as the essential trigger in its etiology, and a scoring system that has defined outcome measures for clinical trials, most recently used to study the genetic variability of MOF response, one of the largest studies ever funded by NIH. We heard the 10-year follow-up.

I have several questions for the authors: Is an additional interpretation of the data presented possible; that is, did the patients who got MOF early on no longer get it and that a group that you did not see as frequently early on are now getting it? Are young sick patients now cared for better only to be replaced by older sick patients? Could you comment. Would this, in fact, explain the lack of incidence change over time yet the mortality did not change. Would you not expect overall mortality to go down, or was there some other group that had an increase in mortality to balance out the decrease?

Dr Moore: If you stratify by severity of injury, mortality has declined steadily in the patients who have a higher severity of injury.

Basil Pruitt, MD, San Antonio, Tex: I enjoyed that presentation of those tantalizing data. With your database, can you tease out the factors responsible for this; that is, less fluid lung protective ventilation? I should think that would be a top order of business. Does this do anything more than reflect a change in the infecting organisms? You know there are [sic] significant comorbid effect of gram-negative organisms, none for gram-positive organism, so is there a change in your endogenous flora? Lastly, it has been said unkindly that if you torture data sufficiently, it will confess to anything. With the MOF free days graph, it looked like if you eliminated the first and last data point that would be a horizontal line.

Dr Moore: Dr Pruitt has hounded the trauma community about overzealous crystalloid resuscitation and I think he is absolutely correct. I am confident we are going to change the approach to resuscitate critically ill, injured, and burned patients in the next 5 years. The question about the relative propensity of gram-negative vs gram-positive organisms is interesting, particularly in light of the recent characterization of diverse Toll receptors.

Donald Fry, MD, Albuquerque, NM: I enjoyed the presentation from your group as usual, and I think almost one could change the title of the manuscript with reference to the changing face of MOF. The disease is really different now than it was 30 years ago. For example, in ours and in Eiseman’s original report, the issue of stress bleeding from the stomach was a major issue and stress bleeding as a clinical entity in most of the critical care units of the United States to my observation has disappeared. I have also seen this progressive disappearance of the profoundly jaundiced patient. Since you have shown a decreasing number in your MOF score, what are the changes within the composition of the organ failure complex as we are seeing it? I have the sense that ARDS [adult respiratory disease syndrome] is now the dominant player. Is there an increasing percentage of the MOF score that really just comes down to severe respiratory distress and that the other components seem
to be fading out? In our original study of 553 patients, renal failure was the trigger that told us when patients were going to die. Is renal failure the seminal event that predicts the death of these patients or is that no longer valid? Finally, I would amplify what Dr Pruitt asked. You have said nothing in the entire presentation about infection or about nosocomial infection. During this period where you identified improved outcomes in these patients, has the frequency of major infectious events in these patients changed? Does infection have anything to do with organ failure? Do our patients die of infection or are they dying with infection?

Dr Moore: I am glad that Dr Fry has not given up on his focus of infection as a driving force. These are interesting questions to address in our database. The issue about stress gastritis is timely. We have not seen it for decades either, but just 2 days ago a multisystem trauma patient bled massively from classic stress gastritis. The presentation is considerably different when you look at early vs late MOF; late MOF is typically triggered by infection and is associated with more profound renal and hepatic failure. In contrast, early MOF is virtually always precipitated by ARDS.

Gregory Jurkovich, MD, Seattle, Wash: Briefly, can the Denver MOF score be influenced by resuscitation strategies? Two of the factors look like they are pretty physiologically based, renal factor, and the liver factor, but can the pulmonary status and the use of inotropes simply be altered by the type of resuscitation strategies that you are practicing, and that the results shown today reflect changes in resuscitation strategies?

Dr Moore: In terms of the MOF score, perhaps the weakest parameter is the cardiac component. But reported alternative methods do not appear to improve scoring.

Juan A. Asensio, MD, Los Angeles: Dr Moore, during the beginnings of the decade of the 1990s, when we knew very little as to when to institute damage control and just bailed out at the very last minute, you could almost predict which were the patients who would develop MOF. As better indicators to predict when damage control have emerged, we have seen a decrease in the incidence of MOF. I do not know if that is what you have seen. From information culled from your database, can you or have you looked at patients who underwent damage control in the early period vs the later period when damage control is instituted much earlier to see if there is a decreasing incidence of MOF.

Dr Moore: The fact that we have implemented damage control surgery over this period has salvaged patients who clearly would have died 10 years ago. So actually, we have increased the at-risk group because of damage control. On the other side, more recently, we have recognized that the abdominal compartment syndrome associated with damage control can precipitate MOF.