CHEST®

Official publication of the American College of Chest Physicians

Causes and Timing of Death in Patients With ARDS*

Renee D. Stapleton, Bennet M. Wang, Leonard D. Hudson, Gordon D. Rubenfeld, Ellen S. Caldwell and Kenneth P. Steinberg

Chest 2005;128;525-532
DOI 10.1378/chest.128.2.525

ISSN:0012-3692

Causes and Timing of Death in Patients With ARDS*

Renee D. Stapleton, MD; Bennet M. Wang, MD, MPH, FCCP; Leonard D. Hudson, MD, FCCP; Gordon D. Rubenfeld, MD, MSc, FCCP; Ellen S. Caldwell, MS; and Kenneth P. Steinberg, MD, FCCP

Background: **Since the early 1980s, case fatality of patients with ARDS has decreased, and explanations are unclear.**
Design and methods: **Using identical definitions of ARDS and organ failure, we analyzed consecutive cohorts of patients meeting syndrome criteria at our institution in 1982 (n = 46), 1990 (n = 112), 1994 (n = 99), and 1998 (n = 205) to determine causes and timing of death.**
Results: **Overall case fatality has decreased from 68% in 1981–1982 to a low of 29% in 1996, plateauing since the mid-1990s (p = 0.001 for trend). Sepsis syndrome with multiple organ failure remains the most common cause of death (30 to 50%), while respiratory failure causes a small percentage (13 to 19%) of deaths. The distribution of causes of death has not changed over time. There was no change in the timing of death during the study periods: 26 to 44% of deaths occurred early (< 72 h after ARDS onset), and 56 to 74% occurred late (> 72 h after ARDS onset). However, the increased survival over the past 2 decades is entirely accounted for by patients who present with trauma and other risk factors for their ARDS, while survival for those patients whose risk factor is sepsis has not changed. Additionally, withdrawal of life support in these patients is now occurring at our institution significantly more frequently than in the past, and median time until death has decreased in patients who have support withdrawn.**
Conclusions: **While these results do not explain the overall case fatality decline in ARDS, they do indicate that sepsis syndrome remains the leading cause of death and suggest that future therapies to improve survival be targeted at reducing the complications of sepsis.**
(CHEST 2005; 128:525–532)

Key words: ARDS; cause of death; epidemiology; multiple organ failure; timing of death; withdrawal of life support

Abbreviations: APACHE = acute physiologic and chronic health evaluation; F_{IO_2} = fraction of inspired oxygen; ISS = injury severity score; MOF = multiple organ failure

When ARDS was originally described by Ashbaugh et al[1] in 1967 in a series of 12 patients, case fatality approached 60% and remained at approximately that level through the early 1980s.[2–4] Reported death rates have varied widely, but a study at our institution by Milberg et al[5] in 1993 found that ARDS case fatality had declined to 36%. Similarly, at another institution, Abel et al[6] found that case fatality declined from 66% in a cohort of patients in from 1990 to 1993, to 34% between 1993 and 1997. Explanations for this temporal decrease are not clear.

For editorial comment see page 479

When causes of death in ARDS patients were analyzed by Montgomery et al[4] in 1982, sepsis syndrome was the major cause of death, while only a relatively small percentage (16%) of deaths were due to insupportable respiratory failure. That study[4] also found that patients who died within the first 72 h after ARDS onset usually died from the presenting injury or illness that preceded ARDS onset. Patients whose deaths occurred > 72 h after ARDS onset most often died from complications (*ie*, new organ failures) that arose after ARDS began. Prior stud-

*From the Division of Pulmonary and Critical Care Medicine, Department of Medicine, Harborview Medical Center, University of Washington School of Medicine, Seattle, WA.
This research was supported by Specialized Center of Research Grant HL-30542 in Acute Lung Injury from the National Heart, Lung, and Blood Institute, National Institutes of Health.
Manuscript received July 23, 2004; revision accepted January 4, 2005.

Correspondence to: Renee D. Stapleton, MD, Division of Pulmonary and Critical Care Medicine; Harborview Medical Center, Box 359762, 325 Ninth Ave, Seattle, WA 98104; e-mail: rstaplet@u.washington.edu.

ies[7,8] have investigated whether a cause-specific decrease in death of ARDS patients accounts for the overall case fatality decline, but at the present time it remains unknown if cause of death in ARDS has changed concurrently with case fatality. Also unknown is whether a reduction in early or late deaths explains the fall in case fatality, or if the reduced case fatality has varied by ARDS risk factor. Furthermore, several studies[9–11] have reported that withdrawal of life support in critically ill patients is occurring more frequently now than in the past, but the timing of withdrawal of life support in relation to the onset of ARDS remains unclear. We hypothesized that the reduction in ARDS case fatality over the past 2 decades was related to a change in the relative frequency of sepsis syndrome and multiple organ failure (MOF) as the cause of death.

Gaining insight into the reported decrease in ARDS case fatality and into changes in ARDS epidemiology is important to fully understand the appropriate targets for new therapies. To investigate causes and timing of death, we analyzed these factors in ARDS patients in 1990, 1994, and 1998. Using identical definitions of ARDS and irreversible organ dysfunction leading to death as those used by Montgomery et al,[4] we then compared these data with those from that original study to identify trends over nearly 2 decades at a single institution. While longitudinal mortality rates have been reported,[12] to our knowledge there has not been a study that has longitudinally examined causes of death in ARDS using prospectively identified patients and applying consistent definitions of organ failure over time.

Materials and Methods

Since 1983, all ARDS patients at Harborview Medical Center (a level I trauma center) have been identified via prospective daily ICU surveillance using the following definition: (1) Pao_2/fraction of inspired oxygen (Fio_2) ratio ≤ 150, or ≤ 200 while receiving positive end-expiratory pressure ≥ 5 cm H_2O; (2) opacities on chest radiography involving at least 50% of three or four quadrants; (3) pulmonary capillary wedge pressure ≤ 18 mm Hg or no other clinical evidence of left atrial hypertension; and (4) no other obvious explanation for these findings.[5,13] These patients are identified by a specific screening protocol that is applied by research personnel such that physician diagnosis is not relied on. At ARDS onset, recorded data include age, gender, APACHE (acute physiologic and chronic health evaluation) II score,[14] injury severity score (ISS),[15] date of ARDS onset, and ARDS risk factor (sepsis syndrome, trauma, or other [pancreatitis, near drowning, inhalation injury, massive transfusion, aspiration, other]). Specific criteria are used to identify risk factors.[13] Criteria for sepsis syndrome are shown in Table 1. Patients are followed up until hospital discharge or death and are classified as survived or deceased; thus, case fatality data are available for each year since 1983.

Data from three cohorts of deceased patients (1990, 1994, 1998) were abstracted by individual authors (K.P.S., B.M.W., and R.D.S., respectively) and compared with the study by Montgomery et al[4] (performed during a 15-month period from 1981 to 1982, which we will call 1982) to identify trends in mortality. Six charts (> 10%) from each of 1982, 1990, and 1994 were also abstracted by R.D.S. to ensure accuracy. These cohorts were chosen because of their relatively even temporal spacing and because they preceded recent advances in ARDS management strategies that improve survival and may have confounded our results.[16] Had we chosen to examine more recent cohorts, we would not have able to adequately adjust for tidal volume in milliliters per kilogram of predicted body weight because height and weight data are not available for earlier cohorts. Charts for deceased patients in each cohort were retrieved and reviewed. For each patient, four features of the death were recorded: (1) cause, (2) timing after ARDS onset, (3) occurrence of withdrawal of life support, and (4) with or without ARDS. Cause of death was further categorized as attributable to the presenting injury/illness or progression of ARDS risk factor present prior to onset, insupportable respiratory failure, or complications that arose after ARDS onset.

Cause of death was defined as irreversible organ dysfunction that either resulted directly in the patient's death or in withdrawal of life support. Identical criteria for grading organ dysfunction, originally established by Montgomery et al,[4] were used in all four patient cohorts (Table 1). Rigorous inspection of temporal relationships of laboratory data, hemodynamic and respiratory parameters, and nursing and physician notes was used to identify one of nine causes of death: sepsis with MOF, respiratory, cardiac, CNS, hematologic, hemorrhage, hepatic, GI, and renal.

Like the study by Montgomery et al,[4] severe sepsis syndrome did not require the presence of suspected or proven infection (Table 1). Sepsis/MOF was defined as sepsis syndrome in combination with two other severe organ system dysfunctions. For a patient to be classified as dying from sepsis without withdrawal of life support occurring, the death must have occurred directly from irreversible septic shock. Withdrawal of life support was defined as the removal of life-sustaining measures and was determined by locating evidence in the chart of a clear intention to discontinue life support. The decision to withdraw life support was made in several patients due to their MOF and grim prognosis. All of these patients had severe sepsis syndrome, thereby meeting the definition of sepsis with MOF. Therefore, patients who died directly from septic shock and those who died after withdrawal of life support secondary to sepsis and MOF were combined into one sepsis/MOF group.

Similar to the study by Montgomery et al,[4] timing of death was considered "early" if it occurred within 72 h after ARDS onset and "late" if > 72 h after ARDS onset.[4] Patients were classified as having died without ARDS only if they achieved unassisted breathing, defined as one of the following criteria: (1) extubation (excluding patients extubated as withdrawal of support); (2) mechanical ventilation on pressure-support mode of ≤ 5 cm H_2O and Fio_2 of ≤ 0.4; or (3) continuation of intubation on a t-piece for airway protection purposes.

A death was categorized as due to the presenting injury/illness or progression of the ARDS risk factor if it was associated with conditions that preceded ARDS onset. For example, if ARDS developed in a trauma patient presenting with severe head injury but eventually had life support withdrawn secondary to neurologic devastation, the death was classified as due to the presenting injury/illness. Similarly, if ARDS developed secondary to sepsis syndrome caused by bowel perforation that was operatively repaired and death subsequently occurred due to progressive sepsis/MOF, the death was also classified as secondary to the presenting illness/injury or progression of the ARDS risk factor. All patients who met criteria for irreversible respiratory failure as

Table 1—*Definitions of Severe and Irreversible Organ Dysfunction

Organ System/Clinical Syndrome	Severe	Irreversible
Sepsis syndrome	At least one criteria from each of the following categories plus one criteria from either category	Severe sepsis syndrome without response to antibiotics and no possible surgical intervention
Infection/inflammation	(1) Temperature $< 35°C$ or $\geq 39°C$ (2) WBC $< 3{,}000/\mu L$ or $> 12{,}000/\mu L$ or $> 10\%$ bands (3) Positive blood culture of accepted pathogen (4) Known or strongly suspected source of systemic infection with culture known pathogens	
Deteterious systemic effect	(1) Unexplained metabolic acidosis with anion gap > 20 (2) Systemic vascular resistance < 800 dyne $\cdot$ s $\cdot$ cm^{-5} (3) Unexplained hypotension with systolic BP < 90 for 2 h or receiving vasopressor medications	
Respiratory	ARDS, bilobar pneumonia, bronchopleural fistula, or PE documented by high-probability ventilation/perfusion scan or pulmonary angiogram	Insupportable oxygenation or ventilation defined as $PaO_2 < 40$ mm Hg on FIO_2-1.0 for > 2 h or respiratory acidosis with pH < 7.1 on maximum ventilator settings
Cardiac	Cardiac output < 2.0 L/min/m^2 or reversible ventricular fibrillation or asystole	Cardiogenic shock or arrhythmia not responsive to treatment
CNS	Glasgow coma scale < 8 for ≥ 3 d	Meets brain death criteria by apnea trial, SSEPs, or other conventional study
Hematologic	Microvascular bleeding with either fibrinogen < 100 mg/dL, prothrombin time and partial thromboplastin time > 1.5 times control, or platelets $< 60{,}000/\mu L$	Ongoing microvascular bleeding not surgically correctable and hypotension not reversible with blood products
Hemorrhage	Systolic BP < 80 for > 2 h (or requiring vasopressor medications) necessitating blood transfusions and excluding other causes of hypotension	Uncontrollable "surgical" bleeding from a nonmicrovascular source
Hepatic	Bilirubin > 5.0 mg/dL and albumin < 2.0 g/dL and prothrombin time or partial thromboplastin time > 1.5 times control	Severe criteria plus hepatic encephalopathy and/or hepatorenal syndrome not responsive to treatment
GI	Resectable ruptured or necrotic bowel, or pancreatitis causing shock (systolic BP < 80 mm Hg for > 2 h or requiring vasopressors)	Inoperable ruptured or necrotic bowel or pancreatitis causing irreversible shock
Renal	Creatinine > 5.0 g/dL or requiring hemodialysis	Renal failure with acidosis, hyperkalemia, and/or hypercalcemia causing irreversible cardiac arrest

*SSEP = somatosensory-evoked potential; PE = pulmonary embolism.

the cause of death were classified as dying secondary to insupportable respiratory failure. Finally, deaths were coded as due to complications after ARDS onset if the cause was related to a condition or new organ failure that was not present prior to ARDS onset. For example, if ARDS developed in a burn patient with inhalation injury but 3 weeks later sepsis developed and the patient died, this death would be classified as secondary to complications after ARDS onset. Patients transferred to other acute care facilities receiving mechanical ventilation were identified, and information was obtained regarding their outcome.

Medians and ranges were used to summarize these data since they are not normally distributed. Statistical comparisons between groups were analyzed using the χ^2 test and Cochran-Armitage test for trend for categorical variables and Wilcoxon signed-rank test for trend for continuous variables; $p < 0.05$ was considered significant. All statistical analyses were performed with SAS software (SAS Institute; Cary, NC) or Stata software (StataCorp; College Station, TX).

Results

The study by Montgomery et al[4] identified 46 ARDS patients at Harborview Medical Center in 1982. During the years 1990, 1994, and 1998, there were 112, 99, and 205 patients, respectively, who met our ARDS criteria. There were no significant differences in gender, ARDS risk factor, or ISS between the four cohorts of patients. However, age and APACHE II score have changed significantly over time, such that ARDS patients now are slightly older and have a slightly greater APACHE II score (Table 2). In 1998, there were 13 patients who were still receiving mechanical ventilation when they left our institution and were transferred to another hospital or long-term ventilatory facility. Five of these patients survived and were weaned from the ventilator, seven of them died while still ventilator dependent, and one had an unknown outcome and was considered to be alive. We do not have data on the seven deceased patients to determine their causes of death.

ARDS case fatality ranged from 55 to 65% in the early 1980s and decreased to 29 to 35% by the late

Table 2—*Characteristics of ARDS Patients

Characteristics	1981–1982 (n = 46)	1990 (n = 112)	1994 (n = 99)	1998 (n = 205)	p Value
Age, yr†	46 (17–86)	43 (4–84)	41 (7–84)	48 (1–86)	0.04
Male gender‡	61	72	59	70	0.55
Trauma/sepsis ARDS risk factors, %‡	41/22	26/43	28/40	27/20	0.41
APACHE II score†	24 (10–43)	23 (8–42)	23 (7–42)	27 (4–46)	0.0001
ISS (trauma patients)†	Not available	26 (0–54)	25 (8–43)	27 (4–51)	0.66

*Data are presented as No. unless otherwise indicated.
†Wilcoxon rank-sum test for trend, median (range).
‡Cochran-Armitage test for trend.

1990s (p = 0.001 for trend; Fig 1). The distribution of specific causes of death, however, has not significantly changed over time in our cohorts, as shown in Table 3 with cause-specific deaths expressed as a percentage of total deaths. Sepsis syndrome/MOF has remained the leading cause of death in all four cohorts of patients (30 to 50%), with CNS as the second most common cause (19 to 29%). Insupportable respiratory failure was responsible for a relatively small and similar percentage of deaths in each cohort (16%, 14%, 19%, and 13%, respectively). Even though ARDS was the direct cause of death in only a few patients, it was present in the majority of patients at the time of death (88%, 86%, 88%, and 96% in 1981–1982, 1990, 1994, and 1998, respectively).

Timing of death in ARDS, divided into early and late deaths and then further categorized as due to presenting injury/illness, respiratory failure, or a complication occurring after ARDS onset, has also not changed significantly over the past 2 decades (Fig 2). Twenty-nine percent of deaths occurred early (< 72 h after ARDS onset) in 1981–1982, 30% in 1990, 44% in 1994, and 26% in 1998 (p = 0.29 for trend). The majority of early deaths in all four cohorts of patients were due to the primary injury or illness. Montgomery et al[4] found in 1982 that the majority of patients dying late died from a complication that arose after ARDS onset.[4] This was not the case in 1990, 1994, and 1998, when late deaths most commonly occurred secondary to the presenting injury or illness.

There has, however, been a significant change in the case fatality of ARDS patients when stratified by risk factor (Fig 3), such that the case fatality of ARDS patients who present with trauma (p = 0.0002 for trend) or other risk factors (p = 0.043 for trend) has decreased, but the case fatality of patients whose risk factor is sepsis (p = 0.255 for trend) has not changed. Additionally,

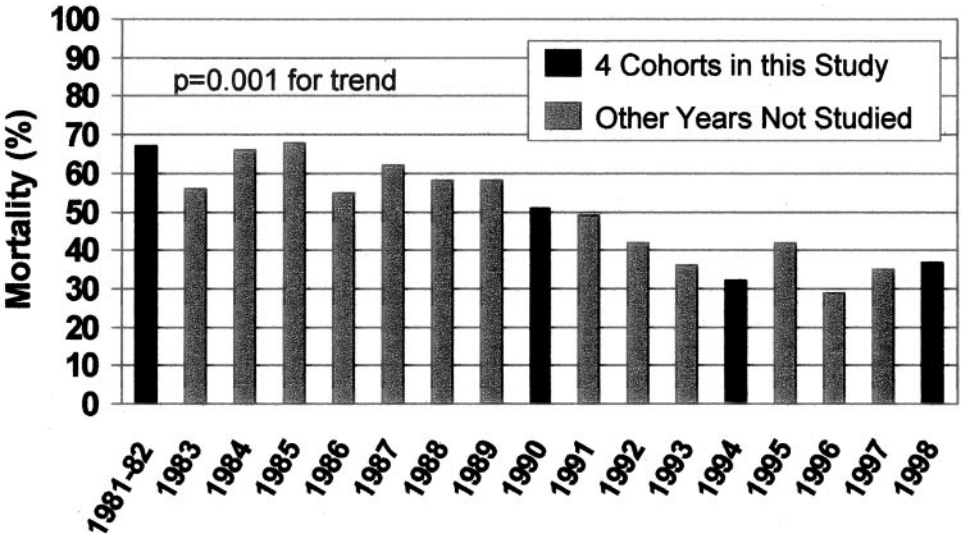

FIGURE 1. Case fatality of ARDS patients at Harborview Medical Center, 1991–1998. Case fatality was near 60% in the early 1980s and decreased to near 30% by the mid-1900s (p = 0.001 for trend, Wilcoxon rank-sum test for trend).

Table 3—*Causes of Death in ARDS Patients*

Variables	1981–1982	1990	1994	1998	p Value*
ARDS cases, No.	46	112	99	205	
ARDS deaths, No.	31	57	32	76	
Cause of death, %					
Sepsis/MOF	35	44	50	30	0.36
CNS	23	19	22	29	0.29
Respiratory	13	14	19	13	0.95
Cardiac	19	7	3	8	0.09
Hepatic	0	4	0	7	0.12
GI	0	4	0	3	0.69
Hemorrhage	6	0	0	4	0.96
Hematologic	3	0	0	1	0.73
Renal	0	9	6	5	0.68

*Cochran-Armitage test for trend.

the percentage of deaths in ARDS patients occurring in the setting of withdrawal of life support has significantly increased over time (40%, 56%, 63%, and 67% of deaths in 1981–1982, 1990, 1994, and 1998, respectively) [p = 0.03 for trend; Fig 4]. Despite the increasing occurrence of withdrawal of life support, the median time of death in all ARDS patients has not changed significantly, as shown in Table 4 (10.0 days after ARDS onset in 1981–1982, 10.4 days in 1990, 3.5 days in 1994, and 7.1 days in 1998; p = 0.38). However, the median time of death in patients who died after support withdrawal has significantly decreased (15.5 days in 1981–1982, 10.5 days in 1990, 3.3 days in 1994, and 7.0 days in 1998; p = 0.04).

Discussion

This study found that the significant decline in ARDS case fatality since the 1980s is associated with neither a change in the distribution of causes of death nor a selective decrease in early or late deaths. Despite increasing age and severity of illness, fewer patients are dying, and the improvement is seen across all causes of death. Sepsis syndrome with MOF remains the leading cause of death, and insupportable respiratory failure is an uncommon cause. The majority of improvement in case fatality can be accounted for by patients with trauma and "other" risk factors for ARDS, while the case fatality of patients whose risk is sepsis has not changed. Additionally, withdrawal of life support is occurring more frequently in ARDS patients at our institution now than in the past, and the median time from ARDS onset to death in patients who have support withdrawn has decreased.

The main strength of this study is that, to our knowledge, it is the only investigation that has examined causes and timing of death in ARDS patients longitudinally, using prospectively identified patients and applying identical definitions. This uniformity in definitions permits direct comparison of patients over time to investigate changes in ARDS epidemiology. Additionally, with 462 patients, this study is larger than most series examining mortality in ARDS. Another strength is that while overall case fatality has declined, ARDS patients at our institution seem to be more ill now than in the past, with increased age and APACHE

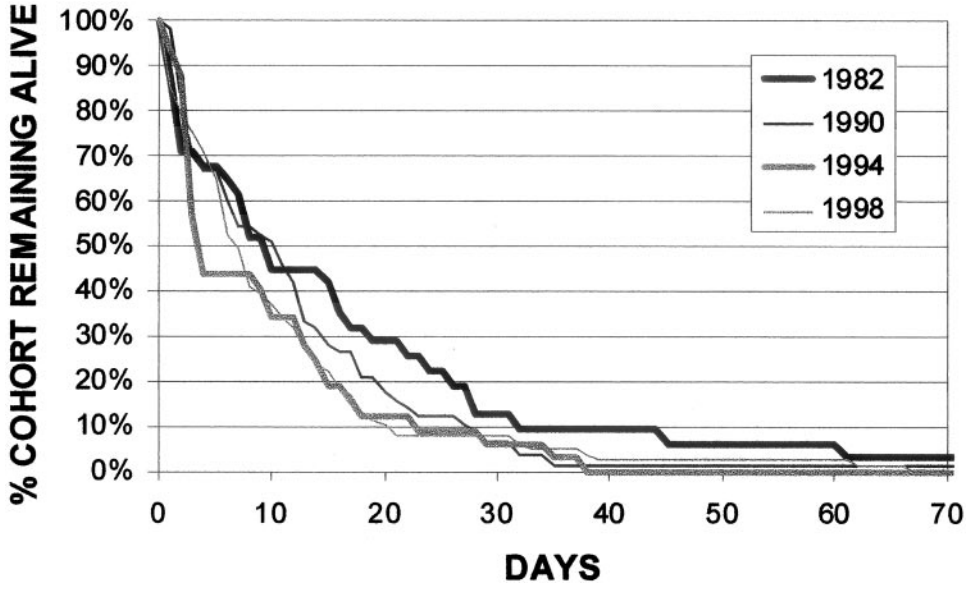

Figure 2. Kaplan-Meier analysis of survival in all four cohorts of ARDS patients, among patients who died. The time until death is similar in these patient cohorts.

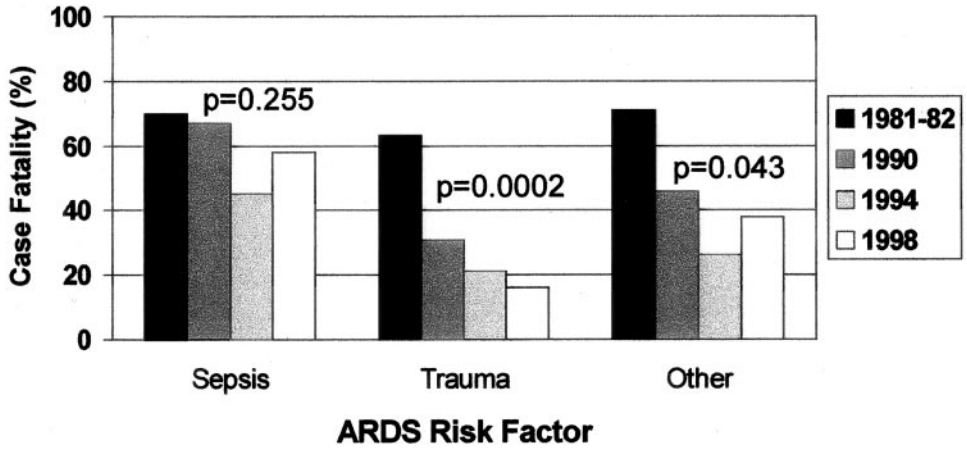

FIGURE 3. ARDS case fatality in all four cohorts stratified by risk factor, showing significant decrease in patients whose risk factor for ARDS is trauma or "other" (p = 0.255 for sepsis, p = 0.0002 for trauma, p = 0.043 for other; Cochrane-Armitage test for trend).

II score on the day of ARDS onset, both factors that are associated with increased mortality.[13,17,18]

This study reconfirms an important result of the study by Montgomery et al,[4] that insupportable respiratory failure is a relatively uncommon cause of death in ARDS patients.[4] Death from respiratory failure occurs in only 13% of all ARDS deaths and 5% of all ARDS cases at our institution. At the same time, ARDS is present in nearly all patients who die.

Most improvement in survival observed over the past 20 years is explained by reduced case fatality in patients with a risk factor other than sepsis. Our trauma patients are younger than those in the other two risk factor groups (median ages, 39.8 years for trauma, 49.0 years for sepsis, and 43.0 years for other). However, the age of trauma and sepsis patients has not changed over time, and APACHE II scores for patients in all three risk factor groups have significantly increased over time (data not shown). Therefore, changes in age or severity of illness between the three risk factor groups do not explain the survival improvement limited to the trauma and "other" patients.

Withdrawal of life support in ARDS has increased over time. In 1998 at our institution, 67% of all ARDS deaths occurred after support withdrawal. This value is similar to the 90% reported by Prendergast and Luce.[9] Furthermore, time from ARDS onset to death in those patients who have support withdrawn is decreasing. The withdrawal of support definition was applied identically in all four cohorts, thus ruling out the possibility that this trend is due to differences in data collection. We also doubt this trend can be explained by an increased prevalence of advanced directives among our patients, since several studies[19–21] have concluded that advanced directives do not affect aggressiveness of care, initiation of do-not-resuscitate orders, or attempts

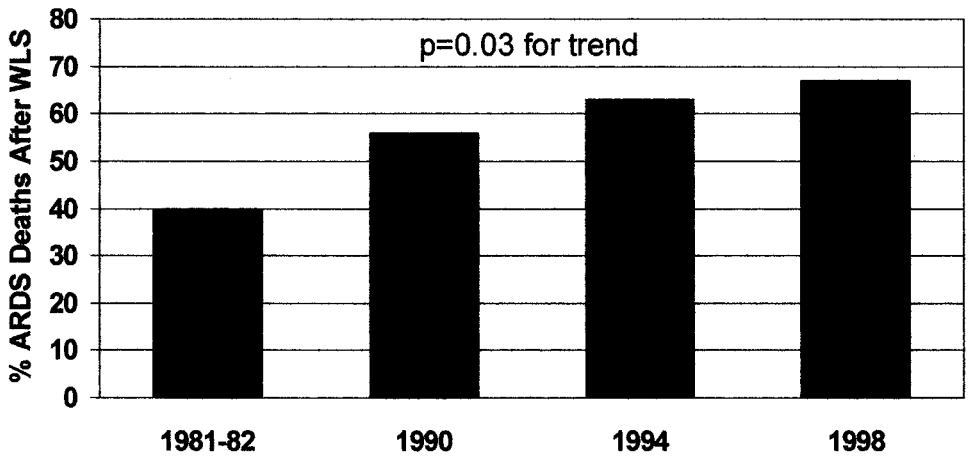

FIGURE 4. Percentage of ARDS deaths after withdrawal of life support (WLS) in all four cohorts (p = 0.03 for trend, Wilcoxon rank-sum test).

Table 4—*Timing of Death With and Without Withdrawal of Life Support

Variables	1981–1982	1990	1994	1998	p Value†
All deaths	10.0 (2.0–24.0)	10.4 (2.6–17.3)	3.5 (2.4–13.9)	7.1 (2.7–14.0)	0.15
With WLS	15.5 (4.5–23.0)	10.5 (2.7–17.4)	3.3 (2.4–14.8)	7.0 (2.4–13.0)	0.04
Without WLS	8.0 (2.0–17.0)	9.6 (1.8–17.3)	6.2 (2.3–12.6)	8.3 (4.8–15.5)	0.78

*Data are presented as median No. of days (interquartile range). See Figure 4 legend for expansion of abbreviation.
†Wilcoxon rank-sum test for trend.

at resuscitation. A more probable explanation is that physicians may be initiating end-of-life discussions earlier and more frequently with families of patients who will likely die.

There are some important limitations to this study. First, identification of cause of death is partially subjective, and interobserver variability could have contributed to variations in assignment. In addition to using consistent definitions, six charts (> 10%) from deceased patients in the earliest three cohorts were reviewed by the author who abstracted the 1998 charts, and the assignment of causes was identical. Thus, we believe that the definitions have been reliably assigned over time. Second, the increase in withdrawal of life support makes identification of true cause of death difficult. In all four cohorts, cause of death after support withdrawal was defined as the irreversible organ dysfunction that directly led to the withdrawal of support. It is possible that these patients might have died from another cause had withdrawal of support not occurred.

Our definitions of ARDS and sepsis may affect the generalizability of these results. The ARDS definition used in this study was established at our institution prior to the American-European Consensus Conference on ARDS.[22] Our definition describes a more severe subset of ARDS patients. Since 1994, we have utilized both definitions for research, but we believed it necessary to use identical definitions over time in this study to longitudinally compare ARDS case fatality. Additionally, our definition of sepsis syndrome predates the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference on defining sepsis.[23] In this study, sepsis syndrome can be present without any direct evidence of infection, and therefore may be reflective of a systemic inflammatory state from any cause. Again, we believed it appropriate to use the definition of Montgomery et al[4] in all four cohorts of patients for consistency.

Generalizability of this study may also be limited by our patient population. The annual number of ARDS patients at our institution has greatly increased over time, from 46 patients in 1982 to > 200 patients in 1998. We believe this is simply a result of increased ICU bed capacity (increased from 36 to 65 ICU beds during the course of the study), leading to changes in regional referral patterns rather than any change in screening techniques or other selection biases. However, we cannot absolutely exclude the possibility of changes in physician awareness or screening, such that more ARDS patients are being identified.

Additionally, a high percentage of trauma-related ARDS cases are seen at our institution. Our results are different than those reported by Suchyta et al[7] in 1992, who applied definitions of organ dysfunction of Montgomery et al[4] to identify cause of death. In that study, respiratory failure accounted for 40% of deaths and sepsis accounted for 32%. This difference may be explained by the marked dissimilarity in patient populations between the two institutions. Trauma was the risk factor in 20 to 41% of our ARDS patients compared with 13% of their patients. On the contrary, our results are very similar to those reported by Ferring and Vincent[8] in 1997, who found an overall ARDS case fatality of 52% and concluded that sepsis syndrome/MOF was still the leading cause of ARDS deaths at 49% while respiratory failure caused 16% of deaths, despite their population being more akin to that of Suchyta et al.[7]

Although not confirmed by this study, several reasons for the overall improved survival of ARDS patients have been hypothesized, including early and aggressive antibiotic use, stress ulcer prophylaxis, and improved nutritional and fluid support.[24–27] The National Institutes of Health ARDS network trial[16] in 2000 found that low tidal volume ventilation significantly improved survival. Additionally, a more recent study[28] reported fewer organ failures in a 1994-to-1999 cohort of ARDS patients when compared to a 1987-to-1990 cohort at a single institution, suggesting that perhaps this has contributed to the decrease in ARDS case fatality. However, that investigation did not examine cause or timing of death specifically.[28]

While we were unable to explain the overall decline in ARDS case fatalities, the finding remains that survival has improved among patients with a variety of organ dysfunctions and has not changed among patients whose ARDS risk factor is sepsis. With sepsis syndrome being both a risk factor for ARDS and the most common cause of death among ARDS patients, it is paramount to examine the interactions between lung injury, systemic inflammation, and development of

MOF. The fact that only a small percentage of ARDS patients die from insupportable respiratory failure likely explains why approaches to improve oxygenation in ARDS, such as nitric oxide and partial liquid ventilation, have not improved survival.[29–31] Furthermore, in the National Institutes of Health ARDS network trial,[16] low tidal volume ventilation significantly improved survival despite an early adverse effect on oxygenation.[16] This finding, along with our results, supports the hypothesis that systemic inflammation induced by lung injury, either ventilator-induced lung injury or ARDS itself, may lead to the development of MOF and death. Therapies designed to only improve gas exchange without reducing organ injury are unlikely to change survival in unselected ARDS patients since few patients die from hypoxemia. Continued improvement in supportive care and in novel approaches to reduce systemic inflammation may be important in further decreasing case fatality in ARDS.

References

1 Ashbaugh DG, Bigelow DB, Petty TL, et al. Acute respiratory distress in adults. Lancet 1967; 2:319–323
2 Fowler AA, Hamman RF, Good JT, et al. Adult respiratory distress syndrome: risk with common predispositions. Ann Intern Med 1983; 98:593–597
3 Baumann WR, Jung RC, Koss M, et al. Incidence and mortality of adult respiratory distress syndrome: a prospective analysis from a large metropolitan hospital. Crit Care Med 1986; 14:1–4
4 Montgomery AB, Stager MA, Carrico CJ, et al. Causes of mortality in patients with the adult respiratory distress syndrome. Am Rev Respir Dis 1985; 132:485–489
5 Milberg JA, Davis DR, Steinberg KP, et al. Improved survival of patients with acute respiratory distress syndrome (ARDS): 1983–1993. JAMA 1995; 273:306–309
6 Abel SJ, Finney SJ, Brett SJ, et al. Reduced mortality in association with the acute respiratory distress syndrome (ARDS). Thorax 1998; 53:292–294
7 Suchyta MR, Clemmer TP, Elliott CG, et al. The adult respiratory distress syndrome: a report of survival and modifying factors. Chest 1992; 101:1074–1079
8 Ferring M, Vincent JL. Is outcome from ARDS related to the severity of respiratory failure? Eur Respir J 1997; 10:1297–1300
9 Prendergast TJ, Luce JM. Increasing incidence of withholding and withdrawal of life support from the critically ill. Am J Respir Crit Care Med 1997; 155:15–20
10 Prendergast TJ, Claessens MT, Luce JM. A national survey of end-of-life care for critically ill patients. Am J Respir Crit Care Med 1998; 158:1163–1167
11 McLean RF, Tarshis J, Mazer CD, et al. Death in two Canadian intensive care units: institutional difference and changes over time. Crit Care Med 2000; 28:100–103
12 Moss M, Mannino DM. Race and gender differences in acute respiratory distress syndrome deaths in the United States: an analysis of multiple-cause mortality data (1979–1996). Crit Care Med 2002; 30:1679–1685
13 Hudson LD, Milberg JA, Anardi D, et al. Clinical risks for development of the acute respiratory distress syndrome. Am J Respir Crit Care Med 1995; 151:293–301
14 Knaus WA, Draper EA, Wagner DP, et al. APACHE II: a severity of disease classification system. Crit Care Med 1985; 13:818–829
15 Baker SP, O'Neill B, Haddon W Jr, et al. The injury severity score: a method for describing patients with multiple injuries and evaluating emergency care. J Trauma 1974; 14:187–196
16 Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. N Engl J Med 2000; 342:1301–1308
17 Suchyta MR, Clemmer TP, Elliott CG, et al. Increased mortality of older patients with acute respiratory distress syndrome. Chest 1997; 111:1334–1339
18 Ely EW, Wheeler AP, Thompson BT, et al. Recovery rate and prognosis in older persons who develop acute lung injury and the acute respiratory distress syndrome. Ann Intern Med 2002; 136:25–36
19 Danis M, Southerland LI, Garrett JM, et al. A prospective study of advance directives for life-sustaining care. N Engl J Med 1991; 324:882–888
20 Schneiderman LJ, Kronick R, Kaplan RM, et al. Effects of offering advance directives on medical treatments and costs. Ann Intern Med 1992; 117:599–606
21 Teno JM, Lynn J, Phillips RS, et al. Do formal advance directives affect resuscitation decisions and the use of resources for seriously ill patients? SUPPORT Investigators. Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments. J Clin Ethics 1994; 5:23–30
22 Bernard GR, Artigas A, Brigham KL, et al. The American-European Consensus Conference on ARDS: definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 1994; 149:818–824
23 Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis: The ACCP/SCCM Consensus Conference Committee. Chest 1992; 101:1644–1655
24 Sutherland KR, Steinberg KP, Maunder RJ, et al. Pulmonary infection during the acute respiratory distress syndrome. Am J Respir Crit Care Med 1995; 152:550–556
25 Schuster DP. What is acute lung injury? What is ARDS? Chest 1995; 107:1721–1726
26 Cook DJ, Reeve BK, Guyatt GH, et al. Stress ulcer prophylaxis in critically ill patients: resolving discordant meta-analyses. JAMA 1996; 275:308–314
27 Hudson LD. New therapies for ARDS. Chest 1995; 108:79S–91S
28 Suchyta MR, Orme JF Jr, Morris AH. The changing face of organ failure in ARDS. Chest 2003; 124:1871–1879
29 Dellinger RP, Zimmerman JL, Taylor RW, et al. Effects of inhaled nitric oxide in patients with acute respiratory distress syndrome: results of a randomized phase II trial; Inhaled Nitric Oxide in ARDS Study Group. Crit Care Med 1998; 26:15–23
30 Lundin S, Mang H, Smithies M, et al. Inhalation of nitric oxide in acute lung injury: results of a European multicentre study; The European Study Group of Inhaled Nitric Oxide. Intensive Care Med 1999; 25:911–919
31 Hirschl RB, Croce M, Gore D, et al. Prospective, randomized, controlled pilot study of partial liquid ventilation in adult acute respiratory distress syndrome. Am J Respir Crit Care Med 2002; 165:781–787

Causes and Timing of Death in Patients With ARDS*

Renee D. Stapleton, Bennet M. Wang, Leonard D. Hudson, Gordon D. Rubenfeld, Ellen S. Caldwell and Kenneth P. Steinberg

Chest 2005;128; 525-532
DOI 10.1378/chest.128.2.525