Eight-Year Trend of Acute Respiratory Distress Syndrome

A Population-based Study in Olmsted County, Minnesota

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Rationale: Significant progress has been made in understanding the pathogenesis of acute respiratory distress syndrome (ARDS). Recent advances in hospital practice may have reduced the incidence of this lethal syndrome.

Objectives: To observe incidence trends and associated outcomes of ARDS.

Methods: This population-based cohort study was conducted in Olmsted County, Minnesota. Using a validated screening protocol, investigators identified intensive care patients with acute hypoxemia and bilateral pulmonary infiltrates. The presence of ARDS was independently confirmed according to American-European Consensus Conference criteria. The incidence of ARDS and associated outcomes were compared over the 8-year study period (2001–2008). **Measurements and Main Results:** Over the 8-year period, critically ill Olmsted County residents presented with increasing severity of acute illness, a greater number of comorbidities, and a higher prevalence of major predisposing conditions for ARDS. The ARDS incidence decreased significantly from 82.4 to 38.9 per 100,000 person-years during the study period ($P < 0.001$). A decline in hospital-acquired ARDS ($P < 0.001$) was responsible for the fall in the incidence density with no change on admission ($P = 0.877$). Overall, mortality and hospital and intensive care unit lengths of stay decreased over time ($P < 0.001$), whereas the ARDS case-fatality did not change significantly.

Conclusions: Despite an increase in patients' severity of illness, number of comorbidities, and prevalence of major ARDS risk factors, the incidence of ARDS in this suburban community decreased by more than half. Correlation of the observed findings with changes in health care delivery may have important implications for the planning of acute care services in other regions.

Keywords: epidemiology; incidence; acute respiratory distress syndrome

Acute lung injury (ALI) and its more severe form, acute respiratory distress syndrome (ARDS), have had a substantial impact on public health in the United States (1). Since the original description of ARDS by Ashbaugh and coworkers in 1967 (2), significant progress has been made in understanding the natural history and pathogenesis of this lethal syndrome. The incidence of ARDS varies greatly across the world (1, 3, 4), in part related to availability of intensive care services (5). Recent data suggest a higher incidence of ARDS in the United

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Population-based studies observed a high incidence of acute respiratory distress syndrome (ARDS) in United States hospitals.

What This Study Adds to the Field

A steady decline in ARDS incidence attributable entirely to a reduced incidence of hospital-acquired ARDS suggests that recent improvements in critical care delivery may in part be responsible for this observation.

States, ranging from 15.3–58.7 cases per 100,000 person-years (1, 6), respectively. Attributable mortality also varies with reported ranges of 41–58% (1, 6, 7).

Data from patients enrolled in the ARDS Network randomized controlled trials document a significant trend toward improvement in 60-day mortality during the period from 1996–2005 (8). Interestingly, a comprehensive systematic review of observational studies noted similar improvements in survival from 1984–1993, but no further improvement between 1994 and 2006 (9). Preliminary studies suggest a decreased incidence of ARDS in specific patient subgroups (10, 11). This reduction in ARDS incidence is believed to be a result of advances in hospital practice and numerous quality improvement initiatives (11). The Institute of Medicine's report (12) that the systems of health care delivery may play an important role in the outcome of hospitalized patients prompted significant changes in critical care practice over the past decade. These changes included not only general quality improvement initiatives (intensivist staffing, infection control, timely antibiotics and resuscitation, resident supervision, and electronic health records) but also the development of specific critical care protocols (mechanical ventilation, sepsis resuscitation and transfusion procedures).

Importantly, randomized controlled trials evaluate highly selected groups of patients and therefore cannot be used to make epidemiologic inferences regarding ARDS. Indeed, even observational studies from large, tertiary care centers may not reflect true changes in the epidemiology of ARDS. In contrast, population-based investigations provide improved insights into the epidemiologic trends of specific syndromes and diseases (1).

The attributes of Olmsted County, Minnesota, make it well suited for conducting population-based studies of disease epidemiology (13). The local population is relatively isolated from other urban centers and all residents who require mechanical ventilation for acute respiratory failure are treated in the intensive care units (ICU) of a single medical center. As a result, all ARDS cases in Olmsted County can be identified with

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remarkably complete detail of the medical care provided. Because of the unique aspects of this health care environment, we chose to explore the trends in the incidence and mortality of ARDS over the past 8 years.

METHODS

After receiving institutional review board approval, we performed a population-based, retrospective cohort study of residents of Olmsted County, Minnesota.

Population

The demographics of Olmsted County residents are typical of a suburban community in the Midwestern United States. The population of 124,277 consisted largely of middle-class whites with minorities representing 13% of the population according to 2000 U.S. census reports. Because of its geographic isolation, critical care services are provided exclusively by two Mayo Clinic hospitals in Rochester, Minnesota. The closest competing medical centers are located in Minneapolis, Minnesota (139.2 km to the north); LaCrosse, Wisconsin (113.6 km to the east); Iowa City and Des Moines, Iowa (316.8 and 332.8 km to the south, respectively); and Sioux Falls, South Dakota (376 km to the west). The population is relatively stable, particularly among the older age groups. The median length of available follow-up for residents 50–59 years of age is 29 years. In light of these demographics and the acuity of ARDS, it is unlikely for an ARDS case to be missed.

The health care system uses an integrated electronic medical record system. Combined with multiple comprehensive, prospectively collected clinical research databases (Rochester Epidemiology Project, Mayo Clinic Life Sciences System [MCLSS], Acute Physiology and Chronic Health Evaluation database), the research environment enables easy and extensive access to detailed clinical information from this patient population (13).

Screening Protocol

The study was conducted at Mayo Clinic in Rochester, Minnesota. This is a tertiary care teaching institution comprised of two hospitals with 1,900 inpatient beds and 210 total ICU beds (164 adult ICU beds). The MCLSS and Rochester Epidemiology Project database were used to identify all patients (≥ 18 yr) from Olmsted County (as determined by the nine-digit ZIP Code of their primary residence) who met criteria for ARDS and who received intensive care services at Mayo Clinic in Rochester from 2001–2008. MCLSS is a collaborative effort between Mayo Clinic and IBM. It is a clinical data warehouse that provides approved users a query tool called Data Discovery and Query Builder. This tool can be used to extract clinical data of patients who received care at Mayo Clinic. Patients who denied the use of their medical records for research are excluded ($<5\%$ of the patients). Additional description of the Rochester Epidemiology Project and electronic infrastructure including MCLSS is provided in the online supplement.

A previously validated screening tool (“ARDS screening tool”) with excellent negative predictive value (0.99) (14) screened all patients who received intensive care services from 2001–2008. To facilitate comparison with previous population-based studies of ARDS (1), the screening tool was designed to identify all patients who met the following criteria within a single 24-hour period: (1) qualifying arterial blood gas analysis: ratio of $\text{PaO}_2/\text{FiO}_2$ less than 200; (2) qualifying chest radiograph report: free text Boolean query containing the words “edema” or “bilateral” and “infiltrate”; and (3) invasive mechanical ventilation for acute respiratory failure or duration of invasive mechanical ventilation greater than 12 hours after an operative procedure. In a case of multiple arterial blood gas values, we selected the worst value during the 24-hour window.

Validation of Screening Protocol

Our ARDS screening procedures were validated using data from all ICU admissions at Mayo Clinic in 2006. In total, 1,707 adult patients from Olmsted County were admitted to an ICU in this 1-year period.

Figure 1. Outline of the acute respiratory distress syndrome screening protocol and case ascertainment. AECC = American-European Consensus Conference; ALI = acute lung injury; ARDS = acute respiratory distress syndrome; ICU = intensive care unit; PF = $\text{PaO}_2/\text{FiO}_2$.

TABLE 1. BASELINE CHARACTERISTICS AND OUTCOME OF PATIENTS AT RISK OF ACUTE RESPIRATORY DISTRESS SYNDROME FROM 2001–2008

	2001 (n = 312)	2002 (n = 315)	2003 (n = 354)	2004 (n = 416)	2005 (n = 422)	2006 (n = 439)	2007 (n = 437)	2008 (n = 437)	P for Linear Trends
Demographics									
Age, yr median (IQR)	70 (52–81)	71 (52–81)	71 (52–82)	69 (53–80)	72 (55–83)	71 (54–82)	70 (53–82)	70 (54–83)	0.22
Female, number (%)	150 (48)	143 (45)	164 (46)	194 (47)	185 (44)	208 (47)	194 (44)	220 (50)	0.66
Severity of illness and comorbidities									
APACHE III score on admission, median (IQR)	51 (36–69)	53 (36–71)	52 (37–73)	59 (40–78)	61 (48–77)	65 (47–85)	57 (42–75)	60 (45–79)	<0.001
Charlson score, median (IQR)	2 (1–4)	2 (1–3)	2 (1–4)	3 (2–4)	3 (2–4)	5 (3–7)	3 (2–4)	3 (2–5)	<0.001
Outcome									
ICU mortality, number (%)	44 (14)	36 (11)	37 (10)	46 (11)	33 (8)	48 (11)	37 (8)	41 (9)	0.02
Hospital mortality, number (%)	64 (20)	54 (17)	60 (17)	61 (15)	57 (14)	71 (16)	57 (13)	71 (16)	0.04
ICU LOS, d, median (IQR)	2.2 (1.1–5)	2.1 (1.1–5.2)	2.1 (1–5.6)	2.4 (1–5.2)	2.2 (1–4.8)	2.2 (1.1–5.1)	1.8 (1–4.4)	1.8 (1–4)	0.02
Hospital LOS, d, median (IQR)	9 (5–15)	9 (5–15)	9 (5–15)	8 (5–14)	8 (5–13)	7 (4–13)	7 (4–12)	7 (4–12)	0.002

Definition of abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation; ICU = intensive care unit; IQR = interquartile range; LOS = length of stay.

In the first phase of validation, trained critical care fellows reviewed all charts and identified patients receiving invasive mechanical ventilation according to the definition noted previously. The presence of American-European Consensus Conference criteria (AECC) for ARDS was determined (15). If either a chest radiograph or arterial blood gas analysis were never obtained, ARDS was considered absent. Similarly, if the ratio of $\text{PaO}_2/\text{FiO}_2$ was greater than 300 during the entire ICU stay, ALI/ARDS was considered absent without further review. All intubated patients were also reviewed by three intensivist researchers (G.S., R.C.C., and O.G.) independently for confirmation of the diagnosis. The interobserver agreement was good (kappa 0.8). Disagreements were resolved after discussion among the three intensive care physicians.

Ascertainment of ARDS Cases

Trained critical care fellows reviewed digital chest radiographs (16), hemodynamic monitoring data, and echocardiography results of all patients identified by the ARDS screening tool. The presence or absence of ARDS was determined according to AECC definition (15). Patients identified as having ARDS were further reviewed by a second independent investigator (G.L.) blind to year sequence. For individuals with more than one episode of ARDS, only data from the first episode were included (1).

Sensitivity Analysis

Because of the subjective nature of the “absence of clinical signs of left atrial hypertension” component of the AECC criteria and the use of noninvasive ventilation in some patients with ARDS, sensitivity analyses were planned *a priori*. These analyses include (1) all cases of bilateral pulmonary infiltrates and hypoxemia (regardless of left atrial hypertension criteria); (2) patients receiving both invasive and noninvasive ventilation; (3) patients intubated and meeting criteria for ALI ($\text{PaO}_2/\text{FiO}_2 < 300$), but not ARDS; and (4) patients meeting criteria for either ALI or ARDS. In addition, we analyzed subsets of patients with ARDS on admission (met AECC criteria within 6 h of hospital admission); hospital-acquired ARDS (met AECC criteria >48 h after hospital admission); and ICU-acquired ARDS (met AECC criteria >48 h after ICU admission) (17).

Predisposing Conditions

The major risk factors for ARDS evaluated in this study include severe sepsis, pneumonia, pancreatitis, high-risk trauma, shock, and transfusion of more than 15 units of blood within a 24-hour period (18). The presence of severe sepsis, pneumonia, pancreatitis, high-risk trauma, and shock in the population of critically ill Olmsted County residents

was determined from the diagnosis ICD-9 codes (19, 20) on admission to the hospital (*see* online supplement). Blood transfusions were identified by review of the blood bank database.

Changes in Health Care Delivery

Institutional changes in delivery of critical care services over the 8-year study period were primarily aimed at decreasing “second hit” ARDS exposures. These exposures include multiple (>15 units) blood transfusions; plasma transfusion from potentially alloimmunized (female) donors (21); high tidal volume mechanical ventilation (22) (>8 ml predicted body weight or plateau airway pressure >30 cm H₂O);

Figure 2. Trends in age- and sex-specific incidence of acute respiratory distress syndrome from 2001–2008 in Olmsted County, Minnesota; dotted lines represent 95% confidence intervals. ALI = acute lung injury.

TABLE 2. CHARACTERISTICS AND OUTCOME OF ACUTE RESPIRATORY DISTRESS SYNDROME CASES IN OLMSTED COUNTY FROM 2001–2008

Characteristics	2001 (n = 75)	2002 (n = 72)	2003 (n = 78)	2004 (n = 79)	2005 (n = 57)	2006 (n = 67)	2007 (n = 44)	2008 (n = 42)	P for Linear Trends
Age, yr, median (IQR)	64 (52–74)	66 (46–77)	65 (47–80)	69 (54–79)	66 (44–80)	68 (47–79)	64 (52–78)	64 (51–80)	0.898
Female, n (%)	31 (41)	36 (50)	34 (44)	35 (44)	22 (39)	33 (49)	15 (34)	20 (48)	0.695
APACHE III score on admission, median (IQR)	64 (48–80)	67 (51–93)	64 (49–83)	75 (52–107)	76 (66–104)	85 (65–117)	84 (58–105)	76 (57–95)	<0.001
Charlson score, median (IQR)	3 (2–4)	3 (2–4)	3 (2–5)	3 (2–5)	4 (2–5)	5 (3–7)	4 (2–8)	4 (3–7)	<0.001
Time from hospital admission to the development of ARDS	38 (9–103)	18 (5–93)	32 (5–70)	41 (9–95)	27 (5–60)	22 (1–75)	11 (2–73)	14 (0–73)	0.041
Outcome									
Case-fatality-hospital, n (%)	21 (28)	27 (38)	23 (30)	30 (38)	21 (37)	26 (39)	12 (27)	19 (45)	0.449
ICU LOS, d, median (IQR)	7 (4–13)	8 (3–18)	7 (3–13)	7 (3–15)	7 (3–10)	5 (2–12)	7 (3–16)	7 (3–11)	0.119
Hospital LOS, d, median (IQR)	16 (10–30)	16 (8–34)	15 (9–24)	19 (11–30)	15 (7–25)	15 (8–32)	21 (13–31)	17 (9–33)	0.951
Ventilator-free days, d	12 (0–24)	10 (0–22)	17 (0–25)	17 (0–24)	19 (0–24)	16 (0–24)	13 (2–24)	14 (0–25)	0.412

Definition of abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation; ARDS = acute respiratory distress syndrome; ICU = intensive care unit; IQR = interquartile range; LOS = length of stay.

inadequate antibiotic treatment (>3 h after hospital admission) (23); and delayed goal-directed resuscitation in severe sepsis and septic shock (23). The number and types of blood products transfused were ascertained from the MCLSS and transfusion databases for all patients in the cohort. Data on structural changes (staffing and electronic records), exposures to adverse mechanical ventilator settings (22), changes in plasma donor procurement (21), leukoreduction (22), antibiotic treatment (23), and goal-directed resuscitation (23) were ascertained from previously published studies. Additional data obtained from hospital quality improvement initiatives were used.

Quality Control

We performed several steps to ensure the validity and reliability of data collection. First, we maintained a consistent MCLSS data extraction query over the entire study period. Second, the characteristics of the electronic ARDS screening tool were confirmed through the manual collection and review of all year 2006 data (review of both screening tool-positive and screening tool-negative patients). Third, all cases were separately reviewed by two investigators who underwent a standardized training protocol before study onset. Fourth, we performed additional search for frequency of chest radiograph and blood gas to check the potential change of diagnostic practice over time.

Statistical Analysis

Increasing (or decreasing) time trends for continuous ARDS risk factors were tested using a linear trend test in an analysis of variance. Increasing (or decreasing) categorical risk factors were tested using a linear term for time in a logistic regression analysis. Age and sex-specific incidence rates for ARDS were calculated, assuming the entire population of Olmsted County (≥ 18 yr) were at risk. Rates were calculated using the incident cases as the numerator. The denominator was the age- and sex-specific person-years derived from decennial census figures. Yearly, intercensus interpolations were calculated using high-degree polynomial. These numerator and denominator values were entered into a Poisson regression model to examine the temporal trends, age, and sex effects on the incidence of ARDS. Generalized additive models using a smoothing spline with four degrees of freedom were used to model the temporal and age trend in ARDS. Incidence rates along with 95% confidence intervals depicted in figures are based on the generalized additive models.

Statistical analyses were performed using the GENMOD procedure (SAS version 8; SAS Institute, Cary, NC) and Spls for generalized additive models (Mathsoft, Seattle WA). The traditional level of P less than 0.05 was used to reject the null hypothesis and all statistical tests were two-sided. Changes in ARDS case fatality over time were tested

TABLE 3. SENSITIVITY ANALYSIS OF ACUTE RESPIRATORY DISTRESS SYNDROME TRENDS

Characteristics	2001 (n = 939)	2002 (n = 885)	2003 (n = 1019)	2004 (n = 1025)	2005 (n = 1009)	2006 (n = 1178)	2007 (n = 996)	2008 (n = 983)	P for Linear Trends
All screening tool positive cases*, n (%)	485 (52)	452 (51)	448 (44)	425 (41)	446 (44)	430 (37)	258 (26)	195 (20)	<0.001
Invasively ventilated screening tool positive cases, n (%)	218 (23)	220 (25)	193 (19)	209 (20)	194 (19)	208 (18)	190 (19)	147 (15)	<0.001
All $\text{PaO}_2/\text{FiO}_2 < 300$ and bilateral infiltrates (AECC), n (%)	118 (13)	102 (12)	119 (12)	115 (11)	92 (9)	102 (9)	71 (7)	68 (7)	<0.001
ARDS (invasively ventilated), n (%)	75 (8)	72 (8)	78 (8)	79 (8)	57 (6)	67 (6)	44 (4)	42 (4)	<0.001
ARDS on admission†, n (%)	12 (1)	18 (2)	21 (2)	22 (2)	16 (2)	25 (2)	16 (2)	18 (2)	0.877
Hospital-acquired ARDS‡, n (%)	34 (4)	27 (3)	27 (3)	31 (3)	19 (2)	27 (2)	20 (2)	15 (2)	<0.001
ICU-acquired ARDS§, n (%)	17 (2)	18 (2)	13 (1)	17 (2)	10 (1)	10 (1)	11 (1)	10 (1)	0.010

Definition of abbreviations: AECC = American-European Consensus Conference; ARDS = acute respiratory distress syndrome; ICU = intensive care unit.

* $\text{PaO}_2/\text{FiO}_2 < 300$ and "edema or bilateral infiltrates."

† AECC criteria met within 6 h of hospital admission.

‡ AECC criteria met >48 h after hospital admission.

§ AECC criteria met >48 h after ICU admission.

in multivariate logistic regression analysis adjusting for severity of illness and comorbidities.

RESULTS

Validation of the Screening Protocol

The electronic ARDS screening tool evaluated the ICU admissions of all 1,707 Olmsted County patients who required ICU care in 2006. Four hundred and thirty patients with a $\text{PaO}_2/\text{FiO}_2$ less than 300 and bilateral infiltrates on digital chest radiographs were identified. Simultaneously, the electronic medical records of the 1,707 patients were independently reviewed. Sixty-seven patients were identified as meeting AECC criteria for ARDS; 27 met criteria only for ALI ($\text{PaO}_2/\text{FiO}_2$ 200–300). The electronic surveillance tool demonstrated a sensitivity of 99% (91–100%) and specificity of 78% (76–80%). A single case of ARDS was missed in the year 2006 where radiology reports used the word “opacities” instead of “infiltrates.” Modified screening that included both “opacities” and “infiltrates” did not identify any additional cases of ARDS. Additional search for the frequency of chest radiograph examinations showed no significant decrease on average chest radiograph exposure of patients on mechanical ventilation (*see* Table E1 in the online supplement). No significant change of blood gas analyses was observed over time (Table E1).

Characteristics and Outcome of the Population-based Cohort

A total of 8,034 Olmsted County patients were admitted to an ICU at Mayo Clinic in Rochester during the study period (2001–2008) (Figure 1). The baseline characteristics and outcome of patients with pertinent risk factors are summarized in Table 1. Over the 8-year study period, we observed an increased severity of illness, greater number of comorbidities, and increasing prevalence of major predisposing conditions for ARDS (Table E2). However, all-cause ICU and hospital mortality, and ICU and hospital lengths of stay decreased over time (Table 1).

Temporal Trends of ARDS Incidence

Of 3,139 episodes identified by the ARDS screening protocol, 795 met AECC criteria (Figure 1). Five hundred and fourteen unique patients met the previously published population-based criteria for ARDS (1) (invasive mechanical ventilation for acute respiratory failure or invasive mechanical ventilation for >12 h after an operative procedure) (Figure 1). Over the 8-year study period, the age- and sex-specified incidence of ARDS in Olmsted County decreased from 81 to 38.3 cases per 100,000 person-years ($P < 0.001$) (Figure 2).

Characteristics and Outcome of ARDS Cases

The baseline characteristics and outcomes of patients with ARDS are shown in Table 2. ICU and hospital lengths of stay decreased over time, whereas case fatality rate and 28 ventilator-free days did not change significantly (Table 2). After adjustment of baseline Acute Physiology and Chronic Health Evaluation III score and Charlson score, the mortality rate still did not change over the time (Table E3).

Sensitivity Analysis

Although the incidence of ARDS on admission (AECC criteria met within 6 h of hospital admission) remained stable over the study period, the incidences of hospital- and ICU-acquired ARDS fell dramatically (Figure 3). Our sensitivity analyses including patients with ALI who did not meet the criteria for ARDS, patients treated without invasive mechanical ventilation, and all screening tool-positive patients ($\text{PaO}_2/\text{FiO}_2 < 300$,

and bilateral infiltrates regardless of the presence or absence of left atrial hypertension), confirmed the reduction in both ALI and ARDS over recent years (Table 3).

Changes in Health Care Delivery

Significant changes in hospital practice aimed at decreasing the incidence of hospital-acquired ARDS consisted of (1) decreased exposure to blood product transfusion (Figure E1); (2) change in donor procurement (male-predominant plasma); (3) low tidal volume mechanical ventilation according to predicted body

Figure 3. (A) Trends of community-acquired acute respiratory distress syndrome incidence from 2001–2008 in Olmsted County, Minnesota; dotted lines represent 95% confidence intervals. (B) Trends of hospital-acquired acute respiratory distress syndrome incidence from 2001–2008 in Olmsted County, Minnesota; dotted lines represent 95% confidence intervals. ALI = acute lung injury.

Figure 4. Changes in hospital care delivery. ¹CPOE = computerized provider order entry; ²P for linear trends less than 0.0001; ³Average tidal volume at the onset of mechanical ventilation (milliliter per kilogram predicted body weight); ⁴MICU = medical intensive care unit.

weight in all ventilated patients (Figure E2); and (4) improved treatment of sepsis and pneumonia (Figure 4). Additional changes included on-site, nighttime intensivist staffing, hospital-wide deployment of a rapid response team, and implementation of electronic medical records (Figure 4).

DISCUSSION

Despite a higher severity of acute illness, greater number of comorbidities, and increased prevalence of major predisposing conditions for ARDS, the incidence of this devastating syndrome has fallen dramatically in Olmsted County residents over the past 8 years. The observed reduction in ARDS cases occurred exclusively in patients with hospital-acquired ARDS because the incidence of ARDS on admission to the hospital remained stable over the study period (Figure 3). Significant concurrent changes in critical care structure and delivery aimed at reducing second "hit" ARDS exposures were noted. Although a cause-effect relationship cannot be verified, the observed findings strongly suggest that ARDS may be in part a preventable hospital-acquired complication, similar to venous thromboembolism, stress ulcer bleeding, and nosocomial infections. These results also imply potential difficulty enrolling patients in future clinical trials on ALI and ARDS.

Several improvements in health care delivery may have contributed to the decreasing temporal trend in ARDS for

Olmsted County residents (Figure 4). After publication of evidence noting adverse outcomes with high tidal volume ventilation (24), an interdisciplinary team of intensivists and respiratory therapists designed a protocol that limits tidal volume to a maximum of 10 ml/kg predicted body weight in all patients receiving invasive ventilation and 6–8 ml/kg predicted body weight for patients at risk of ALI/ARDS. This protocol was initiated in the year 2003. Recently, a randomized clinical trial confirmed the relationship between initial tidal volume and the development of ARDS (25).

The transfusion practices at our institution have changed substantially (Figure 4). A restrictive, evidence-based red blood cell transfusion strategy has now been used in the ICUs at Mayo Clinic since 2006 (11, 26). Several studies have demonstrated a strong correlation between transfusion and development of ALI/ARDS (11, 21, 22, 27, 28). Previous studies have also shown that male donor-only fresh frozen plasma transfusions are associated with better outcome (29–31). In light of these data, fresh frozen plasma transfusion at Mayo Clinic was restricted to male only-donors starting in November 2007.

Additional changes in the structure and delivery of critical care services during the study period include the rapid administration of appropriate empiric antibiotics for suspected pneumonia; improvements in sepsis resuscitation (sepsis order-set and dedicated sepsis team); the hospital-wide rapid response team; 24-hour in-house intensivist staffing model (32); and the

implementation of electronic medical records (Figure 4). The study design did not allow us to determine the effect (if any) of these interventions on the observed findings.

There are a number of important limitations with this investigation. Epidemiologic studies using clinical data that lack a prospective, systematic protocol for patient evaluation must consider the possibility that apparent changes in incidence are the artifactual results of changes in case ascertainment. Although the use of daily routine chest radiographs is discouraged, significant changes in clinical condition (worsening acute hypoxemia, respiratory distress) usually prompt radiographic evaluation of hospitalized patients in our institution. Therefore, it is extremely unlikely that the observed decrease of ARDS incidence could be explained by ascertainment bias.

However, patients may be misclassified because of inherent limitations in the definition of ARDS: the variability in radiographic interpretation and the exclusion of left atrial hypertension. We minimized the risk of misclassification by maintaining strict quality control and an independent review of each screen-positive case by at least two trained physicians. In addition, screening and confirmation criteria remained consistent throughout the study period. Although we focused on ARDS (to minimize the potential for missing milder cases), in our sensitivity analyses (Table 3), inclusion of both ALI and ARDS, regardless of the use of invasive or noninvasive ventilation, identified a greater number of cases, but similar trends in the incidence of ALI and ARDS. To control for investigator bias, an independent review of all screening tool-positive cases was also performed. A similar trend across the 8-year study period was noted with this evaluation (Table 3). The misclassification is unlikely to have occurred because we did not notice an increase of other causes of hypoxemia and bilateral infiltrates (suggesting misclassification of ALI into cardiogenic pulmonary edema or atelectasis) in parallel with a decrease in ALI (Table 3, sensitivity analysis). Although a significant drop in chest radiograph frequency during hospital stay was observed over time, no change in mechanical ventilated patients and the proportion of days $\text{Pa}_{\text{O}_2}/\text{Fi}_{\text{O}_2}$ less than 300 without chest radiographs does not affect the consistency of our screening tool to detect clinically significant ARDS over time (Table E1).

Although we believe that changes in critical care structure and delivery were the major factors contributing to the temporal reduction in the incidence of ARDS, a cause-effect relationship cannot be determined by nonexperimental design. Additional advancements in the care of both outpatients and hospitalized patients almost certainly contributed to the reduce rates of ARDS. The extent of this contribution and details of the specific interventions resulting in a lower ARDS incidence would only be speculative at this point. Additional factors, such as greater emphasis on the goals of end-of-life care, could have also resulted in fewer patients with ARDS being admitted to the ICU. Conceivably, this too may have falsely lowered our ARDS incidence rate. The increased number of ICU admissions and greater prevalence of major predisposing conditions for ARDS over the course of the study period argue against this concern.

Finally, perhaps the greatest limitation of this investigation is the single-region, single-institution nature of the study population. Although strengthened by its population-based nature, unique aspects of either Olmsted County residents or care delivered at Mayo Clinic Rochester may limit the generalizability of the study results. Nonetheless, although baseline incidences of ARDS may vary throughout the world, the improved processes of care and associated reductions in ARDS incidence witnessed in this unique geographic location should generalize broadly.

Conclusions

This population-based study revealed a significant decrease in the incidence of ARDS in Olmsted County residents over the past 8 years. Correlation of the observed findings with significant concurrent changes in critical care structure and delivery suggests that the incidence of ARDS and its associated consequences can be attenuated by changes in health care delivery, specifically when aimed at prompt recognition and timely treatment of major predisposing conditions for ARDS. The avoidance of pertinent “second hit” hospital exposures may also have important implications for the planning of acute care services in other institutions. Although the unchanged case-fatality rate indicates an ongoing need for studies directed at the treatment of established ARDS, increasing evidence points to a potentially more important role for ARDS prevention.

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