Promoting Global Research Excellence in Severe Sepsis (PROGRESS): Lessons from an International Sepsis Registry

R. Beale, K. Reinhart, F.M. Brunkhorst, G. Dobb, M. Levy, G. Martin, C. Martin, G. Ramsey, E. Silva, B. Vallet, J.-L. Vincent, J.M. Janes, S. Sarwat, M.D. Williams, for the PROGRESS Advisory Board

Abstract

Background: The PROGRESS Registry (Promoting Global Research Excellence in Severe Sepsis) was designed to provide comparative data reflecting everyday clinical practice, thereby allowing participating institutions to explore and benchmark medical interventions in severe sepsis.

Materials and Methods: PROGRESS was an international, noninterventional, prospective, observational registry collecting data that describe the management and outcomes of severe sepsis patients in intensive care units (ICUs). Patients were enrolled who had been diagnosed with severe sepsis (suspected or proven infection and ≥ 1 acute sepsis-induced organ dysfunction) at the participating institutions, where de-identified data were entered directly into a secured website. PROGRESS was governed by an independent international medical advisory board.

Results: PROGRESS took place in 276 ICUs in 37 countries, and 12,881 patients were identified as having severe sepsis. There was considerable variation among countries in enrollment levels, provision of standard treatment and supportive therapies, and ICU and hospital outcomes. Eight countries accounted for 65.2% of the enrolled patients. Males (59.3%) and Caucasian (48.6%) patients predominated the patient cohort. Diagnosis of severe sepsis was prior to ICU admission in 45.7% of patients, at ICU admission in 29.1% of patients, and after ICU admission in the remainder. Globally, ICU and hospital mortality rates were 39.2% and 49.6%, respectively. The mean length of ICU and hospital stay was 14.6 days and 28.2 days, respectively.

Conclusions: The PROGRESS international sepsis registry demonstrates that a large web-based sepsis registry is feasible. Wide variations in outcomes and use of sepsis therapies were observed between countries. These results also suggest that additional opportunities exist across countries to improve severe sepsis outcomes.

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Abbreviations: APACHE: Acute physiology and chronic health evaluation; AUROC: Area under the receiver operating curve; ICU: Intensive care unit; INDEPTH: Integrated database for the evaluation of severe sepsis and drotrecogin alfa (activated) therapy; LODS: Logistic organ dysfunction system; MODS: Multiple organ dysfunction score; PROGRESS: Promoting Global Research Excellence in Severe Sepsis; ROC: Receiver operating curve; SAPS: Simplified acute physiology score; SIRS: Systemic inflammatory response syndrome; SOFA: Sequential organ failure assessment; SOAP: Sepsis occurrence in acutely ill patients

Introduction

Several recent randomized controlled studies [1–5] have substantially changed our approach to patients with

R. Beale *(corresponding author)*
Adult Intensive Care Unit, Guy's and St. Thomas' NHS Foundation Trust, St. Thomas' Hospital, Lambeth Palace Road, London SE1 7EH, London, UK; e-mail: Richard.Beale@gstt.nhs.uk
K. Reinhart, F.M. Brunkhorst
Dept. of Anesthesiology and Intensive Care, Friedrich Schiller University, Jena, Germany
G. Dobb
School of Medicine and Pharmacology, Royal Perth Hospital, Perth, WA, Australia
M. Levy
Brown University School of Medicine, Providence, RI, USA
G. Martin
Division of Pulmonary, Allergy, and Critical Care, Emory University, Atlanta, GA, USA
C. Martin
London Health Sciences Center, London, ON, Canada
G. Ramsey
West Hertfordshire Health Trust, Hemel Hempstead, UK
E. Silva
Hospital Israelita Albert Einstein, Sao Paolo, Brazil
B. Vallet
Dept. of Anesthesiology and Intensive Care, University Hospital of Lille, University of Lille 2, Lille, France
J.-L. Vincent
Dept. of Intensive Care, Erasme University Hospital, Brussels, Belgium
J.M. Janes, S. Sarwat, M.D. Williams
Lilly Research Laboratories, Eli Lilly and Co, Indianapolis, IN, USA

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severe sepsis as well as our recognition of what sepsis is and its healthcare impact [6, 7]. Modern healthcare systems are under pressure to deliver better patient outcomes and value, with greater emphasis on ''evidence-based'' medicine [8, 9], and sepsis care is at the forefront of this process, as illustrated by The Surviving Sepsis Campaign with its evidence-based sepsis guidelines and care bundle change-management program [9, 10]. Paradoxically, these efforts have highlighted how poorly clinical practice is understood, and even sepsis prevalence data vary widely [11–13]. Although research databases from large sepsis studies are of high quality, they only contain data from a subset of septic patients and rarely fully describe everyday clinical practice which, in actual fact, may not be widely adopted – even where generally accepted evidence exists [14]. Moreover, in most published sepsis trials, the enrolled patients are predominantly from North America and Europe, even though severe sepsis is a global disease. It is therefore important to understand fully its epidemiology and treatment.

PROGRESS (Promoting Global Research Excellence in Severe Sepsis) was therefore designed as an internet-based international sepsis registry to increase the awareness of sepsis and its management. We describe here the initial results of this novel initiative.

Materials and Methods

Study Design

PROGRESS was a global, noninterventional, multicenter, prospective, observational registry study of patients with severe sepsis (sepsis and acute organ dysfunction) treated in an intensive care unit (ICU). The key organizational components included (1) support from a major pharmaceutical company with experience in the sepsis field (Eli Lilly and Company, Indianapolis, IN) using its standard research operating procedures, (2) patient anonymity, (3) Institutional Review Board and patient consent where necessary, (4) the payment of a small fee for each patient enrolled (provided by the company) to assist with the costs of data entry, and (5) the use of a steering committee with clear governance rules covering data access, ownership, and publications. Registry participation required that the site lead physician and designated colleagues completed a brief training exercise, following which they were given password access to the website for data entry. Each site had an ''Institution Administrator'' who was responsible for adding and deleting institution personnel authorized to perform study-related activities. No attempt was made to alter standard care at participating institutions, and there were no study-specific interventions. Data collection was aimed at capturing an accurate description of the practice of severe sepsis management at that time, and study entry was strictly anonymous, with patients tracked using a study-specific identifier code without connection to the hospital record or any personal identifier. Software development and website maintenance were funded by Eli Lilly and Company.

Patients

Patients with severe sepsis, defined as evidence of infection with at least one sepsis-induced organ dysfunction (see Disease Diagnostic Criteria – Appendix 1) and admitted to a participating ICU, could be included in the study. Both adult and pediatric patients were allowed, but only adults are considered in this report (Figure 1). Consecutive patient data entry was encouraged to maximize data validity, and patients treated on more than one occasion were given a unique record number for each severe sepsis hospitalization. Major data-collection fields included patient demographics, comorbid conditions, disease diagnostic criteria, measures of disease severity, details of the primary infection site, source, causative pathogen (if known), patient outcome, and ICU treatment modalities. Clinical features were quantified utilizing standard scoring systems. The total sequential organ failure assessment (SOFA) score [15], multiple organ dysfunction score (MODS) [16] and logistic organ dysfunction system (LODS) [17] score were based on the most abnormal score recorded within ±12 h of the severe sepsis diagnosis. The total acute physiology and chronic health evalu-

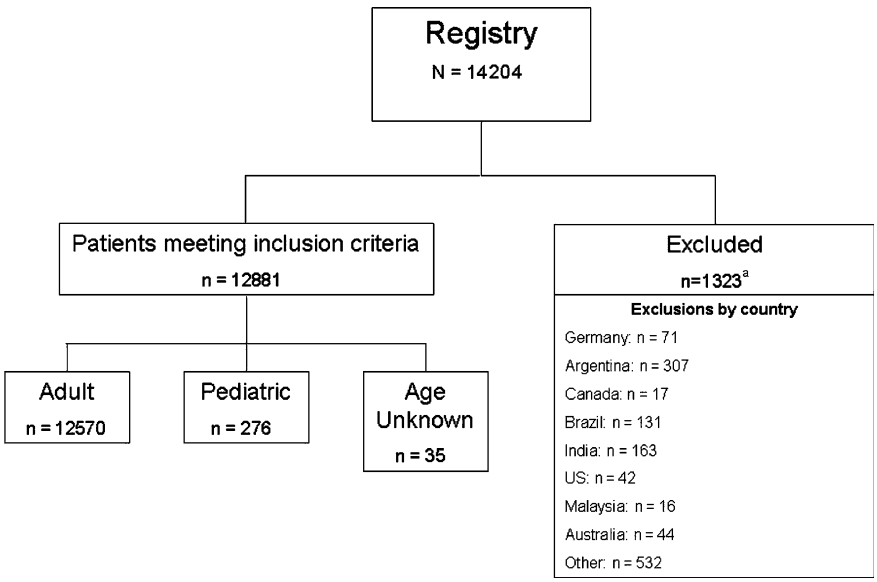

Figure 1. Flow chart of enrolled patients.
[a]1315 patients without severe sepsis + 8 patients' data entered before website complete and officially available in December 2002.

ation (APACHE) II [18,19] and simplified acute physiology score (SAPS) II [20] were calculated based on the most abnormal measurements recorded within 24 h of patient admission to the ICU.

Data validation was performed via online checks at data entry or at submission of the electronic form. Data were maintained and stored by Eli Lilly and Company, and source documents were archived at each site according to usual practices. Study oversight and database access control were provided by an Advisory Board appointed by Eli Lilly and Company according to a predefined written agreement.

Data Reporting

Online reporting allowed centers to generate reports using all records from their institution, state/province, country, region, or all records entered worldwide. Participating physicians could view all the data from their own institution, but not the detailed data for other institutions.

Statistical Methods

The analysis included patients with severe sepsis for the period December 2002 to December 2005. Nonseptic patients were excluded. All statistical analyses were performed using SAS ver. 9.1 (SAS Institute, Cary, NC), and significance tests were performed at a two-sided alpha level of 0.05. Data for binary variables were summarized using percentages. Continuous and multinomial variables were summarized using means and standard deviations.

Receiver operating curve (ROC) analysis, including area under the ROC (AUROC), was used for comparison of prognostic methods as predictors of overall ICU mortality for patients with severe sepsis. The SE of ROC was calculated using the formula based on *Hanley and McNeil* [21]. Study investigators were responsible for their data quality, and internal consistency checks of reliability and validity were performed on baseline characteristics (e.g. disease severity scores, chronic conditions, and comorbidities). The internal data consistency checks were performed by testing the association between various baseline characteristics using Pearson's χ^2-square test [22].

Results

After 36 months, the PROGRESS Registry had received data on 12,881 patients with severe sepsis from 276 institutions in 37 countries. In order of number of patients, these were Germany (n = 1,885), Argentina (n = 1,326), Canada (n = 1,232), Brazil (n = 982), India (n = 841), USA (n = 762), Malaysia (n = 686), Australia (n = 679), Mexico (n = 516), Philippines (n = 493), Belgium (n = 372), Chile (n = 351), Peru (n = 300), Singapore (n = 255), Poland (n = 211), Columbia (n = 193), Taiwan (n = 182), Israel (n = 182), Thailand (n = 176), New Zealand (n = 148), Turkey (n = 130), Netherlands (n = 121), Algeria (n = 111), Hong Kong (n = 100), Saudi Arabia (n = 100), Romania (n = 84), Egypt (n = 79), Hungary (n = 76), Lebanon (n = 68), Austria (n = 56), Slovakia (n = 48), China (n = 47), Kuwait (n = 32), Venezuela (n = 24), Puerto Rico (n = 21), South Africa (n = 11), and United Arab Emirates (n = 1). The results are presented for all patients (global) and for the highest eight recruiting countries (Germany, Argentina, Canada, Brazil, India, USA, Malaysia, and Australia). Of the ICUs, 49.3% were mixed medical and surgical units, 22.1% were medical units, 16.7% were surgical units, and the remaining were coronary, burn, neurological, and pediatric ICUs. Institution and ICU characteristics are summarized in table 1 (includes adult and pediatric patients).

Demographic data are presented in table 2 for 12,570 adult patients. The pattern of ICU referral showed that 76.5% of patients were ''transferred within hospital,'' with 27.5% from wards, 22.3% from the emergency department, 20.6% from the operating room, and 6.0% from intermediate care and chronic care. A total of 13.4% of patients came from other hospitals, and 6.7% of patients were admitted directly from the community (the ''admitted directly from community'' category included patients who stayed less than 6 h in the emergency department). The remaining patients came from other ICUs (3.1%) or an unknown admission source (0.4%).

A total of 52.7% of infections were community acquired, 27% were acquired in the hospital but outside the ICU, and 17.3% were acquired within ICU. In 3% of patients, the place of acquisition was unknown. The primary site of infection was the lung in 45.3% of cases, abdomen or pelvis in 22.9%, urinary tract in 7.7%, blood in 6.4%, skin in 5.0%, other in 5.2%, unknown in 2.6%, meninges in 1.5%, bone and joints in 1.4%, indwelling catheter or vascular access site in 1.4%, and dialysis access site in 0.7%. Also, 41.4% of patients had Gram-negative organisms, 32.4% had Gram-positive organisms, and in 34%, the infection type was not determined. Fungal infections occurred in 8.7% of patients and viral infections in 1.3%, with geographic variations in this rate. Parasitic infections were rare, accounting for less than 1% of infections. A total of 22.1% of cases required surgical drainage, and 19.9% required ''another surgical procedure'' for source control.

Severe sepsis was diagnosed in 45.7% of patients prior to ICU admission, in 29.1% at ICU admission, and in the remainder after ICU admission. Of those, 98% manifested two or more systemic inflammatory response syndrome (SIRS) criteria, and 86.9% had three or more SIRS criteria (90.4% tachycardia, 87.8% tachypnea, 82.5% leukocytosis or leucopenia, and 74.8% alteration in temperature). A total of 89.8% of patients had multiple organ dysfunction (23.1% three-organ dysfunction, 20.4% two-organ dysfunction, and 20.1% four-organ dysfunction). The proportion of patients with specific organ dysfunctions were as follows: 81.2% had respiratory dysfunction, 74.6% cardiovascular dysfunction, 45.0% renal dysfunction, 42.2% metabolic dysfunction, 32.6% hematological dysfunction, 31.7% central nervous system dysfunction, and 18.0% hepatic dysfunction. Comorbidities were common: 20.9% of patients had diabetes, 16.5% chronic lung disease, 15.0% active malignancy, 13.8% congestive heart failure, 10.7% chronic renal insufficiency, 6.2% chronic liver

Table 1
Hospital and intensive care unit characteristics.

Hospital and ICU characteristics	All patients								
	Global (n = 12,881)	Germany (n = 1,885)	Argentina (n = 1,326)	Canada (n = 1,232)	Brazil (n = 982)	India (n = 841)	US (n = 762)	Malaysia (n = 686)	Australia (n = 679)
Total number of institutes	276	13	18	12	8	21	33	4	4
Type of Institute, n (%)[a]									
University	65 (23.6)	7 (53.8)	2 (11.1)	–	1 (12.5)	2 (9.5)	6 (18.2)	3 (75.0)	–
University affiliated	111 (40.2)	4 (30.8)	11 (61.1)	6 (50.0)	3 (37.5)	4 (19.0)	7 (21.2)	–	1 (25.0)
Community	100 (36.2)	2 (15.4)	5 (27.8)	6 (50.0)	4 (50.0)	15 (71.4)	20 (60.6)	1 (25.0)	3 (75.0)
Total hospital beds (mean ± SD)	654.2 ± 531.6	1113.4 ± 495.1	207.9 ± 101.8	–	350.0 ± 269.3	359.2 ± 242.9	645.8 ± 486.0	654.3 ± 435.2	565.0 ± 218.4
Total number of ICUs	335	15	19	12	11	32	60	5	4
ICU Type, n (%)[a]									
Medical	74 (22.1)	5 (33.3)	1 (5.3)	–	2 (18.2)	10 (31.3)	21 (35.0)	–	–
Surgical	56 (16.7)	4 (26.7)	–	–	1 (9.1)	6 (18.8)	12 (20.0)	–	–
Surgical (neuro)	8 (2.4)	–	–	–	–	2 (6.3)	4 (6.7)	–	–
Mixed	165 (49.3)	6 (40.0)	15 (78.9)	12 (100.0)	7 (63.6)	8 (25.0)	13 (21.7)	4 (80.0)	4 (100.0)
Coronary	16 (4.8)	–	–	–	1 (9.1)	4 (12.5)	7 (11.7)	–	–
Burn	1 (0.3)	–	–	–	–	–	1 (1.7)	–	–
Other	15 (4.5)	–	3 (15.8)	–	–	2 (6.3)	2 (3.4)	1 (20.0)	–
Total ICU beds (mean ± SD)	18.1 ± 37.5	19.1 ± 10.1	16.4 ± 6.9	16.5 ± 5.7	15.1 ± 7.1	16.4 ± 8.7	21.4 ± 17.6	14.4 ± 5.2	26.8 ± 11.5
Ventilator beds (%)[a]	86.6	95.4	68.3	–	94.8	49.5	98.0	95.0	78.6

ICU: intensive care unit; [a] Percentages that have been rounded for presentation purposes may not add up to 100% exactly

Table 2
Patient characteristics.

Patient characteristics	Adult patients only								
	Global (n = 12,570)	Germany (n = 1,855)	Argentina (n = 1,269)	Canada (n = 1,215)	Brazil (n = 969)	India (n = 803)	US (n = 761)	Australia (n = 669)	Malaysia (n = 641)
Gender (%)[a]									
Males	59.3	63.7	58.7	60.0	57.7	66.6	55.3	58.6	61.8
Age, years (mean ± SD)	60.4 ± 17.5	64.2 ± 14.5	60.9 ± 18.5	61.2 ± 16.3	61.2 ± 18.4	54.8 ± 17.6	61.7 ± 16.8	56.7 ± 18.0	50.1 ± 17.9
Age group, years[a] (%)									
18 to <30	7.0	2.6	7.6	4.7	7.5	12.3	4.1	10.6	17.5
30 to <45	12.2	8.4	11.7	10.0	13.0	14.3	12.5	16.6	21.8
45 to <65	33.4	32.2	34.0	38.5	29.0	40.0	36.1	31.2	34.8
65 to <72	16.4	21.5	14.1	14.0	16.0	16.1	13.8	15.9	12.6
72+	31.0	35.3	32.6	32.8	34.5	17.3	33.5	25.7	13.3
Ethnicity (%)[a]									
Caucasian	48.6	99.1	67.8	–	5.3	1.0	70.0	89.8	–
African	2.1	0.2	0.1	–	3.8	–	19.8	0.5	0.2
East/South East Asian	19.0	0.3	0.2	–	0.6	34.5	1.2	2.7	90.3
West Asian	5.3	0.2	0.1	–	0.6	61.4	0.3	1.0	9.5
Hispanic	22.1	0.2	31.2	–	85.4	0.1	7.8	0.6	–
Other	2.9	–	0.6	–	4.3	3.0	0.9	5.4	–
Medical/surgical (%)[a]									
Medical	62.3	41.9	64.4	66.1	61.2	78.6	79.8	66.4	69.4
Surgical	37.7	58.1	35.6	33.9	38.8	21.4	20.2	33.6	30.6
Elective	10.7	21.2	5.8	13.2	10.1	6.3	7.9	5.5	3.9
Emergency	27.0	36.9	29.8	20.7	28.7	15.1	12.3	28.1	26.7

[a] Percentages that have been rounded for presentation purposes may not add up to 100% exactly

Table 3
Patient management.

Patient management	Adult patients only								
	Global (n = 12,570)	Germany (n = 1,855)	Argentina (n = 1,269)	Canada (n = 1,215)	Brazil (n = 969)	India (n = 803)	US (n = 761)	Australia (n = 669)	Malaysia (n = 641)
Supportive therapy (%)									
Ventilation	85.4	89.2	78.3	89.0	92.1	64.6	76.1	89.2	98.6
Fluid resuscitation	78.3	94.9	86.3	–	94.0	64.1	85.2	86.0	93.0
Vasopressor	78.6	93.5	69.4	62.0	76.1	60.2	77.4	88.6	89.2
Renal replacement	21.3	33.4	11.7	14.9	21.3	15.3	18.5	25.9	22.8
Sedation	68.6	92.8	72.5	–	80.7	40.2	73.2	92.7	95.8
Unfractionated heparin	39.9	62.9	61.2	72.4	54.2	7.9	30.6	60.8	31.5
LMW heparin	34.5	49.4	14.11	15.5	45.9	21.8	31.5	16.3	16.1
Mechanical VTE prophylaxis	21.6	34.3	4.7	–	4.8	23.4	66.8	72.8	1.4
Enteral nutrition	72.4	79.8	72.2	79.2	74.5	75.6	56.5	78.0	76.3
Parenteral nutrition	33.1	66.7	8.8	25.8	8.5	49.8	27.2	17.6	22.0
Systemic antibiotics	99.0	99.0	98.0	99.3	99.6	99.6	99.5	99.7	95.5
Albumin	19.3	6.5	8.7	–	10.0	37.9	20.8	53.4	29.0
Platelets	14.8	21.3	5.4	–	11.2	12.3	14.7	25.4	32.1
Adjunctive therapy (%)									
Antithrombin	3.0	12.0	0.1	–	0.8	0.1	0.9	11.8	–
Gamma globulin	1.5	1.3	0.4	–	2.3	0.4	1.2	2.4	0.9
Nitric oxide	1.5	1.9	0.1	–	–	–	0.8	10.0	0.2
Low-dose steroids	36.1	50.9	29.3	37.9	59.9	29.8	29.7	29.3	11.1
High-dose steroids	12.6	11.1	14.4	14.7	5.2	10.2	22.6	8.5	6.9
DrotAA	7.0	5.3	1.7	8.3	6.7	3.6	27.1	7.9	1.9

VTE: Venous thromboembolism; LMW, low molecular weight; DrotAA: drotrecogin alfa

Table 4
Intensive care unit outcomes in severe sepsis patients.

Intensive care unit outcomes	Adult patients only								
	Global (n = 12,570)	Germany (n = 1,855)	Argentina (n = 1,269)	Canada (n = 1,215)	Brazil (n = 969)	India (n = 803)	US (n = 761)	Australia (n = 669)	Malaysia (n = 641)
Overall ICU mortality (%)	39.2 (4,933/12,570)	36.3 (674/1,855)	46.6 (591/1,269)	30.3 (368/1,215)	56.1 (544/969)	37.4 (300/803)	33.0 (251/761)	22.0 (147/669)	56.8 (364/641)
Severity score mean[a] ± SD (n)									
APACHE II	23.3 ± 8.3 (9,191)	27.0 ± 8.3 (1,384)	22.9 ± 7.5 (1,110)	23.4 ± 7.9 (1,171)	22.8 ± 7.5 (919)	19.8 ± 7.2 (427)	26.1 ± 8.4 (232)	20.6 ± 7.7 (660)	24.2 ± 8.7 (446)
Total SOFA	9.3 ± 3.9 (5,135)	10.5 ± 3.5 (1,021)	6.9 ± 3.8 (639)	–	8.5 ± 3.7 (923)	10.1 ± 3.9 (90)	10.5 ± 3.9 (81)	10.1 ± 3.6 (171)	10.4 ± 3.7 (554)
SAPS II	49.1 ± 17.4 (3,000)	49.9 ± 15.7 (800)	48.4 ± 17.6 (128)	–	46.1 ± 13.7 (548)	36.4 ± 22.1 (7)	57.3 ± 23.2 (38)	–	51.6 ± 20.0 (556)
MODS	6.5 ± 3.6 (2,418)	6.5 ± 2.6 (11)	7.4 ± 4.1 (82)	6.5 ± 3.2 (1,193)	6.6 ± 3.1 (384)	12.8 ± 7.2 (13)	–	–	–
APACHE III	74.2 ± 33.3 (747)	59.8 ± 28.5 (16)	67.8 ± 27.6 (20)	–	72.5 ± 22.0 (22)	76.1 ± 19.6 (17)	35.0 ± 0 (1)	31.5 ± 7.8 (2)	–
LODS	6.9 ± 3.7 (986)	7.5 ± 2.8 (11)	7.9 ± 3.7 (71)	–	5.2 ± 2.8 (451)	–	–	–	–
ICU stay mean (days)	14.6 ± 16.1	19.2 ± 17.9	12.9 ± 15.2	15.4 ± 17.5	14.8 ± 15.1	10.2 ± 9.2	12.3 ± 13.1	15.5 ± 15.3	12.4 ± 16.0
For survivors	15.3 ± 16.6	19.6 ± 17.6	14.3 ± 16.7	15.6 ± 17.8	16.4 ± 16.7	10.4 ± 9.4	12.5 ± 12.7	15.9 ± 15.8	14.3 ± 15.6
For non-survivors	13.4 ± 15.4	18.4 ± 18.3	11.3 ± 13.1	14.9 ± 16.9	13.6 ± 13.6	9.9 ± 8.9	12.1 ± 13.9	13.7 ± 13.5	11.0 ± 16.1
ICU discharge location (%)[b]									
Community	2.2	1.2	1.6	0.9	1.2	7.0	1.8	–	1.5
Other ICU	1.8	4.8	0.3	0.3	0.5	4.8	0.6	–	0.7
Intermediate care	19.5	15.9	15.6	0.4	13.9	19.7	27.5	6.9	38.6
Ward	67.1	54.2	75.1	90.1	83.0	55.6	58.2	91.2	58.5
Other hospital	6.7	17.0	2.5	7.4	0.7	12.9	3.5	1.7	0.7
External care	2.2	5.7	4.3	0.8	0.5	–	7.8	0.2	–
Other/unknown	0.5	1.2	0.6	0.1	0.2	–	0.6	–	–

[a]For definition of abbreviations, see Abbreviation section at beginning of article; [b] Percentages that have been rounded for presentation purposes may not add up to 100% exactly

Table 5
Hospital outcomes in severe sepsis patients.

Hospital outcomes	Adult patients only								
	Global (n = 12,570)	Germany (n = 1,855)	Argentina (n = 1,269)	Canada (n = 1,215)	Brazil (n = 969)	India (n = 803)	US (n = 761)	Australia (n = 669)	Malaysia (n = 641)
Overall hospital mortality, % (n)	49.6 (5,659/11,417)	43.4 (781/1,799)	56.6 (602/1,063)	50.4 (416/825)	67.4 (649/963)	39.0 (307/788)	42.9 (310/723)	32.6 (203/623)	66.1 (423/640)
Hospital stay mean ± SD (days)	28.2 ± 30.0	34.1 ± 26.5	21.1 ± 21.4	31.9 ± 45.3	33.2 ± 36.4	14.5 ± 11.6	20.9 ± 18.6	38.4 ± 39.4	23.7 ± 26.9
For survivors	33.7 ± 31.1	39.7 ± 26.6	26.1 ± 24.0	37.5 ± 34.8	45.8 ± 50.8	16.2 ± 12.0	23.1 ± 19.0	42.7 ± 39.8	31.9 ± 26.6
For non-survivors	22.7 ± 27.8	26.6 ± 24.5	17.3 ± 18.4	26.5 ± 53.1	27.1 ± 24.7	11.9 ± 10.5	18.1 ± 17.8	29.1 ± 36.9	19.5 ± 26.1
Hospital discharge location (%)									
Community	68.0	48.5	68.6	59.2	92.0	80.7	41.2	59.0	88.9
Chronic care	12.3	13.7	10.6	15.1	3.5	2.5	51.1	18.6	1.4
Other hospital	16.4	30.2	6.3	25.7	4.2	16.6	5.1	22.4	9.2
Other/unknown	3.3	7.6	14.5	–	0.3	0.2	2.6	–	0.5

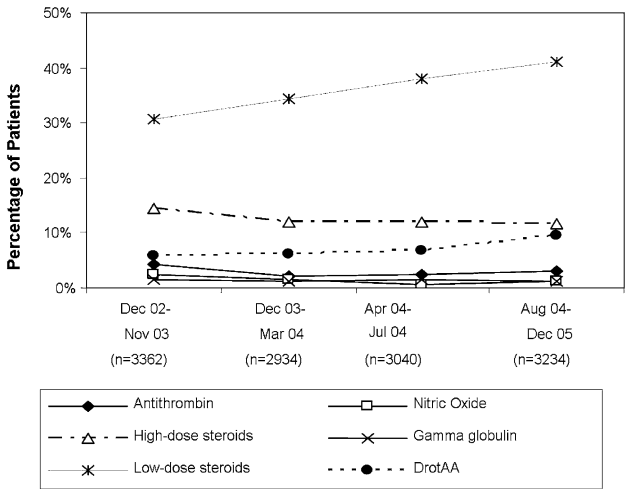

Figure 2. Adjunctive therapy over time.

disease, and 21.4% a chronic disabling condition listed as ''other.'' In addition, 8.9% of patients were receiving chronic steroid therapy, 4.6% chemotherapy, 1.6% radiotherapy, and 3.1% ''other'' immunosuppressants.

There was considerable geographical variation in the ICU and hospital outcomes, and in the provision of standard treatment and supportive therapies, as shown in tables 3, 4, and 5. As expected, nearly 100% of patients were treated with antibiotics (99%). The percentages of patients requiring other supportive therapies and adjunctive therapies are presented in table 3. Globally, the ICU mortality rate was 39.2%, and hospital mortality rate was 49.6%. The mean length of ICU stay was 14.6 (±16.1) days, the mean length of hospital stay was 28.2 (±30.0) days, and 68.0% of hospital survivors were discharged back to the community rather than to another care facility. Figure 2 shows adjunctive therapy usage over the study in quartiles. Low-dose steroid use increased from approximately 30% initially to 40% toward the end of the study. The use of drotrecogin alfa (activated), high-dose steroids, nitric oxide, gamma globulin, and antithrombin was low and relatively unchanged throughout.

Data Validity and Consistency

Since PROGRESS was an online registry, no formal data monitoring was performed to check for data validity. Therefore, internal checks were performed to check for data consistency and validity. Significant associations were observed between the following nominal variables: cardiovascular organ dysfunction and being on a vasopressor ($p < 0.0001$); respiratory organ dysfunction and being on a ventilator ($p < 0.0001$); active cancer and chemo/radiotherapy ($p < 0.0001$); abdominal/pelvic as primary site of infection and infection source control (surgical drainage/surgical procedure ($p < 0.0001$); hematologic organ dysfunction and platelet transfusion ($p < 0.001$). A clinical trial database of severe sepsis studies, sponsored by Eli Lilly and Company, (INDEPTH) was also assessed to test for external validity [23]. In INDEPTH, APACHE II was employed as a prognostic method for 28-day hospital mortality. There was a total of 4,455 patients who had an APACHE II measurement. The AUROC was 0.65 with a SE of 0.01. This predictive performance is consistent with that found in the PROGRESS registry (for APACHE II: AUROC 0.688 ± 0.006, n = 9,191). The AUROCs for APACHE III, organ failure, SAPS II, total SOFA, and MODS are included in figure 3.

Discussion

PROGRESS is the largest sepsis registry to date to show how severe sepsis is actually treated in many different countries. While the approximately 13,000 patients enrolled over 3 years did not include all patients admitted to the participating ICUs, this rate of recruitment reflects how common severe sepsis is globally and makes an

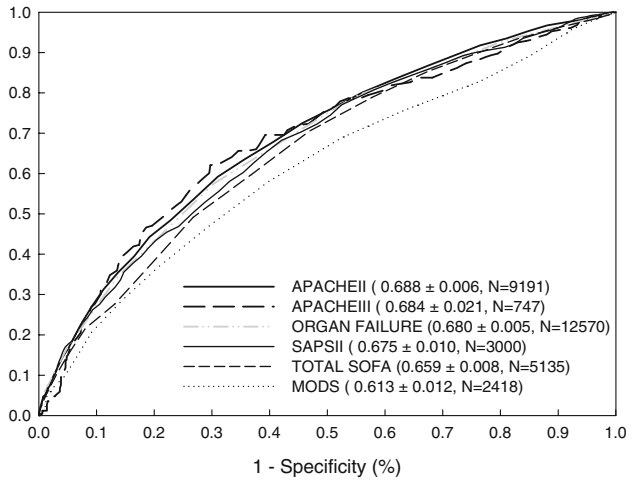

Figure 3. Area under curve for mortality in intensive care units (ICUs) by different prognostic methods. For definition of abbreviations, see Abbreviation section at beginning of article.

interesting contrast with the much smaller numbers enrolled for major new sepsis studies [24, 25], although these often use similar numbers of ICUs over a similar time period [4]. The approximately 50% hospital mortality demonstrates poor outcomes despite recent treatment advances [2–5], and there were significant regional differences in supportive care, adjunctive therapies usage, and outcome. Finally, PROGRESS demonstrates that a large web-based sepsis registry is feasible and potentially an important tool for future sepsis research.

Apart from being a data registry, PROGRESS was also a tool for sites to generate reports using records from their institution, state/province, country, region, or worldwide. This allowed ICU benchmarking to track and perhaps improve outcomes (as recommended by the Institute for Healthcare Improvement) [26], and the web-based design facilitated participation by countries without established ICU data registries, thereby providing new comparative information about the treatment of sepsis in different health systems. Achieving this required an approach somewhere between a traditional disease registry and a clinical trial of a new drug. This model allowed effective cooperation between academia and industry and is a model for future registries.

Although the aggregate ICU and hospital mortality rates of approximately 40% and 50% in PROGRESS are not unexpected, they are significantly higher than those reported in two recent epidemiologic studies in severe sepsis [27, 28]. There was considerable variation between countries, with Australia reporting the lowest hospital mortality (33%) and Brazil the highest (68%). Differences in baseline disease severity and age may help explain some of these differences, and it is important to exercise caution when comparing raw mortality between countries or attempting to draw conclusions regarding the impact of patient management. Organization of the ICU also varied. Mixed ICUs were the most common model, but separate medical and surgical ICUs were particularly favored in the USA and Germany. ICU bed availability and timing of ICU admission may also have contributed significantly to regional differences in outcomes. Most patients (76.5%) were admitted to the ICU from elsewhere in the institution, and a similar number were diagnosed with severe sepsis either prior to (45.7%) or at (29.1%) ICU admission, suggesting that the problem of unrecognized sepsis and development of organ failure remains an important and widespread problem. This result is consistent with those from other series of patients [29]. This lack of recognition of sepsis probably contributed to the high mortality and underscores the importance of better care processes and earlier intervention [2, 24, 30], together with the opportunity for improving outcomes, as recommended by the Surviving Sepsis Campaign [10, 38].

The Surviving Sepsis Campaign's evidence-based guidelines and care bundles appeared around the same time as PROGRESS [9, 10] and have recently been updated [38], with the major premise that evidence-based treatments for sepsis are often applied ineffectively (or not at all) in routine practice. Following publication of these care bundles there have been a number of recent publications suggesting that the introduction of evidence-based protocols in countries around the world may improve survival [39–43]. A tool like PROGRESS to facilitate collection of ''real life'' data and to examine geographic variations in practice was therefore felt to be valuable, and it is perhaps in this context that our results are most relevant. For example, when the use of adjunctive therapies was analyzed over time, we observed a dramatic increase in the use of low-dose steroids during the study, whereas the use of drotrecogin alfa (activated) remained relatively low throughout.

There were also marked differences in the use of supportive and adjunctive therapies by country. Mechanical ventilation, fluid resuscitation, and vasopressors were widely used, but fewer patients (21.3% overall) required renal replacement therapy, with the majority of the latter found in Germany and the least in Argentina. Prophylaxis against venous thromboembolism was usually (but not always) employed, with most countries favoring unfractionated heparin. Enteral nutrition was the preferred feeding approach, yet there was also significant parenteral nutrition usage, especially in Germany, where parenteral nutrition was used almost as much as enteral nutrition, implying substantial overlap between the two approaches. Also, a large number of surgical patients were enrolled in Germany, which may have contributed to the results. Albumin therapy was used most frequently in Australia, India, and Malaysia, perhaps explained in part by lower costs for albumin in these countries.

In terms of specific sepsis therapies, antithrombin was used in approximately 12.0% of patients from both Germany and Australia, despite a recent negative large phase three placebo-controlled study in severe sepsis [31]; this was a higher percentage of patients than those receiving drotrecogin alfa (activated) in these countries. Overall, drotrecogin alfa (activated) was used in only 7% of cases, with its use being much higher in the USA (27%) than anywhere else, perhaps partly explained by the selection of institutions who were participating in open-label trials of the compound. Low-dose steroid therapy was used on average in one-third of this global population, with significant regional differences. The numbers of ICUs enrolling patients varied between countries, ranging from four in Australia to 32 in India, so it is impossible to say how representative these units are of overall practice in their respective countries. Nevertheless, it is clear that there are substantial differences in practice among, and probably within, countries and also considerable variation from what might be regarded as ''evidence-based'' practice, underpinning the logic behind the Surviving Sepsis Campaign care bundles [10]. Recently, the occurrence of sepsis in acutely ill patients (SOAP) study reported on approximately 1,000 severe sepsis patients observed over 2 weeks in ICUs in 24 European countries [28], with an ICU mortality of 32.2%; this study also found marked regional differences in outcome and use of standard and supportive treatments [32, 33].

One major weakness of our approach was the reliance upon local data entry without formal data monitoring against source records or screening logs to provide the true incidence of severe sepsis in the overall ICU population. Furthermore, although consecutive patient enrollment was encouraged to eliminate bias in patient selection, it was not possible to characterize the sampling regimes that were actually employed. Another major weakness was the possibility that the units we report from were not representative of their countries, which is more likely in countries with wider variations within their healthcare systems. Related to this issue, the large differences among countries in the numbers of patients enrolled at each site may suggest a selection bias. In addition, investigators were paid a small amount to offset some of the study costs, also raising the possibility of selection bias. However, we believe the modest compensation required to help fund the study logistics was reasonable, the patients recruited clearly had severe sepsis, and the results of internal data consistency checks were robust. Of the nearly 13,000 patients enrolled in a 36-month period, 86% had multiple organ dysfunctions, and the ICU and hospital mortalities are consistent with other published series of severe sepsis patients [34–37]. Therefore, we believe that the data entered into PROGRESS provide a fair representation of clinical practice in patients with severe sepsis within the participating institutions and ICUs of their type in the top recruiting countries.

Conclusions

PROGRESS shows that it is possible to obtain high-quality descriptive data on large numbers of patients with severe sepsis around the world rapidly using a registry approach. Since sepsis is the leading cause of mortality in general ICUs and is the subject of a major campaign to improve treatment and outcome, understanding everyday clinical practice and then the reasons for treatment variation and delay are vital. Our data suggest that initiatives aimed at early recognition, diagnosis, and appropriate treatment currently have considerable scope to improve patient outcomes. Finally, we believe that the insights provided by tools such as PROGRESS will be extremely helpful in designing and implementing future severe sepsis research.

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Conflict of interest statement. Richard Beale, Konrad Reinhart, Frank Brunkhorst, Geoffrey Dobb, Mitchell Levy, Greg Martin, Claudio Martin, Graham Ramsay, Eliezer Silva, Benoit Vallet, and Jean-Louis Vincent have all participated in Eli Lilly and Company-sponsored clinical trials. Richard Beale, Konrad Reinhart, Frank Brunkhorst, Geoffrey Dobb, Mitchell Levy, Greg Martin, Claudio Martin, Graham Ramsay, Eliezer Silva, Benoit Vallet, and Jean-Louis Vincent are members of the PROGRESS Advisory Board and were paid a consultant fee. Jonathan Janes, Samiha Sarwat, and Mark Williams are employees and stockholders of Eli Lilly and Company.

Appendix 1: Definitions

Disease Diagnostic Criteria

The diagnostic criteria for severe sepsis used in this study were based on an adaptation of the operational definition developed by the Consensus Panel of the American College of Chest Physicians and the Society of Critical Care Medicine [44]. The criteria are as follows:

Presence of a Proven or Suspected Infection

- *Suspected infection*. A highly suggestive clinical presentation. Examples include pneumonia; abdominopelvic syndromes, such as cholangitis, cholecystitis,

and perforated viscus; surgical wound or other cutaneous infections; gross purulence; urosepsis; purpura fulminans.
- *Proven infection*. Objective identification of a pathogen by one or more methods, including culture of patient specimens, Gram stain, tissue stain, PCR, or other recognized methods.

Presence of One or More Acute Organ Dysfunctions

Patients were required to have at least one of the following acute organ dysfunctions due to sepsis. The following definitions were provided in the protocol as examples; slightly different examples were provided on the web page instructions.

- *Cardiovascular*. Hypotension in the absence of causes other than sepsis. For example, an arterial systolic blood pressure (SBP) of 90 mm Hg, a mean arterial pressure (MAP) of 70 mm Hg for at least 1 h despite adequate fluid resuscitation, > 40 mm Hg drop in SBP from baseline, or the need for vasoactive agents to maintain SBP > 90 mm Hg or MAP > 70 mm Hg.
- *Respiratory*. Acute lung injury due to sepsis and associated with serious hypoxemia. For example, O_2 saturation < 90% on room air, PaO_2 < 70 mm Hg, or PaO_2/FiO_2 < 280.
- *Renal*. Oliguria (average urine output < 0.5 ml/kg h) for 1 h despite adequate fluid resuscitation, < 30 ml/h for 3 h, or < 700 ml/24 h) or the need for renal replacement therapy as a result of severe sepsis.
- *Hematologic*. Thrombocytopenia; for example, platelet count < 100,000 mm^{-3} or a 50% decrease in platelet count from the highest value recorded over the previous 3 days.
- *Metabolic*. Unexplained metabolic acidosis: defined by (1) pH < 7.30 or base deficit > 5.0 mEq/l and (2) a plasma lactate level > 1.5-fold the upper limit of normal for the reporting laboratory. Measurement of pH or base deficit and lactate level were required to have occurred within a clinically relevant time interval such that a causal relationship existed between the measured values.
- *Neurologic*. Evidence of encephalopathy with, for example, a Glasgow Coma score < 13.
- *Hepatic*. Markedly increased serum bilirubin level or jaundice.

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