Quality Improvement Initiative for Severe Sepsis and Septic Shock Reduces 90-Day Mortality: A 7.5-Year Observational Study*

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***See also p. 374.**

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Dr. Scheer assumes full responsibility for the integrity of the submission as a whole, from inception to published article. He contributed to the literature search and data interpretation. Dr. Fuchs contributed to the data collection and data interpretation. Dr. Kuhn contributed to the data collection and data interpretation and was part of the study management committee. Dr. Vollmer performed the data analysis and contributed to the data interpretation. Dr. Rehberg contributed to the data interpretation and literature search. Dr. Friesecke contributed to the study idea and its initiation and to the data interpretation. She was part of the management committee. Dr. Abel contributed to the study initiation and commented the article. He was part of the management committee. Dr. Balau commented the article and was part of the management committee. Dr. Bandt contributed to the data analysis and data interpretation. He commented the article. Dr. Meissner contributed to the study design and study initiation. He commented and approved the final version. Dr. Hahnenkamp commented, amended, and approved the final version of the article. Dr. Gründling contributed to the literature search and data interpretation. He initiated the study and was part of the management committee. Dr. Gründling has full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis, including and especially any adverse effects. Drs. Scheer Fuchs, Kuhn, Rehberg, Vollmer, Friesecke, and Gründling drafted, amended, and approved the final version.

Drs. Scheer, Fuchs, Kuhn, Vollmer, Rehberg, Friesecke, Abel, Meissner, and Gründling have presented their study on "Sustained reduction of 90-day mortality of severe sepsis and septic shock as a result of a continuous training program for physicians and nursing staff" at XVI Congress of the European Shock Society on September 24–26, 2015. Drs. Scheer, Fuchs, Kuhn, Vollmer, Rehberg, Abel, and Gründling have presented their study on "Sustained reduction of intensive care- and hospital length of stay for severe sepsis and septic shock patients by a continuous quality improvement program over 7.5 years" at XVI Congress of the European Shock Society, September 24–26, 2015.

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Objective: To investigate the impact of a quality improvement initiative for severe sepsis and septic shock focused on the resuscitation bundle on 90-day mortality. Furthermore, effects on compliance rates for antiinfective therapy within the recommended 1-hour interval are evaluated.

Design: Prospective observational before-after cohort study.

Setting: Tertiary university hospital in Germany.

Patients: All adult medical and surgical ICU patients with severe sepsis and septic shock.

Intervention: Implementation of a quality improvement program over 7.5 years.

Measurements: The primary endpoint was 90-day mortality. Secondary endpoints included ICU and hospital mortality rates and length of stay, time to broad-spectrum antiinfective therapy, and compliance with resuscitation bundle elements.

Main Results: A total of 14,115 patients were screened. The incidence of severe sepsis and septic shock was 9.7%. Ninety-day mortality decreased from 64.2% to 45.0% ($p < 0.001$). Hospital length of stay decreased from 44 to 36 days ($p < 0.05$). Compliance with resuscitation bundle elements was significantly

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improved. Antibiotic therapy within the first hour after sepsis onset increased from 48.5% to 74.3% ($p < 0.001$). Multivariate analysis revealed blood cultures before antibiotic therapy (hazard ratio, 0.60–0.84; $p < 0.001$), adequate calculated antibiotic therapy (hazard ratio, 0.53–0.75; $p < 0.001$), 1–2 L crystalloids within the first 6 hours (hazard ratio 0.67–0.97; $p = 0.025$), and greater than or equal to 6 L during the first 24 hours (hazard ratio, 0.64–0.95; $p = 0.012$) as predictors for improved survival.

Conclusions: The continuous quality improvement initiative focused on the resuscitation bundle was associated with increased compliance and a persistent reduction in 90-day mortality over a 7.5-year period. Based on the observational study design, a causal relationship cannot be proven, and respective limitations need to be considered. (*Crit Care Med* 2017; 45:241–252)

Key Words: bundle; education; outcome; training program

With hospital mortality rates ranging from 27% to 55% (1, 2) and increasing incidences (2, 3), severe sepsis and septic shock continue to represent major causes of death. International guidelines have defined different treatment components that should be established within 6 hours ("resuscitation bundle") and 24 hours ("management bundle"), respectively (4). Although most of the individual elements have been a subject of controversy, compliance with these bundles has been repeatedly shown to reduce hospital mortality in short-term studies (5–9). In this context, early diagnosis and treatment initiation seem to be of major importance for successful therapy (10). Thus, current guidelines define even shorter time frames after diagnosis, for example, 1 hour for administration of broad-spectrum antibiotics (4).

To accomplish these treatment goals, continuous training is necessary, as recently supported by a 7.5-year follow-up study of the Surviving Sepsis Campaign (SSC) (11). Every additional quarter of participation in the campaign was associated with a decrease in the odds ratio for hospital mortality. However, long-term studies are rare, and the influence of guideline compliance on mortality beyond hospital stay remains unknown. Furthermore, compliance with the 1-hour interval for antibiotic administration and its influence on mortality has not been investigated so far.

We hypothesized that continuous training of ICU staff is associated with a reduction of 90-day mortality and that an increase in compliance with the 1-hour interval for broad-spectrum antibiotic administration is positively correlated with the outcome of severe sepsis and septic shock patients. Therefore, the present observational study was performed as part of a quality improvement program at a university hospital including all adult medical and surgical ICU patients with severe sepsis and septic shock over a period of 7.5 years.

METHODS

Design, Site, and Patients

The present prospective observational trial was conducted as part of a quality improvement program at the medical (18 beds) and surgical ICUs (27 beds) of the University Hospital of Greifswald, Greifswald, Germany. During the preimplementation period (January 2006 to December 2007), bundle compliance and outcomes were recorded for patients with severe sepsis and septic shock. These data were compared with the results observed after the establishment of a quality improvement program (postimplementation period, January 2008 to July 2013). The local ethics committee approved the study (identifier: BB 133/10). The requirement for informed consent was waived based on the observational and quality enhancing nature of the study. This article was written in consideration of the Revised Standards for Quality Improvement Reporting Excellence guidelines (12).

All ICU patients were screened daily by a constant study team (three nurse practitioners and four consultants in intensive care) for severe sepsis or septic shock according to the definitions of the American College of Chest Physicians and the Society of Critical Care Medicine (ACCP/SCCM) (13). Patients aged older than or equal to 18 years, who fulfilled these criteria, were included into the study.

Interventions

The quality improvement program (certified by the European Foundation for Quality Management) started in January 2008 and has been in continuous operation since then. The program included quarterly continued training courses as well as sepsis-related morbidity and mortality conferences for physicians and nurses in the emergency department and ICUs. Furthermore, lectures about epidemiology, pathophysiology, definition, prevention, diagnosis, and therapy of severe sepsis and septic shock for all hospital staff were held regularly. Pocket cards and posters summarizing information on sepsis diagnosis and treatment were made available to the hospital staff (**Figs. S1** and **S2**, Supplemental Digital Content 1, http://links.lww.com/CCM/C102). In addition, educational materials and news were published on a specific website (http://www.sepsis-dialog.de). Further details of the program are described in the **supplemental data** (Supplemental Digital Content 1, http://links.lww.com/CCM/C102).

The treatment protocol focused on the resuscitation bundle of the SSC including the following elements: immediate septic source control, measurement of lactate level, taking blood cultures before administration of antibiotics, calculated broad-spectrum antiinfective therapy within 1 hour after diagnosis, measurement of central venous oxygen saturation (target, ≥ 70%) and central venous pressure (target, ≥ 8 or ≥ 12 mm Hg in ventilated patients), administration of crystalloids in case of arterial hypotension (mean arterial pressure, ≤ 65 mm Hg) or lactate greater than or equal to 4 mmol/L, and vasopressor (norepinephrine) use in case of persistent arterial hypotension.

Outcomes

The primary study endpoint was 90-day mortality. Secondary endpoints included mortality rates in the ICU, the hospital, and after 28 days, length of stay (LOS) before diagnosis, ICU LOS after diagnosis and hospital LOS, time to broad-spectrum

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antiinfective therapy, and compliance with the elements of the resuscitation bundle. Predefined subgroups included medical and surgical ICU patients.

Data Collection

During the study period, demographic data, including ICU affiliation (medical or surgical), age, sex, severity of sepsis (severe sepsis or septic shock), lactate level at sepsis onset, Acute Physiology and Chronic Health Evaluation (APACHE) II score during the first 24 hours after sepsis onset, site of sepsis and origin of infection, as well as mortality rates and LOS data (**Fig. S3**, Supplemental Digital Content 1, http://links.lww.com/CCM/C102) were recorded. Furthermore, the amounts of fluids used for resuscitation and time intervals to accomplishment of the resuscitation bundle elements were assessed. Sepsis onset (time zero) was defined as the first time point when patients fulfilled the ACCP/SCCM criteria for severe sepsis or septic shock based on laboratory and hemodynamic variables as well as notes in the patient management system (**Fig. S4**, Supplemental Digital Content 1, http://links.lww.com/CCM/C102). Adequate antibiotic therapy was defined as calculated IV broad-spectrum treatment consistent with current guidelines and/or effective treatment based on antimicrobial susceptibility testing results. The recorded data were entered into an electronic database (SEPSIS INFORMATIONSSYSTEM ZUR QUALITÄTSSICHERUNG; G.punkt Medical Services, Magdeburg, Germany).

Statistical Analysis

Data were analyzed for the entire study population and for both subgroups. Differences between groups in continuous variables were analyzed using Student *t* test or the Wilcoxon-Mann-Whitney *U* test; Fisher exact test was used for categorical variables. Continuous variables are represented as means and standard deviations, categorical variables as relative proportions. Survival functions were analyzed using Kaplan–Meier estimates. Patients with incomplete 90-day mortality date were censored. A log-rank test was performed to compare survival distributions. *p* values less than 0.05 were considered significant.

Multivariate Cox proportional hazards regression analysis was used to estimate the impact of independent variables. The relevant ICU, medical or surgical, respectively, as well as the categories for pre- and postimplementation periods were added as dummy variables. To avoid overfitting, the full Cox model was reduced through backward elimination to a relevant final model with *P* values below 10% for each predictor. Continuous variables were previously standardized and categorized, if necessary (**Table S1**, Supplemental Digital Content 1, http://links.lww.com/CCM/C102) (14). Baseline hazard function was estimated till day 90 after sepsis onset. Statistical analyses were carried out using MATLAB R2015a (MathWorks, Natick, MA).

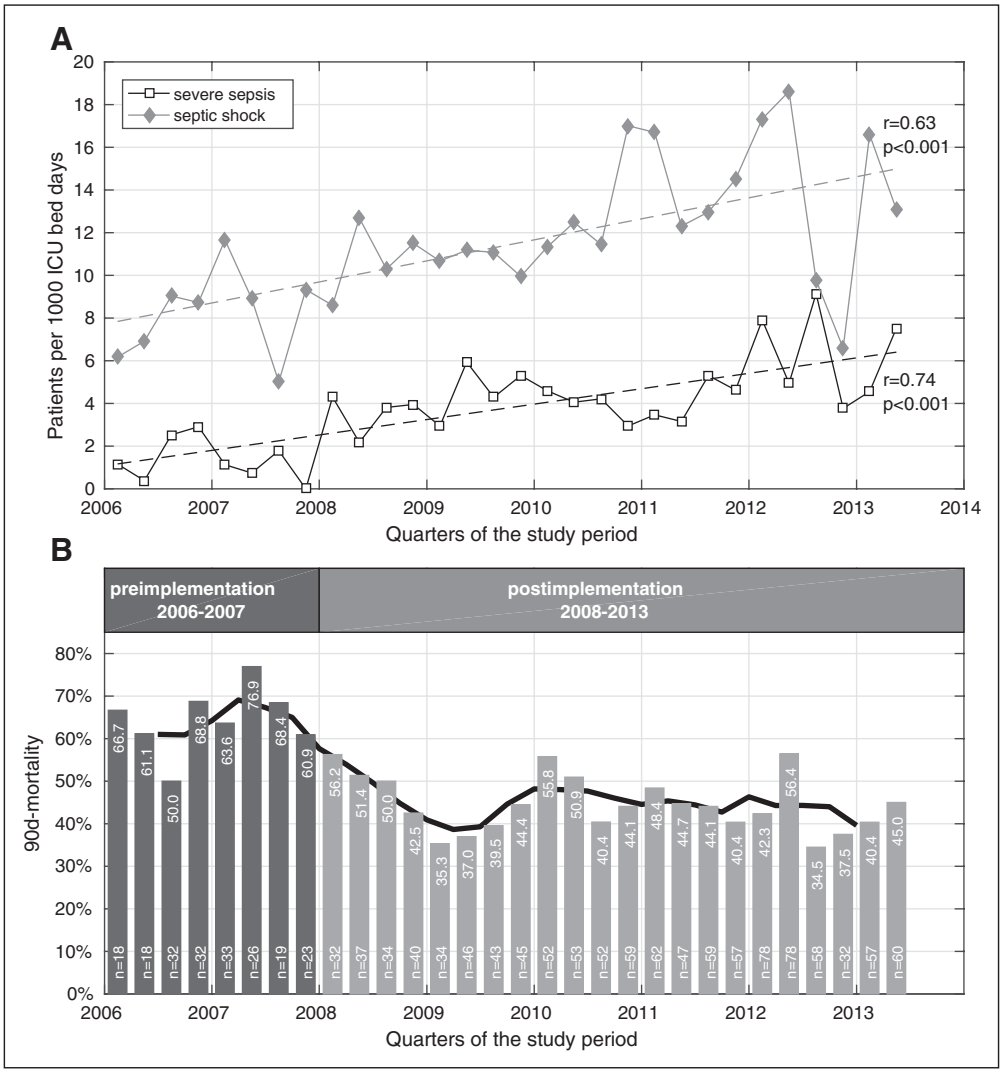

Figure 1. A, Incidence of severe sepsis and septic shock for every quarter of the study period (2006–2013). Incidence rates are given as patients per 1,000 ICU bed days. The gradient of the regression line for severe sepsis is 0.72. The gradient of the regression line for septic shock is 0.99. **B**, 90-day mortality of severe sepsis and septic shock for every quarter of the study period (2006–2013). The *black line* represents the moving average per year.

RESULTS

A total of 14,115 patients aged older than or equal to 18 years were screened. The overall incidence of severe sepsis or septic shock was 9.7% (1,373 patients). There was a continuous increase in incidence rates over the study period (**Fig. 1*A***). A total of 204 patients in the

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preimplementation group were compared with 1,169 patients in the postimplementation group. Predefined subgroups included 71 versus 424 medical ICU patients in the pre- and postimplementation period and 133 versus 745 surgical ICU patients.

Patients

Patient characteristics are presented in **Table 1** in biennially intervals. There were no statistical differences between the pre- and the postimplementation group in respect to age and sex. Lactate levels at sepsis onset were comparable except for 2010–2011 in the medical ICU. APACHE II scores during the 24 hours after sepsis onset were lower after initiation of the quality improvement program ($p < 0.01$). The majority of patients suffered from septic shock during the study period. At the surgical ICU, however, the percentage of severe sepsis increased during the postimplementation period ($p < 0.001$). Furthermore, the quality improvement program was associated with a reduced rate of ICU ($p < 0.01$) and hospital-acquired infections ($p < 0.05$), whereas the rate of community-acquired infections increased ($p < 0.001$).

Compliance With Resuscitation Bundle

Compliance rates with individual bundle elements are presented in **Table 2**. Following the start of the quality improvement project, antibiotic therapy was initiated more frequently within 1 hour ($p < 0.001$) and within 6 hours after diagnosis

TABLE 1. Patient Characteristics: Biennially Intervals of the Medical and Surgical ICU

	Preimplementation	Postimplementation		
	2006–2007	2008–2009	2010–2011	2012–2013
Medical patients (*n*)	71	125	154	145
Surgical patients (*n*)	133	204	301	240
Gender (male) (%)				
Medical	64.8	64.5	61.7	64.8
Surgical	69.9	60.8	62.5	62.1
Total	68.1		62.5	
Age (yr) (mean ± SD)				
Medical	68.7 ± 10.1	65.9 ± 14.4	63.1 ± 14.5[a]	65.9 ± 14.5
Surgical	66.9 ± 12.4	66.9 ± 12.3	66.9 ± 12.4	68.7 ± 12.8
Total	67.5 ± 11.7		66.5 ± 13.3	
Severity at diagnosis				
Severe sepsis (%)				
Medical	22.5	28.0	31.2	33.8
Surgical	9.8	27.5[b]	18.9[c,d]	30.0[e,f]
Total	14.2		27.1[b]	
Septic shock (%)				
Medical	77.5	72.0	68.8	66.2
Surgical	90.2	72.5[b]	81.1[c,d]	70.0[e,f]
Total	85.8		72.9[b]	
Lactate at sepsis onset (mmol/L) (mean ± SD)				
Medical	4.8 ± 5.1	4.2 ± 3.9	3.4 ± 3.5[d]	3.6 ± 4.4
Surgical	3.2 ± 3.1	3.3 ± 3.6	2.9 ± 2.8	3.0 ± 3.4
Total	3.7 ± 4.0		3.3 ± 3.5	
Acute Physiology and Chronic Health Evaluation II (during first 24 h after sepsis onset)[g] (mean ± SD)				
Medical	28.7 ± 6.6	22.6 ± 8[b]	26.6 ± 8.7[b]	25.8 ± 7.9[d]
Surgical	23.0 ± 7.3	25.3 ± 7.5[e]	20.8 ± 7.6[a,b]	19.3 ± 7.1[c,f]
Total	24.8 ± 7.6		22.9 ± 8.2[e]	

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TABLE 1. (*Continued*). Patient Characteristics: Biennially Intervals of the Medical and Surgical ICU

	Preimplementation	Postimplementation		
	2006–2007	2008–2009	2010–2011	2012–2013
Site of sepsis infection				
Community acquired[h] (%)				
Medical	54.9	69.6[c]	63.6	66.2
Surgical	23.3	32.8	42.5[c,f]	51.2[c,f]
Total	34.3		51.2[b]	
Hospital acquired (%)				
Medical	33.8	28.0	22.7	26.2
Surgical	48.1	39.2	43.9	34.6[c,d]
Total	43.1		34.6[c]	
ICU acquired (%)				
Medical	11.3	2.4[c]	13.6[b]	7.6
Surgical	28.6	27.9	13.6[b,f]	14.2[f]
Total	22.5		14.2[e]	
Origin of infection				
Pneumonia and respiratory tract (%)				
Medical	42.0	48.0	47.1	56.7
Surgical	24.2	27.7	28.9	25.7
Abdominal (%)				
Medical	30.4	27.6	17.1[d]	15.0[d]
Surgical	64.4	61.9	48.4[a,e]	50.2[a]
Bone and soft part (%)				
Medical	2.9	1.6	6.4	6.3
Surgical	4.5	2.0	7.7[e]	7.2
Urogenital (%)				
Medical	4.3	8.9	17.1[a]	14.2
Surgical	2.3	3.0	6.3	7.6[d]
Catheter infection (%)				
Medical	5.8	5.7	6.4	5.5
Surgical	3.0	2.5	3.8	3.4
Other (%)				
Medical	14.5	8.1	5.7	2.4[a]
Surgical	1.5	3.0	4.5	5.9

p values in relation to the previous year: [c]$p < 0.05$, [e]$p < 0.01$, and [f]$p < 0.001$.

p values in relation to the preimplementation interval (2006–2007): [d]$p < 0.05$, [a] $p < 0.01$, and [f]$p < 0.001$.

[g]Scores on the Acute Physiology and Chronic Health Evaluation II range from 0 to 71, with higher scores indicating greater severity of illness.

[h]Sepsis diagnosis within 48 hr after hospitalization.

The "Total" values represent the preimplementation and postimplementation periods from 2008-2013.

than in the preimplementation period (both $p < 0.001$). Mean time to first calculated antibiotic therapy in patients without preemptive antibiotics was 355 ± 88 min in the preimplementation group and 203 ± 70 minutes in 2012–2013 ($p < 0.001$). Furthermore, central venous oxygen saturation was measured in almost 49% of the patients within 6 hours after implementation of the training program, but in only 22% in the preimplementation group ($p < 0.001$). Blood cultures were taken more often before administration of antibiotics ($p < 0.01$) in the postimplementation period. The percentage of blood cultures obtained before administration of antibiotics was higher in medical (pre: 56.3%; post: 74.5%;

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TABLE 2. Compliance With Sepsis Bundle Elements and Outcome

	Preimplementation	Postimplementation		
	2006–2007	2008–2009	2010–2011	2012–2013
Medical patients (*n*)	71	125	154	145
Surgical patients (*n*)	133	204	301	240
First hour				
Obtain blood cultures before administration of antibiotics (%)				
Medical	56.3	51.2	63.0	74.5[a,b]
Surgical	24.1	41.2[c]	33.9[d]	36.7[d]
Total	35.3		46.4[c]	
Antimicrobial therapy started (%)[e]				
Medical	50.7	80.0[f]	79.9[g]	77.2[g]
Surgical	47.4	57.4	75.1[f,g]	79.6[g]
Total	48.5		74.3[f]	
Measure lactate level (%)				
Medical	100.0	94.4	98.7	99.3
Surgical	100.0	98.5	100.0	94.2[f,b]
Total	100.0		97.6[a]	
First 6 hr				
Antimicrobial therapy started (%)[e]				
Medical	85.9	97.6[c]	94.8[d]	92.4
Surgical	71.4	81.9[a]	91.7[c,g]	90.8[g]
Total	76.5		90.9[f]	
Measure central venous oxygen saturation (%)				
Medical	7.0	62.4[f]	53.3[g]	45.5[g]
Surgical	29.3	48.5[f]	48.8[g]	43.3[b]
Total	21.6		49.3[f]	
Crystalloid (L) (mean ± SD)				
Medical	0.9 ± 0.9	1.7 ± 1.5[f]	1.5 ± 1.4[b]	1.4 ± 1.3[b]
Surgical	1.3 ± 0.9	1.8 ± 1.3[f]	2.4 ± 2[f,g]	2.2 ± 1.6[g]
Total	1.2 ± 0.9		1.9 ± 1.6[f]	
HES (130/0.4) (L) (mean ± SD)				
Medical	0.4 ± 0.4	0.3 ± 0.4[a]	0.2 ± 0.4[g]	0.1 ± 0.3[a,g]
Surgical	0.4 ± 0.4	0.1 ± 0.2[f]	0.0 ± 0[f,g]	0.0 ± 0[g]
Total	0.4 ± 0.4		0.1 ± 0.3[f]	
First 24 hr				
Crystalloid (L) (mean ± SD)				
Medical	2.9 ± 2.9	5.5 ± 5[f]	4.0 ± 3.1[c,d]	3.6 ± 2.9
Surgical	4.2 ± 2.4	5.9 ± 3.9[f]	6.0 ± 4[g]	5.8 ± 3.9[g]
Total	3.8 ± 2.6		5.3 ± 4.0[f]	
HES (130/0.4) (L) (mean ± SD)				
Medical	0.9 ± 0.8	0.7 ± 0.7[a]	0.5 ± 1[b]	0.3 ± 0.6[a,g]
Surgical	1.0 ± 0.7	0.1 ± 0.3[f]	0.0 ± 0.1[f,g]	0.0 ± 0[g]
Total	0.9 ± 0.7		0.2 ± 0.5[f]	

(*Continued*)

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TABLE 2. (*Continued*). Compliance With Sepsis Bundle Elements and Outcome

	Preimplementation	Postimplementation		
	2006–2007	2008–2009	2010–2011	2012–2013
Outcome				
ICU mortality (%)				
Medical	54.9	35.2[a]	34.4[b]	25.5[g]
Surgical	54.1	34.3[f]	29.2[g]	27.9[g]
Total	54.4		30.7[f]	
Hospital mortality (%)				
Medical	60.6	38.4[c]	46.8	37.9[b]
Surgical	58.6	37.7[f]	35.5[g]	35.8[g]
Total	59.3		38.1[f]	
28-d mortality (%)				
Medical	59.4	36.8[c]	36.8[b]	27.1[g]
Surgical	50.4	31.4[f]	28.3[g]	33.5[b]
Total	53.5		31.7[f]	
90-d mortality (%)				
Medical	69.1	48.6[c]	53.2[d]	44.8[b]
Surgical	61.7	41.7[f]	42.7[g]	43.3[g]
Total	64.2		45.0[f]	
Length of stay before diagnosis (d) (median [IQR])				
Medical	1.1 [0.1–5.4]	0.5 [0.1–2.7]	0.4 [0.1–6.8]	0.4 [0.0–4.1]
Surgical	6.5 [2.4–14.6]	6.7 [0.6–13.2]	3.5 [0.3–10.0] [c,g]	1.7 [0.3–9.4][g]
Total	4.8 [0.8–11.9]		1.8 [0.2–9.4][f]	
ICU length of stay after diagnosis (d) (median [IQR])[h]				
Medical	23.7 [5.7–42.1]	15.7 [3.2–32.6]	11.8 [3.8–28.1]	12.6 [2.8–37.8]
Surgical	18.8 [7.8–45.2]	14.8 [6.6–28.8]	10.9 [4.6–24.5][a,g]	7.9 [3.5–19.7][a,g]
Total	20.4 [6.6–43.1]		10.8 [4.0–26.2][f]	
Hospital length of stay (d) (median [IQR])[h]				
Medical	42.5 [24.5–55.8]	33.0 [20.0–60.5]	42.2 [24.8–63.8]	37.5 [25.7–60.1]
Surgical	51.1 [28.8–75.7]	44.2 [26.2–64.9]	35.9 [21.9–56.2][a,b]	32.0 [21.0–54.0][b]
Total	43.9 [28.1–67.1]		36.1 [22.3–58.0][a]	

HES = hydroxyethyl starch, IQR = interquartile range.

p values in relation to the previous year: [a]$p < 0.05$, [c]$p < 0.01$, and [f]$p < 0.001$.

[e]Including preemptive antibiotic therapy.

p values in relation to the preimplementation interval (2006–2007): [d]$p < 0.05$, [b]$p < 0.01$, and [g]$p < 0.001$.

[h]Of survivors only.

The "Total" values represent the preimplementation and postimplementation periods from 2008-2013.

$p < 0.05$) than in surgical patients (pre: 24.1%; post: 36.7%; $p < 0.01$). There was an increase in the amount of administered crystalloids within 6 hours ($p < 0.001$) as well as within 24 hours ($p < 0.001$) in the postimplementation period. Hydroxyethyl starches (HES 130/0.4) were almost avoided for the 6- and the 24-hour interval. These changes were consistent in the overall population as well as in both subgroups.

Outcome

Results for LOS factors and mortality rates are presented in Table 2 and **Figure 1*B***. LOS before diagnosis ($p < 0.001$), ICU LOS after diagnosis ($p < 0.001$), and total hospital LOS ($p < 0.01$) were reduced in the post- versus the preimplementation group. These results were consistent in medical and surgical ICU patients. Because of large variations in the

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medical subgroup, a statistical significance could be demonstrated only in surgical patients. Mortality rates in the ICU, the hospital, after 28 days, and 90 days (each $p < 0.001$) were lower after initiation of the program in the total study population. Kaplan-Meier estimates of survival are represented in **Figure 2**.

Subgroup Analysis of Septic Shock Patients

A subgroup analysis included only septic shock patients ($n = 1{,}027$, 75% of the study population). These patients were comparable in respect of age (67 yr), lactate (≥ 4.0 mmol/L), and APACHE II (25.1 points) in 2006–2007 (preimplementation) and 2008–2009 (postimplementation). The decline of 90-day mortality between these two periods was 18.2% (66.9% preimplementation and 48.7% postimplementation; $p < 0.001$). In the following years, the mortality remained constant (**Table S3**, Supplemental Digital Content 1, http://links.lww.com/CCM/C102; **Fig. S5**, Supplemental Digital Content 1, http://links.lww.com/CCM/C102).

Predictors of 90-Day Mortality

Table 3 demonstrates the results of the multivariate Cox proportional hazards regression analysis. Age more than 60 years, lactate greater than 3 mmol/L, APACHE II during the first 24 hours after sepsis onset, and non–ICU-acquired sepsis were predictors for increased mortality. The implementation period, admission at the medical ICU, blood cultures before antibiotics, adequate calculated antibiotic therapy, administration of 1–2 L crystalloids within the first 6 hours, greater than or equal to 6 L during the first 24 hours, and avoidance of HES were predictors for increased survival.

DISCUSSION

The present observational study suggests long-term effects of a continuous training program focusing on the resuscitation bundle of the SSC on 90-day mortality of adult ICU patients with severe sepsis and septic shock. The quality improvement program was associated with a sustained decrease in 90-day mortality from 64.2% in 2006/2007 to 45.0% from 2008 to 2013. In addition, increased bundle compliance was associated with reduced hospital LOS and ICU LOS after diagnosis.

Previous studies on bundle compliance did not consider 90-day mortality but support the validity of the present data by comparable reductions in ICU and hospital mortality rates (8, 9). There are also studies with lower hospital mortality rates even before the implementation (5, 15). However, those patients were younger and had lower APACHE II or Acute Physiology Scores, lower lactate levels, and a lower proportion of septic shock patients. All of these factors have been shown to represent independent predictors for mortality in the present study (Table 3) and the literature (16–19).

The second major outcome of the present study is that after program initiation almost 75% of the patients were started on antibiotics within the first hour after diagnosis. The importance of early treatment initiation has been reemphasized recently in a retrospective analysis of the SSC database including 28,150 patients (20). For each hour delay in antibiotic administration, there was a linear increase in the risk of hospital mortality. In addition, adequate antibiotic administration has been identified as an independent predictor of reduced hospital mortality (5, 15). Likewise, the Cox proportional hazards model revealed the adequate calculated antibiotic treatment as an independent predictor of a reduced mortality in the present study. Furthermore, the present quality improvement program was associated with a decrease in the time to calculated antibiotic administration with regard to a reliable defined sepsis onset (time zero). In the literature, this time interval ranges from 2.15–2.6 hours for broad-spectrum antibiotics (7) to 12.3–16.6 hours for an appropriate antibiotic coverage (8).

A major strength of the present study is that all patients were included with no exceptions. This practical approach potentially results in data closely reflecting ICU reality. As a consequence, patients in the present study were older and had higher APACHE II scores and a higher rate of septic shock as compared to previous trials (7, 8, 15, 21). The continued training program represents an additional strength. Contrary to previous trials with shorter time intervals, the Hawthorne effect (22) might be negligible with a study period of 7.5 years. In addition, long-term evaluation and reevaluation ensure sustained high compliance rates for the bundle elements (Table 2). Otherwise, the positive effects might disappear rapidly, as suggested by a multicenter study with a before and after design (7).

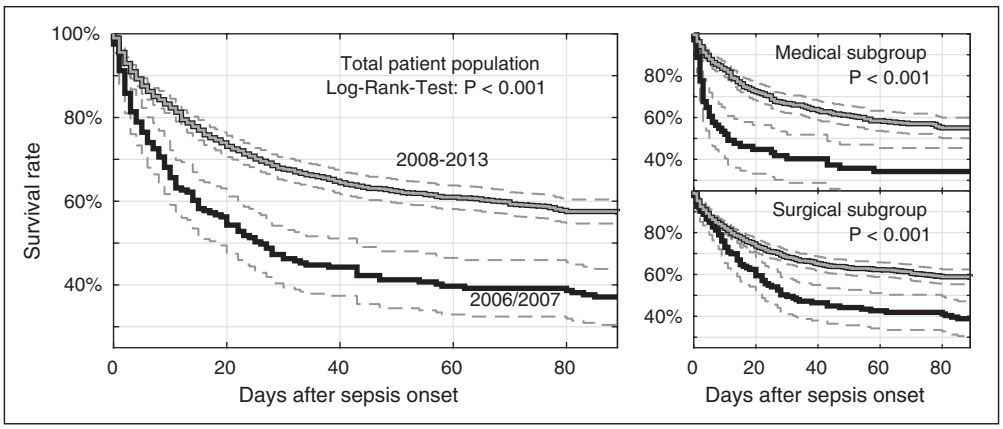

Figure 2. Kaplan-Meier estimates of 90-d survival for pre- and postimplementation. Preimplementation displayed as *dark gray line*. Postimplementation displayed as *light gray line*. The *dashed line* represents the 95% CI.

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TABLE 3. Cox Proportional Hazards Regression Analysis of Patient Characteristics and Bundle Elements

	Full Model		Final Model through Backward Elimination	
	Hazard Ratio (95% CI)	*p*	Hazard Ratio (95% CI)	*p*
Before implementation (2006–2007)	Reference		Reference	
During implementation (2008–2013)	0.742 (0.57–0.97)	0.029	0.689 (0.54–0.88)	0.003
Gender				
Female	Reference			
Male	0.98 (0.83–1.16)	0.815		
Age, yr				
< 60	Reference		Reference	
60–74	1.32 (1.06–1.64)	0.012	1.311 (1.06–1.63)	0.014
≥ 75	1.667 (1.34–2.08)	< 0.001	1.658 (1.33–2.07)	< 0.001
Severity				
Severe sepsis	Reference			
Septic shock	1.086 (0.88–1.34)	0.450		
Lactate at sepsis onset, mmol/L				
< 3	Reference		Reference	
3–6	1.41 (1.15–1.73)	0.001	1.39 (1.14–1.70)	0.001
> 6	2.278 (1.79–2.90)	< 0.001	2.232 (1.78–2.80)	< 0.001
Acute Physiology and Chronic Health Evaluation II score (increase of 8.1 points)	1.646 (1.50–1.81)	< 0.001	1.686 (1.54–1.85)	< 0.001
Place of admission				
Surgical ICU	Reference		Reference	
Medical ICU	0.76 (0.58–0.99)	0.046	0.762 (0.62–0.94)	0.011
Site of sepsis				
ICU	Reference			
Emergency department	0.869 (0.67–1.12)	0.286		
Non-ICU	1.134 (0.88–1.46)	0.323	1.263 (1.07–1.50)	0.007
Origin of infection				
Other than respiratory tract or abdominal	Reference			
Pneumonia and respiratory tract	0.982 (0.79–1.22)	0.871		
Abdominal	0.973 (0.78–1.21)	0.804		
Bundle Elements				
Blood cultures before antibiotic therapy				
No	Reference		Reference	
Yes	0.688 (0.57–0.82)	< 0.001	0.71 (0.60–0.84)	< 0.001
Time to antibiotic therapy, hr				
≤ 1	Reference			
1–6	1.125 (0.92–1.37)	0.242		
> 6	1.215 (0.96–1.54)	0.104		

(*Continued*)

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TABLE 3. (*Continued*). Cox Proportional Hazards Regression Analysis of Patient Characteristics and Bundle Elements

	Full Model		Final Model through Backward Elimination	
	Hazard Ratio (95% CI)	*p*	Hazard Ratio (95% CI)	*p*
$Scvo_2$ within 6 hr				
No	Reference			
Yes	0.975 (0.82–1.16)	0.780		
Calculated antibiotic therapy				
Not adequate	Reference			
Adequate	0.646 (0.52–0.80)	< 0.001	0.631 (0.53–0.75)	< 0.001
Preemptive adequate	1.129 (0.86–1.48)	0.380		
Preemptive not adequate	0.915 (0.68–1.23)	0.554		
Crystalloids first 6 hr, L				
< 1	Reference			
1–2	0.843 (0.67–1.07)	0.153	0.81 (0.67–0.97)	0.025
> 2	1.046 (0.80–1.37)	0.743		
Crystalloids first 24 hr, L				
< 2	Reference			
2–6	0.893 (0.69–1.15)	0.380		
≥ 6	0.709 (0.51–0.99)	0.042	0.78 (0.64–0.95)	0.012
Hydroxyethyl starches (130/0.4) during first 24 hr				
No	Reference		Reference	
Yes	1.256 (1.01–1.57)	0.044	1.26 (1.01–1.57)	0.037
Swab from focus of infection				
No	Reference			
Yes	0.954 (0.77–1.18)	0.662		

Cox analysis included 1,350 patients (23/1,373 patients were excluded because of more than 3 missing values). Hazard ratio less than 1 represents beneficial predictors and hazard ratio greater than 1 adverse predictors.

After 1 year, the progress reported in the former study was already lapsed. Further strengths include the enrolment of ICUs from different departments not only resulting in a unique comparison between medical and surgical ICU patients in this context but also increasing the validity of the present results. Furthermore, the strict definition of sepsis onset (time zero) that was retrospectively timed according to laboratory and hemodynamic factors derived from the available records needs to be emphasized. Accordingly, the time for the 1- or 6-hour interval started already before the clinical diagnosis, if the attending physician did not immediately get to know the respective factors or did not draw the correct conclusion. Finally, the present training program primarily focused on the resuscitation and not on the management bundle. This priority is supported by a recent study based on the SSC database with 29,470 patients (11). High versus low compliance with the resuscitation bundle resulted in a more pronounced mortality reduction than high versus low compliance with the management bundle.

There are also limitations that need to be discussed. Based on the study design, our data cannot provide evidence for a causal relationship between the quality improvement program and the reduced mortality. The lower APACHE II scores in the post- versus preimplementation group potentially raise the suspicion that a lower disease severity rather than the intervention itself was responsible for the observed benefits. First of all, these differences might be caused by an earlier diagnosis and treatment initiation at the emergency department and the wards due to an increased awareness, a central goal of a quality improvement program. This theory is supported by a higher transfer rate to the ICU (suggested by an increased sepsis incidence, Fig. 1*A*), a rising trend of community-acquired sepsis cases at the ICU (Table 1) and a shorter LOS before sepsis (Table 2). Second, established

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statistical methods (Cox regression models) were used to correct for differences in severity between pre- and postimplementation groups. However, such models are restricted since they cannot control for unmeasured patient characteristics and secular effects. Third, a subgroup analysis of only septic shock patients (n = 1,027; 75% of all included patients) was performed. In these well-defined patients with the highest disease severity, mortality in the postimplementation group also decreased by 18.2% ($p < 0.001$), whereas age, lactate, and APACHE II remained unchanged compared to the preimplementation group (Table S3, Supplemental Digital Content 1, http://links.lww.com/CCM/C102; and Fig. S5, Supplemental Digital Content 1, http://links.lww.com/CCM/C102). Fourth, APACHE II scores were only one baseline characteristic. Age (23) and lactate levels (17–19) are established risk factors associated with mortality (also identified in the present analyses). Notably, with only one exception in the medical subgroup during the 2010 and 2011 interval, both of these central prognostic factors did not differ statistically between the pre- and the postimplementation group. Although this is still no evidence, these results taken together with the statistical methods strongly attenuate the above referred to suspicion.

Finally, mortality rates decreased markedly (≈ 20%) after implementation of the program and remained stable for the rest of the study period (Fig. 1*B*; Table 2). This time course additionally supports the impact of our intervention, because mortality reductions caused by increased standards of generalized care over long time periods are associated with an evenly distributed decline as recently reported by Kaukonen et al (24) A causal relationship between the intervention and the reduced 90-day mortality is additionally suggested by the coincidence with an immediate increase in compliance with bundle elements (Table 2).

Another potential limitation represents the higher incidence of severe sepsis and septic shock in the post- versus the preimplementation group. This might lead to the conclusion that due to the increased awareness less severely ill patients were identified and included into the study finally resulting in the observed benefits on mortality rates and LOS data. Notably, in the subgroup of septic shock patients, there was a similar increase in incidence (Fig. 1*A*). It is very unlikely that these most severely ill and well-defined patients were overlooked in the preimplementation period and that the increase is just based on an improved screening. In fact, the increased incidence in our hospital reflects the global increase in Germany as reported by Fleischmann et al (25) for a similar time period (2007–2013). In Australia and New Zealand, the incidence also almost doubled from 2005 (6,987 patients) to 2012 (12,512 patients) (24). Notably, the quarterly plotted incidence rates per 1,000 ICU bed days in the present article (Fig. 1*A*) demonstrate a rather continuous increase for severe sepsis and septic shock. Regression lines suggest an increase by about 1.0 case per 1,000 ICU bed days for septic shock and by 0.7 for severe sepsis every year. Contrary, a higher incidence based on an increased awareness would result in a sudden increase incidence.

CONCLUSIONS

In summary, the present 7.5-year observational, single-center study suggests that a continued training program focused on the resuscitation bundle of the SSC is associated with a sustained reduction in 90-day mortality. In addition, it supports previous data on declined ICU, hospital, and 28-day mortality as well as shorter ICU and hospital LOS following implementation programs of the SSC guidelines. Furthermore, compliance with the individual bundle elements increased; especially, the rate of calculated antibiotic administration within 1 hour improved to almost 75%. Based on the study design, however, a causal relationship cannot be verified.

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