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Surviving Sepsis Campaign Bundles Adherence and Their Limits in Surgical Patients with Septic Shock in an ICU

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Authors' contributions

This work was carried out in collaboration between all authors. Authors MW, FL and FP participated in study conception, study design, data analysis, interpretation and drafting of the manuscript. All authors read and approved the final manuscript.

Research Article

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ABSTRACT

Aims: The Surviving Sepsis Campaign (SSC) guidelines aimed to reduce heterogeneity of conventional therapy and mortality. The present study was performed in septic shock to describe the adherence to the 2008 SSC guidelines, confounding factors, and limitations.
Study Design: Prospective observational study.
Place and Duration of Study: Clinic of Anaesthesiology, University Hospital Medical School, and Clinical Economics at the Institute of History, Philosophy and Ethics in Medicine, University of Ulm, between January 2008 and June 2009.
Methodology: The adherence to 36 items of the 6-hour and 24-hour bundles of the 2008 SSC guidelines was investigated in 98 surgical patients with septic shock.
Results: The adherence to the 36 items varied between 0% and 95%. Besides the categories "adherent" and "nonadherent", additional categories "partially adherent", "not-applicable" and "unknown" were used. None of the single items alone was essential for survival. Patients with septic shock on admission (n=68) had significantly higher SOFA scores (degree of organ dysfunctions) compared to patients developing septic shock in the ICU (n = 30).
Conclusion: As many confounders are limiting the adherence to complex guidelines,

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the complete adherence will hardly be possible in severe diseases such as septic shock. Our results suggest that efforts associated with early diagnosis and active encouragement outside the ICU are necessary to improve applicability and adherence to the SSC guidelines in patients with septic shock in order to reduce the time lag of diagnosis and treatment, which may be reached by focusing on few essential points.

Keywords: Critical illness; intensive care units; guideline adherence; sepsis bundles; shock; septic/mortality/therapy.

ABBREVIATIONS

ALI - acute lung injury; APACHE II - Acute Physiology and Chronic Health Evaluation II score; ARDS - acute respiratory distress syndrome; CI - confidence interval; CVP - central venous pressure; ICU - intensive care unit; iv - intravenous; MAP - mean arterial pressure; rhAPC - recombinant human activated protein C; SAPS II - Simplified Acute Physiology Score II; SAPS 3 - Simplified Acute Physiology Score 3; $SCVO_2$ - central venous oxygen saturation; SMART - Sepsis Management Alert Response Team; SOFA - Sequential Organ Failure Assessment score; RCT- randomized controlled trial; RR - relative risk; SSC - Surviving Sepsis Campaign; 95%CI - 95% confidence interval; ΔU - delta utility;

1. INTRODUCTION

The “Surviving Sepsis Campaign” (SSC) guidelines [1, 2] aimed to reduce heterogeneity of conventional therapy and mortality under the scope of evidence-based medicine. Thus, it might be suspected that an adherence rate to these guidelines as high as possible should be achieved to reach these aims. However, the achievement of these aims may be hampered by conflicting interests. The SSC guidelines [1, 2] have been published in 2004 and updated in 2008 to provide recommendations for best current care directly targeting severe sepsis and general care of critically ill patients. These guidelines intend to improve outcome. However, besides beneficial effects for patients, application of some guidelines may also lead to undesirable effects, such as harm to patients, more burdens on patients and staff, and enhanced costs. For example, the expensive application of recombinant human activated protein C (rhAPC) in septic shock may be a two-sided sword, reducing mortality on the one side but also increasing side effects such as bleeding and the economic costs on the other side [1, 2]. Due to the extent of the SSC guidelines, elements of the guidelines were “bundled” into two sets of targets to be completed within 6 hours regarding “initial infection and perfusion issues” (Table 3 in the SSC 2008 publication) and within 24 hours regarding “hemodynamic support and adjunctive therapy items” (Table 4 in the SSC 2008 publication) in the original paper [2]. The 6-hour (Table 3 in the SSC 2008 publication) and 24-hour bundles (Table 4 in the SSC 2008 publication) of the 2008 SSC were intended to support best care during the early phase of severe sepsis. Under the scope of quality management, we assessed the adherence to the SSC guidelines in our ICU to define the present status and subsequently set aims for improvement.

Therefore, the present study was performed to find out:

1. The degree of adherence of the 6-hour and 24-hour bundles of the 2008 SSC guidelines in surgical ICU patients with septic shock;
2. Factors resulting in adherence of less than 100%.

2. MATERIALS AND METHODS

2.1 Patients and Data Collection

A prospective observational single-centre study in surgical critically ill patients admitted to an University adult ICU has been performed.

From January 1st, 2008 through June 30th, 2009, all admissions were surveyed daily supported by a patient data management system regarding sepsis and shock. Due to daily scoring, no patients in septic shock were missed in the time period investigated. Patients were admitted to the Anaesthesiology ICU of the University Hospital Ulm after major trauma, vascular, lung, brain or abdominal surgery. All 98 surgical patients in septic shock treated from January 1st, 2008 through June 30th, 2009 were analysed regarding the association between item “adherent“ or “nonadherent“ concerning 36 items of the 6-hour (Table 3 in the SSC 2008 publication) and 24-hour bundles (Table 4 in the SSC 2008 publication) of the 2008 SSC guideline and outcome. Besides the categories “adherent“ and “nonadherent“, the additional categories “partially adherent“,“not-applicable“ and “unknown“ were used (Table 1). The degree of fulfillment of an item was regarded as “partially adherent“, if the required conditions could be met most of the time with occasional exceptions, or if an action did not fulfill the required conditions completely, e.g., a partial search for a focus. “Not-applicable” was used, if an item did not fit in the clinical situation, e.g., to adhere to the mechanical ventilation of sepsis-induced acute lung injury (ALI)/ARDS items, if patients did not suffer from ALI/ARDS. “Unknown” was used, if data were missing to answer the question whether a goal was reached, e.g., if central venous pressure (CVP) has not been measured, we did not know, whether CVP was in the range of 12 – 15 with ventilation.

To find out factors contributing to adherence less than 100%, potentially confounding factors were monitored, such as applicability of the item, indications and contraindications, location of the patient before ICU or time delay from septic shock to admission to the ICU. All surgical patients admitted to the ICU were surveyed routinely computer-assisted for severity of disease and of organ dysfunctions, and presence of sepsis, on a daily basis. Severity of disease on admission was monitored by the Simplified Acute Physiology Score 3 (SAPS 3) [3] and the Acute Physiology and Chronic Health Evaluation (APACHE) Score II [4]. Severity of organ dysfunctions were assessed by the Sequential Organ Failure Assessment (SOFA) score [5] on a daily basis. Sepsis was defined using the 2003 SCCM/ESICM/ACCP/ATS/SIS sepsis definitions [6]. Severe sepsis was defined as sepsis plus organ dysfunction [6]. Organ dysfunctions regarding sepsis were defined according to the limitations for organ dysfunction variables and tissue perfusion variables (hyperlactatemia) as given in the original publication [6].

Table 1. Degree of adherence to the 6-hour and 24-hour bundle items of the 2008 SSC guidelines in 98 surgical ICU patients with septic shock

SSC guideline 2008	6-hour bundle																					24-hour bundle																
	Infection bundle									Perfusion bundle												Management bundle																
	≥2 blood cultures	≥1 blood culture percutaneous	≥1 blood culture vascular access > 48h	Culture site clinically indicated	Imagingg focus	Anatomic site focus	Source control focus	Remove iv access	Iv antibiotics < 1h	Initial resucsitation	CVP 8 - 12w/o ventilation	CVP 12 - 15 with ventilation	MAP ≥ 65 mmHg	Urine ≥ 0.5 ml/kg*h	SCVO2 ≥ 70	SVO2 ≥ 65	Fluid challange	Differential diagnosis of shock	Noradrenaline MAP ≥ 65	Adrenaline MAP ≥ 65	Dobutamine	Cardiac index not supranormal	Hydrocortisone	Iv insulin	Blood glucose 80 - 150	Blood glucose 1 - 4 h	No bicarbarbonate pH ≥ 7.15	Red blood cells 7 - 9 g/l	Platelets <_5000	Platelets 5000 - 30000	Platelets ≥ 50000	6 ml with ALI/ARDS	Pmax ≤ 30 ALI/ARDS	45° ALI/ARDS	30° - 45° ALI/ARDS	RhAPC ≤ 24 hours
Adherent	23	6	23	40	24	24	22	8	41	18	2	11	93	64	13		41	27	93	6	1	3	63	44	47	49	14	25	7	7	5	3	30		36	
Not applicable	40	38	40	39	36	36	47	73	34		69	18			1	98	5	62	1	92	96	95	3				74	58	91	91	90	59	59	60	60	94
Partially adherent				1	19	19	12		1	76		4	5	14	1		17		3					39	33	33						8	3	1	2	
Unknown											26	38			83																			36		2
Nonadherent	35	54	35	18	19	19	17	17	22	4	1	27		20			35	9	1		1		32	15	18	16	10	15			3	28	6	1		2

Numbers of patients in the categories adherent to nonadherent in the 36 item s of the 6-hour and 24-hour sepsis bundles. ALI - acute lung injury; ARDS - acute respiratory distress syndrom e; CVP – central venous pressure; iv – intravenous; MAP – mean arterial pressure; $SCVO_2$ – central venous oxygen saturation

Septic shock was defined as sepsis plus shock [6]. Shock was defined as hypotension despite adequate volume resuscitation, a systolic blood pressure of ≤ 90 mmHg, or the need of vasopressors to keep blood pressure ≥ 90 mmHg according to the 2003 sepsis definitions [6]. Only cases ≥ 18 years were selected for the present evaluation because SAPS II score [7] and the 2003 SCCM/ESICM/ACCP/ATS/SIS sepsis definitions [6] have been developed for patients ≥ 18 years, and the SOFA score [5] for patients ≥ 12 years.

2.2 Statistical Analyses

Mann-Whitney-U-test was performed ($p < 0.05$) to find out differences between groups of patients. Differences were considered as statistically significant with $p < 0.05$.

3. RESULTS

In total, 98 surgical patients in septic shock treated from January 1st, 2008 through June 30th, 2009 were analysed regarding the association between the item “adherent“ or “nonadherent“ concerning 36 items of the 6-hour and 24-hour bundles of the 2008 SSC guideline and outcome. 26 out of 98 patients (27 %, 95% CI, 18,1 % - 36,4 %) died on the ICU. On admission, APACHE II score was 21 in median (range 10-47), and SAPS 3 was 50 in median (range 14-85).

The degree of the category “adherent“ of the 36 items varied between 0% and 95% (Table 1). E.g., the recommendation for the application of noradrenaline, to reach a mean arterial pressure ≥ 65 mmHg, has been adhered to in 93 out of 98 patients (95%). Fig. 1 depicts the mean values and standard deviations of the categories „adherent“ to „not applicable“ for the relative adherence to the 6-hour and 24-hour bundles of the SSC 2008 guideline in the 98 patients in septic shock.

Some reasons were detected that led to adherence of less than 100%. Since no pulmonary artery catheters have been placed in the septic shock patients, the degree of adherence to the recommendation to increase the mixed venous saturation ≥ 65 % is unknown in all 98 patients. Alternatively, satisfying the venous oxygen saturation target, O_2 saturation could have been performed via the superior vena cava central venous lines, however, was not performed in our ICU. The use of adrenaline in addition to noradrenaline was not indicated in 92 out of 98 patients, and, thus, not applicable in 94% of patients. Also, in the majority of patients (94 out of 98), treatment with rhAPC was not applicable since patients did not fulfill the inclusion criteria or due to contraindications.

Since we have investigated the adherence to the 6-hour and 24-hour bundle of the SSC guidelines, it is essential to mention that 30 patients only, developed septic shock during their stay in the ICU. On admission, 15 patients suffered from severe sepsis, and 15 patients did not fulfill the criteria of severe sepsis or septic shock. 68 patients were admitted to the ICU in septic shock form other locations, such as surgical wards (n = 6), intermediate care unit (n = 13), head/nose/ear ICU (n = 3), medical ICU (n = 7), ICU from another hospital (n = 15) or operating theatre (n = 22).

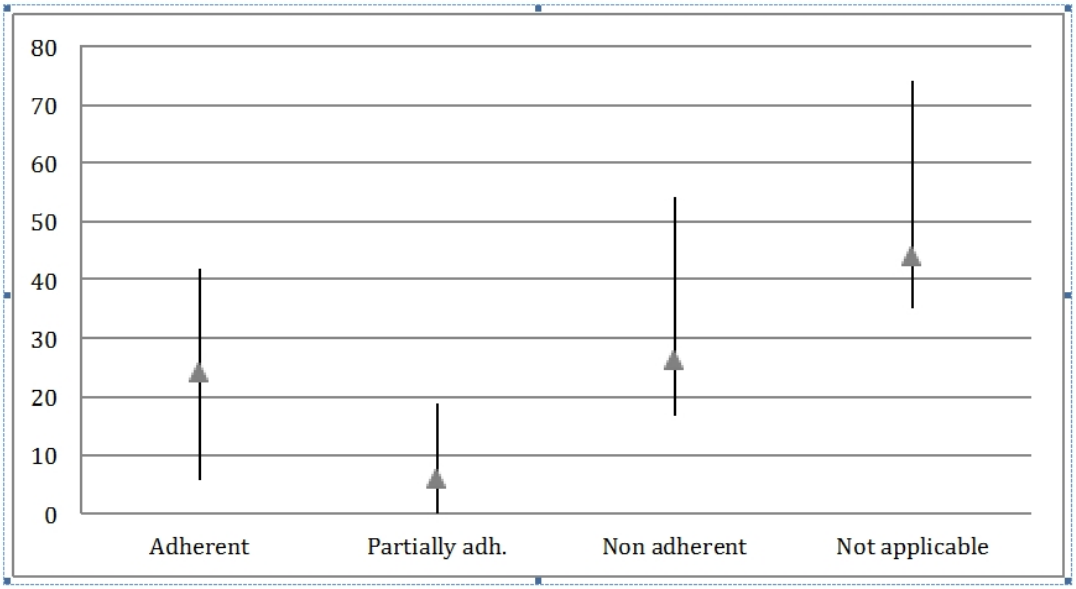

Fig. 1. Relative adherence to the 6-hour and 24-hour bundles of the SSC 2008 guideline in 98 patients in septic shock

Mean values in % and standard deviations (SD) of the categories „adherent“ to „not applicable“

Patients with septic shock on admission (n=68) had significantly higher maximal SOFA scores (degree of organ dysfunctions) (median 11, range 5-18) compared to patients developing septic shock on the ICU (n = 30; median 9, range 1-18).

In one out of the 36 items only, i. e., patients with the item urinary output (0,5 ml/kg*hour) “nonadherent“ (n = 20) demonstrated significantly higher SAPS 3 values (degree of severity of disease) at the beginning of septic shock (median 59; 41-85) than patients with this item “adherent“ (n = 64; median 49.5; 31-67), however, without difference in mortality.

Regarding mortality, no single item alone was essential for survival. No correlation was found between survival and a single item “adherent“ or “nonadherent“. A combination of items could not be tested due to low number of patients and varying applicability of items to the 98 patients.

4. DISCUSSION

The main results of the present study regarding the degree of adherence to the SSC guidelines are that many confounders, such as severity of organ dysfunctions and disease, and location when developing septic shock (type of ward), are limiting the adherence to the complex guidelines. Our results suggest that efforts associated with early diagnosis and active encouragement outside the ICU are necessary to improve applicability and adherence to the SSC guidelines in patients with septic shock in order to reduce the time lag, infections, perfusion abnormalities and organ dysfunctions are treated.

4.1 Degree of Adherence

It is important to assess the degree of adherence to the SSC guidelines in your ICU to define the present status of diagnosis and therapy. Subsequently, the SSC guidelines can be used in a continuous improvement cycle for diagnosis and therapy of sepsis in the four-step quality model – the plan-do-check-act (PDCA) cycle. In this regard, e.g., we became aware that the degree of adherence to take blood cultures within the first hour in septic shock had to be improved in our ward. A representative survey [8] revealed that current perceived vs. practiced adherence to the SSC guidelines of therapy of severe sepsis in German intensive care units complied poorly. The degree of adherence to key features of the SSC guidelines in our patients was higher than in the nationwide German survey on real performance [8], e.g. 48% compared to 33% of patients regarding intensive insulin therapy, 66% vs. 30% with cortisone, 8% vs. 3% with ventilation with low tidal volumes, and comparably low with 0% vs. 1% with rhAPC. Taken together, the degree of adherence to guidelines is profoundly overestimated.

4.2 Degree of Adherence and Outcome

Comparison of the effects of adherence to the SSC guidelines on clinical endpoints seriously interfere with subgroups of patients, physician specialty, and the setting, i.e., accident / emergency areas, wards, intermediate care unit, or ICU.

The expected number of newly diagnosed cases with severe sepsis in Germany amounts to 76-110 per 100,000 adult inhabitants [9]. Mortality rates in severe sepsis (1 - 4%) and in septic shock (20 - 72%) differ profoundly [10-12]. With these profound differences in mortality rates between patients with severe sepsis and those with septic shock, it has to be assumed that the degree of adherence of guidelines will have marked differences in the effect on clinical endpoints aimed to reach. Thus, in studies mixing up patients with severe sepsis and septic shock, conflicting results on the effects of achievement of guidelines are to be expected.

Despite comparable severity of disease reflected by APACHE II scores around 21, the presently available mortality rate of 62.4 % in a nationwide assessment in Germany [9] was profoundly greater than in our patients with septic shock (26.5%) (Fig. 2). In this nationwide assessment, patients from medical and surgical ICUs were included. It has been reported that in comparable APACHE II score ranges, the mortality rates of medical patients were higher than those of surgical patients [4]. Thus, the difference in mortality rates with similar severity of disease as defined by the APACHE II score between the nationwide assessment and our data may in part be explained by the differences in patient populations. Patients in the nationwide sepsis study were recruited between January 2003 and January 2004 [9], i.e., before the SSC 2004 and 2008 guidelines were published. Thus, the guidelines may have contributed to the lower mortality rate in our patients compared to those in the nationwide survey. It has been demonstrated in 15,022 subjects that the compliance with the entire 6-hour resuscitation bundle and the 24-hour management bundle of the 2004 guidelines increased, and the adjusted odds ratio for mortality improved the longer a site was in the Campaign, resulting in an adjusted absolute drop of 5.4% over two years [13]. In 101 consecutive patients with severe sepsis or septic shock on wards or in accident / emergency areas [14], the non-compliant 6-hour bundle group had a more than twofold significant increase in hospital mortality. In the 71 of the 101 patients admitted to critical care units, reported mortality was significantly lower in the compliant (29%) than in the non-

compliant group (55%) [14]. Thus, compliance to the 6-hour bundles significantly reduced mortality, however, to a level of 27 - 29%, only, predicted by the APACHE II score. In the present study, patients with the item urinary output (0,5 ml/kg*hour) “nonadherent“ demonstrated significantly higher SAPS 3 values at the beginning of septic shock than patients in whom this item could be adhered, pointing out that these patients were more severely ill, and thereby, with presumably worse prognosis for beneficial treatment effects.

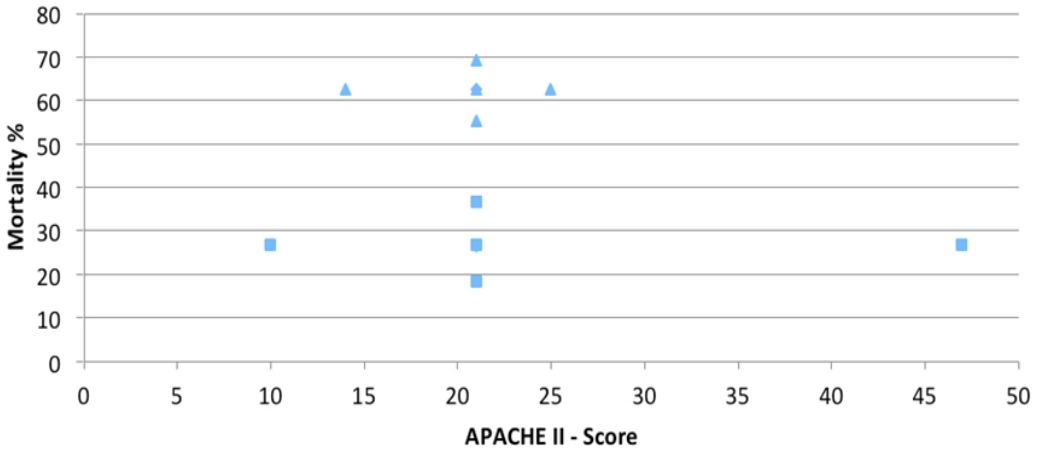

Fig. 2. Mortality and APACHE II score

Median and 95% confidence interval of the German Sepsis Competence Network (Engel, 2007, n = 190, triangles) and our patients (n = 98, squares)

It has been reported [15] that adherence to SSC guidelines and management of patients with severe sepsis / septic shock was influenced by physician specialty (physicians for emergency medicine, critical care medicine and internal medicine). In emergency departments, 17% (44/255) of patients with severe sepsis / septic shock, only, were documented as septic by the emergency department staff, and in 41% of those the standard of care for sepsis was received [16]. 71% of patients with severe sepsis / septic shock had no documented discussion or consideration of referral to the ICU [16]. Due to daily scoring in our study, no patients in septic shock were missed in the time period investigated.

Taken together, besides degree of adherence to the guidelines, differences in patient populations, severity of disease, severity of organ dysfunctions, predicted risk of death, setting, and standard of care before implementation of guidelines contribute to outcome.

4.3 Most Important Bundle Goals

More than 30 goals in two bundles are a challenge regarding a high degree of adherence in the clinical setting. Thus, it would be helpful to know which bundle goals are the most important regarding clinical endpoints. Regarding the mortality of 27% in our patients with septic shock, none of the single items of the 6-hour and 24-hour bundles alone was essential for survival. In logistic regression analysis [17], a delayed initiation of antimicrobials (> 3 hours) was the only item out of six associated with a significantly unfavorable outcome ($p = 0.04$) in patients with septic shock admitted directly from the emergency department to the intensive care unit. Using an overhead alert system known as Code SMART (Sepsis

Management Alert Response Team), a significantly greater compliance with timely antibiotic administration, lactate draw, and steroid use was achieved [18]. Raw survival and survival adjusted for age, leucopenia, and severity of illness scores (by a factor greater than 32), were significantly greater in the Code SMART group [18]. After a "plan-do-study-act" campaign in an emergency department in patients with severe sepsis or shock [19], guidelines were significantly more frequently followed (fluids administration, earlier administration of antibiotics and lactate determination rate, 46% vs. 12%). If lactate clearance was greater than 10% within 6-hours, APACHE II scores after 72 hours and 60 day mortality were significantly lower [19]. Thus, besides finding out the most important bundle goals, such as early antibiotics and restoration of circulation, guideline effects resulting in indicators, such as lactate clearance as surrogate marker for improved perfusion, may be worthwhile to reach clinical endpoints.

4.4 Factors Contributing to High Adherence and Beneficial Outcome

Several factors have been reported to improve diagnosis and therapy of sepsis. Guidelines and their difficult conversion are facing each other, as demonstrated in our study (Fig. 1) and by others [8, 14, 20]. The degree of adherence to key features of the SSC guidelines in our study was higher than in the nationwide German survey [8]. Daily computer-assisted scoring and knowledge translation by quickly available operating procedures in written and computer-based form regarding the SSC bundles and active encouragement may have contributed to the higher level of adherence in our patients. In our study, despite comparable degree of adherence of the guidelines, patients with septic shock on admission developed significantly higher maximal SOFA scores compared to the patients developing septic shock in the ICU, probably due to the time lag perfusion abnormalities and organ dysfunctions were treated. These data are in agreement with our data that besides degree of adherence it is essential to get the patients as soon as possible to timely start the adequate therapy. It has been demonstrated that continuous reevaluation and teaching is necessary to keep improvement in adherence to guidelines. In a national educational effort [20] to promote a 6-hour resuscitation bundle and a management 24 hour bundle of care for severe sepsis and septic shock was associated with improved guideline compliance and lower hospital mortality (44.0% vs. 39.7%; $p = 0.04$). However, during long-term follow-up, compliance rates were still low, and the improvement in the resuscitation bundle lapsed by one year [20].

Taken together, screening tools and alert systems may improve compliance with sepsis bundle elements and improve outcome from severe sepsis and septic shock in that less severely ill patients with less organ dysfunctions and with better presumed prognosis will be treated.

4.5 Cautions with Adherence

Subsequent original studies and metaanalyses were published during the study period. Since rhAPC, intensive insulin therapy and hydrocortisone were discussed very controversial during the study period, recommendations were followed when applicable to our subgroup of surgical patients. Controversial results with new studies not confirming positive results reported within the initial randomized controlled trial (RCT) may have strong impact on adherence to present guidelines and on the next generation of recommendations. This has been the case with initial original studies regarding rhAPC [21], hydrocortisone [22] or intensive insulin therapy [23], and subsequent original trials [24-26] in distinct subgroups of patients. In detail, e.g. rhAPC in the initial RCT [21] significantly reduced mortality. However,

in a subsequent meta-analysis [27], rhAPC demonstrated no significant effect on mortality. Moreover, recently, in the PROWESS-SHOCK trial [24], rhAPC failed to show a survival benefit, resulting in a voluntary market withdrawal of rhAPC. In nearly all of our patients (94 out of 98), treatment with rhAPC was not applicable due to non-fulfillment of the inclusion criteria or to contraindications. We have to be very careful, whether beneficial effects published in subgroups of patients can be transferred to the subgroups of patients and the context in which we treat. Proportional advocacy by physicians requires a critical weighing of risk and benefit in every clinical decision [28]. As soon as evidence changes, we should adopt adherence to guideline goals. We have to focus on high evidence bundle goals, perhaps get rid of low-evidence bundle goals, and should no longer adhere to bundle goals, if subsequent studies provide evidence of harm. Taken together, we have to be very cautious in adhering to guidelines, and to regularly check and reevaluate whether recommendations fit for our patient subpopulations any longer.

4.6 Limits of the SSC Guideline

Individual items of guidelines for complex syndromes, such as sepsis, will always be applicable to varying proportions of patients, only, as demonstrated in Table 1. Our data suggest that conversion of the guidelines will be more and more difficult with increasing complexity. In this context, the law of Gossen can be adapted to guidelines, in that with every additional item (quantity; q) of a guideline or therapy, applicability and therapeutic success cannot be increased in a linear way, but the increment of a resulting benefit (delta utility; ΔU), i.e., translation into action or the treatment success, is asymptotic and may even decrease (Fig. 3). This limit will be markedly lower in complex diseases than in less complex situations. The guideline limit renders evidence of the influence of guidelines on therapeutic success more difficult. Since the time from validation to implementation of a new clinical practice is typically 17 years, delays in the adoption of sepsis bundles are not surprising [29]. In times of limited resources, the SSC guidelines have been judged as a cost-effective option for treating severe sepsis in that the adjusted incremental cost-effectiveness ratio of the SSC protocol was 4,435 € per life years gained [30]. In our patients, adherence to the 36 items varied between 0% and 95% (Table 1). Taken together, costs, practicability and degree of adherence to guidelines may be improved, if guidelines focus on few essential points, relevant in a high proportion of patients. In addition, the optional items may be listed according to clearly defined subgroups of patients who benefit best.

Our study has potential limitations in that data have been collected in a small sample size over an 18 month period in a single university ICU in critically ill surgical adult patients. Thus, conclusions regarding outcome and regarding other subgroups of patients, such as medical and pediatric ICU patients, have to be drawn with caution.

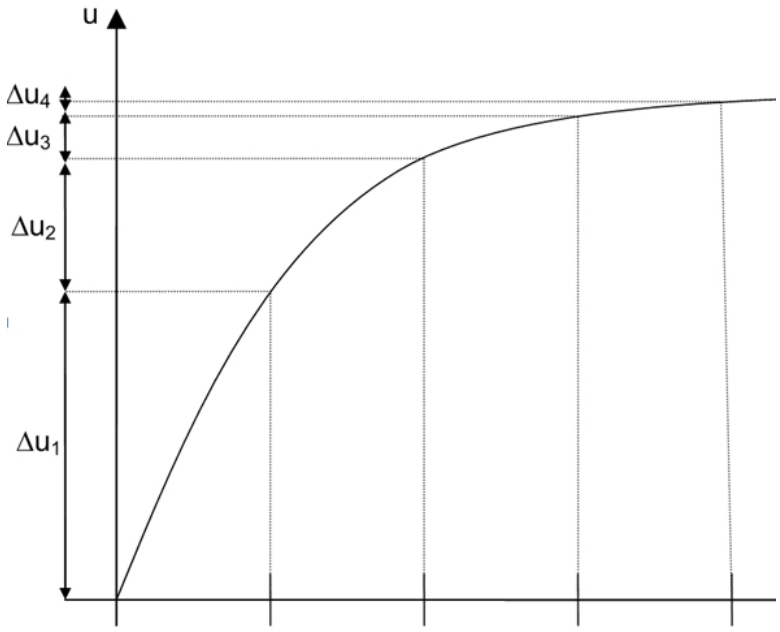

Fig. 3. Law of Gossen

With every additional item (quantity; q) of a guideline or therapy, applicability and therapeutic success cannot be increased in a linear way, but the increment of a resulting benefit (delta utility; ΔU) is asymptotic and may even decrease

5. CONCLUSIONS

In the appraisal of the degree of adherence to guidelines, a huge amount of confounders limiting the adherence to the complex guidelines have been found, such as severity of organ dysfunctions and disease, and location when developing septic shock (type of ward). Our results suggest that efforts associated with early diagnosis and active encouragement outside the ICU are necessary to improve applicability and adherence to the SSC guidelines in patients with septic shock in order to reduce the time lag, infections, perfusion abnormalities and organ dysfunctions are diagnosed and treated with lowest possible costs.

CONSENT

The Independent Ethics Committee of the University Ulm waived informed consent because this was an observational study, and no additional interventions were performed.

ETHICAL APPROVAL

The prospective study is in compliance with the Helsinki declaration and was approved by the Independent Ethics Committee of the University Ulm.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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