



## Relative Impact of the 2012 SSC Guideline Recommendations under the Scope of Numbers Needed to Treat (NNTs)

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### Authors' contributions

This work was carried out in collaboration between all authors. All designed the study and wrote the protocol. Authors FL and MW wrote the first draft of the manuscript. Author FL managed the literature searches and analyses of the study. All authors read and approved the final manuscript.

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### ABSTRACT

The surviving sepsis campaign (SSC) guidelines aimed to reduce mortality in severe sepsis and septic shock. The present study was performed to find out which and how many recommendations of the 2012 SSC update were based on significant effects from clinical studies in adult patients with severe sepsis and septic shock, leading to numbers needed to treat (NNTs). Every reference of the SSC 2012 guideline regarding clinical trials in adult patients was screened for absolute risk reduction regarding mortality to calculate NNTs.

17 relevant clinical trials out of 338 were identified. The NNTs ranged between 3.55 to 23.24. Significant reductions of mortality were detected, and items recommended in the SSC guidelines regarding early goal directed therapy (EGDT)/standard operating procedures (SOP)/sepsis bundles, early therapy with antibiotics, combined antibiotic therapy, and use of norepinephrine. Therapy with

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norepinephrine and the 6h bundles revealed the lowest NNTs. Significant reductions in mortality with restricted or no recommendations regarded therapy with hydrocortisone, therapy with high-dose antithrombin III, and enteral feeding with eicosapentaenoic acid, gamma-linolenic acid and antioxidants.

In conclusion, only a few recommendations of the 2012 SSC guidelines are based on significant beneficial effects coming from clinical trials in patients with severe sepsis and septic shock. When transferring study results and NNTs, physicians should take into account the own setting and own subgroup of patients. If feasible, costs of additional treatment success may be quantified underlying NNTs.

*Keywords: Sepsis; septic shock; severe sepsis; surviving sepsis campaign guidelines; number needed to treat.*

## ABBREVIATIONS

*ARR= Absolute Risk Reduction; ATIII= Antithrombin III; CI= Confidence Interval; COATS= Costs of Additional Treatment Success; CVP= Central Venous Pressure; EGDT= Early Goal Directed Therapy; MAP= Mean Arterial Pressure; NNT= Number Needed to Treat; rhAPC= Recombinant Human Activated Protein C; SBP= Systolic Blood Pressure; ScVO2= Central Venous Oxygen Saturation; SSC= Surviving Sepsis Campaign; SOP= Standard Operating Procedure.*

## 1. INTRODUCTION

In 2003, a prospective observational German study revealed a hospital mortality of about 55 % for patients with severe sepsis and septic shock [1]. Thus, severe sepsis and septic shock are life-threatening conditions.

In 2004, the Surviving Sepsis Campaign Guidelines were published with the aim to provide standards for management and to reduce mortality in severe sepsis and septic shock [2]. In 2008 [3] and 2012 [4], updates of those guidelines followed.

Treatment of severe sepsis according to these guidelines demonstrated beneficial effects and even reduced mortality rates [5,6].

In times of limited resources and expensive diagnostic and therapeutic options, physicians have to make decisions not only regarding medical aspects but also regarding rational and prioritized diagnosis and therapy under the scope of individual costs and the financial burden for hospitals and societies.

In publications, physicians are familiar with absolute risk reduction (ARR) and numbers needed to treat (NNTs) in clinical decision making to reach specific aims and clinical endpoints. The NNT reflects the number of individuals who have to be treated to prevent one additional event in the experimental group as compared to the control group [7].

Preferably, physicians would like to make decisions based on clinical studies delivering significant beneficial results with high effectiveness.

With the 2008 SSC guidelines as an example, we already published a simple tool for physicians using NNTs to assess the effectiveness of treatment options and the costs of additional treatment success (COATS) [8] for clinical decision making and as a justification to different stakeholders of health care systems.

The main goal of this paper is to evaluate the relative impact of the available 2012 SSC guideline recommendations using the NNT concept. This could help clinicians to assess the relative impact of these interventions in planning the utilization of limited resources.

Therefore, the present publication reviewed the SSC 2012 guidelines to find out, which and how many recommendations of the 2012 SSC guidelines resulting from clinical trials are based on significant results, and which NNTs are provided regarding reduction of mortality in adult patients with severe sepsis and septic shock.

## 2. REVIEW

### 2.1 Methods

We reviewed all of the 636 references cited in the SSC 2012 guideline [4]. Pediatric trials were excluded. We focused on clinical trials. The selected clinical trials had to deal with the septic

shock and the treatment also had to lead to a statistically significant reduction in mortality.

An absolute risk reduction (ARR) was not often stated directly in the publications. Therefore, ARR was calculated underlying the published data [9]:

$$ARR = p_1 - p_2; p = \frac{e}{n};$$

$e$  = amount of events in group

$n$  = group size

$p_1$  = probability of event in group 1

$p_2$  = probability of event in group 2;

Underlying the ARR, 95% confidence intervals were calculated [9]:

$$ARR \pm 1.96 \sqrt{p_1 \frac{(1-p_1)}{n_1} + p_2 \frac{(1-p_2)}{n_2}}$$

NNTs and their 95% confidence intervals were calculated [7]:

$$NNT = \frac{1}{ARR}$$

If no amount of events was published, the amount of events was calculated backwards out of the published risks.

### 3. RESULTS

In total, 636 references are cited in the SSC 2012 guidelines. 495 references did not refer to pediatric patients. 338 of the 495 references reflected clinical trials. 17 clinical trials with significant effects in adult patients with severe sepsis and septic shock were identified out of these 338 trials (Tables 1, 2).

Distinct therapeutic actions led to a statistically significant reduction of mortality in patients with severe sepsis and septic shock, and were recommended in the SSC guidelines [4] (Table 1):

- Early goal directed therapy (EGDT)/ standard operating procedures (SOP)/ sepsis bundle
- Early therapy with antibiotics
- Combined antibiotic therapy
- Use of norepinephrine

Some other therapeutic actions with statistically significant reduction in mortality in patients with severe sepsis and septic shock, however, were not or just in some cases recommended in the SSC 2012 guidelines (Table 2):

- Therapy with hydrocortisone
- High-dose antithrombin III
- Enteral feeding with eicosapentaenoic acid, gamma-linolenic acid and antioxidants

### 3.1 Interventions with Significant Positive Results with Recommendation in the SSC 2012 Guideline

#### 3.1.1 Standard operating procedures (SOPs)/ sepsis bundles

Different ways to reach distinct treatment aims have been reported underlying standard operating procedures (SOPs). Early-Goal-Directed-Therapy (EGDT) showed a NNT of 6.61 in a study with 263 patients [10] and in a Chinese study with 303 patients with fluid resuscitation guided by central venous pressure, systolic blood pressure or mean arterial pressure, and urinary output plus central venous oxygen saturation it had a NNT of 6.38 relating to a reduction of mortality [11].

Regarding SOPs for the treatment of patients with severe sepsis and septic shock, a study with 60 patients, in which an evidence-based SOP (consisting of ScVO<sub>2</sub> >70%, fluid administration, red blood cell transfusion, dobutamin/ norepinephrine/vasopressin, intensive insulin therapy, hydrocortisone administration, recombinant human activated protein C) showed a NNT of 3.75 [12], and a study with another SOP (microbiologic diagnosis, antibiotic therapy, fluid therapy, dopamine/dobutamine/ norepinephrine, ScVO<sub>2</sub> > 70%) with 120 patients, a NNT of 5.45 [13] for reducing mortality.

Using sepsis bundles has been demonstrated to be beneficial. A study with 330 patients regarding the introduction of a sepsis bundle (CVP/ScVO<sub>2</sub> monitoring, antibiotics, early goal-directed therapy with the scope on CVP, MAP, SBP, ScVO<sub>2</sub>, steroids, monitoring lactate clearance) showed a NNT of 5.33 [14]. Another trial with 101 patients regarding the 6h and 24h sepsis bundles showed for the 6h bundle (blood cultures, antibiotics, serum lactate measurement, fluid administration, vasopressor, blood

transfusion) a NNT of 3.86 [15], and for a further trial (antibiotics, fluid therapy, norepinephrine /dopamine/vasopressin, intensive glucose therapy, hydrocortisone, rhAPC) with 174 patients a NNT of 6.21 [16].

Focusing on the complete SSC guidelines, reduction of mortality was reached with a NNT of 23.24 in a study with 2319 patients [6], and in another study with 480 patients with a NNT of 5.05 [5].

### **3.1.2 Antibiotics**

Reviewing the publications regarding antibiotic therapy, in a subgroup of 925 patients, early treatment with antibiotics within 1h of diagnosis significantly reduced mortality with a NNT of 8.90 [17]. A study with 291 patients showed an association between the right timing of antibiotic administration and mortality in septic shock, with a NNT of 8.28 [18]. The early combination of antibiotic therapy showed an improved survival in a study with 2446 patients with a NNT of 13.74 [19]. A subgroup analysis of 92 patients for the combination with macrolids revealed an improved survival with a NNT of 4.72 [20].

### **3.1.3 Norepinephrine**

There was a positive effect of norepinephrine on outcome. In the treatment with vasopressors, norepinephrine reduced mortality in a study with 97 patients with a NNT of 3.55 [21].

## **3.2 Interventions with Significant Positive Results with Restricted or No Recommendation in the SSC 2012 Guideline**

Some interventions are restricted or not recommended in the SSC guidelines despite showing significant benefit in some trials. Firstly, the 7-day treatment with low doses of hydrocortisone and fludrocortisone reached a better outcome for patients with septic shock in a study with 229 patients with a NNT of 9.21 [22]. Secondly, treatment of 302 patients with high-dose antithrombin III (ATIII) improved survival in one study with a NNT of 8.27 [23]. Thirdly, beneficial effects of enteral feeding with eicosapentaenoic acid, gamma-linolenic acid, and antioxidants were shown in a study with 98 patients with a NNT of 5.16 [24].

## **4. DISCUSSION**

The main results of the present paper are that only a few recommendations of the 2012 SSC guidelines are based on significant beneficial effects coming from clinical trials in patients with severe sepsis and septic shock. Moreover, in the multifactorial pathophysiologic circumstances of severe sepsis and septic shock, with the exception of early antibiotic therapy and norepinephrine with a lower NNT compared to other vasopressors, single interventions demonstrating beneficial effects are hard to find. Especially, multifactorial designs, such as early goal directed therapy, 6h sepsis bundles and SOPs, demonstrated significant beneficial effects with low NNTs regarding mortality in the patients with severe sepsis and septic shock.

### **4.1 Interventions with Marked Reduction of Mortality and SSC Recommendation**

In the SSC 2012 guidelines, in the clinical studies with beneficial effects in patients with severe sepsis and septic shock, the underlying NNT's ranged from 3.75 to 23.24 (Tables 1, 2).

#### **4.1.1 Vasopressors**

In a multifactorial process, such as severe sepsis and septic shock, a single action, which has to be done to reduce mortality in severe sepsis and septic shock will hardly be detected. Maybe, some actions might improve essentially the outcome, e.g., such as norepinephrine as the primary vasopressor. The use of norepinephrine led to an ARR of 28% with a NNT of 3.55 [21] in comparison with other vasopressors in the study of Martin et al. from 2000 (55% versus 82%). A recent study from China showed also the importance of early treatment with norepinephrine in patients with septic shock. The group with norepinephrine within the first 2 hours had a 28-day mortality of 29.1% in contrast to the group with a later beginning of the treatment with norepinephrine with a 28-day mortality of 43.3% [25]. This leads to an ARR of 14.2 and a NNT of 7.02. Martin et al. showed a benefit for the treatment with norepinephrine in comparison to high dose of dopamine in septic shock with an ARR of 28% in mortality [21]. However, there is also some controversy about norepinephrine. De Backer et al. [26] showed no beneficial effects on mortality with norepinephrine compared to

dopamine. Nevertheless, there were more side effects in the group treated with dopamine. There are main differences between the two studies. Firstly, the dosage of dopamine and norepinephrine was diverse. There was a maximum dosage of  $20 \mu\text{g.kg.min}^{-1}$  of dopamine in the study of De Backer et al. versus a maximum dosage of  $25 \mu\text{g.kg.min}^{-1}$  of dopamine in the study of Martin et al. [19,35]. The maximum dosage of norepinephrine was  $5 \mu\text{g.kg.min}^{-1}$  in the study of Martin et al. versus  $0.19 \mu\text{g.kg.min}^{-1}$  in the study of De Backer [21,26]. If treatment with norepinephrine/dopamine was not successful, epinephrine was added in both studies. It should also be mentioned, that in the trial of Martin et al. dopamine up to a dosage of  $15 \mu\text{g.kg.min}^{-1}$  was part of the baseline therapy in both groups [21]. Secondly, it is unsure whether APACHE II scores were comparable. In the study of De Backer et al. [35], the median of APACHE II score was 20 (15-28) in the dopamine group and 20 (14-27) in the norepinephrine group. In the study of Martin et al. [19], the mean APACHE II score was  $28 \pm 4$  in the group with norepinephrine and  $28 \pm 3$  in the group without norepinephrine. Thus, the different results may be due to the divergent setting and/or the treatment in the two trials.

#### **4.1.2 Sepsis bundles, SOPs**

Almost every study in our investigation, e.g., also the one regarding the effect of norepinephrine [21], had a therapy with antibiotics and fluid resuscitation in their baseline. This consequently supports the importance of a therapy with antibiotics, fluid resuscitation and norepinephrine as a vasopressor as effective key therapeutic actions in therapy of severe sepsis and septic shock. The ARR of the 6h sepsis bundle was 26% (23% versus 49%) with a NNT of 3.86 [15]. The 6h bundles have been regarded as a kind of core bundles, which are essential for an effective therapy of severe sepsis and septic shock [27].

Based on our results on the 2012 SSC guidelines one would have recommend strongly EGDT with its best NNT of 3.86. However, now, we got evidence that EGDT does not improve patient outcome. As examples and to show how the scheme of Tables 1 and 2 may be used for studies not included in the guidelines and/or published thereafter, Table 3 denotes studies

beyond the 2012 SSC guidelines concerning estimation of beneficial effects regarding patients, interventions, ARRs and NNTs to estimate the beneficial effect and transfer to respective patient subpopulations and settings. Two large randomized multicenter studies have recently demonstrated that EGDT does not improve patient outcome and no subgroup could be identified in which this intervention improves outcomes [28,29]. The recently published ARISE Trial showed no benefit for the treatment with EGDT in severe sepsis [28]. The trial included 1600 patients in the emergency departments and/or intensive care units of 51 centers mostly in Australia and New Zealand. The APACHE II score of the investigated population was lower than in the trial of Rivers et al. or the ProCESS trial, i.e.,  $15.4 \pm 6.5$  in the group of EGDT and  $15.8 \pm 6.5$  in the group of usual care. Thus, there might be a limitation of the effectiveness of EGDT in less severely ill patients. In the multicenter ProCESS trial with 1341 patients [29], the authors wanted to reproduce the results of Rivers et al. [10]. However, a significant reduction of mortality was not observed in ProCESS. The comparison of both trials reveals important differences: the 60 days mortality in the usual care group of the ProCESS trial was 18.9% with an APACHE II Score of  $20.7 \pm 7.5$  at the beginning of their treatment during the years 2008 and 2013 [29]. Years ago, in the trial of Rivers et al., during 1997 and 2000, patients receiving the standard therapy had a 60 days mortality of 56.9% with an APACHE II Score of  $20.4 \pm 7.4$  at the beginning of their treatment [10]. Thus, despite of comparable severity of disease as delineated by the APACHE scores around 20, 60 day mortality was markedly lower in the ProCESS trial than in the Rivers trial [10,28]. At least, two items might be different. First, the populations might not be similar. In the trial of Rivers et al., the population was older, had a higher initial serum lactate level and more heart and liver diseases [10,29]. Second, increasing awareness of sepsis, educational initiatives, implementation and a continuous improvement cycle of the Surviving Sepsis Campaign guidelines led to management improvements in patients with severe sepsis and septic shock. Management has been improved, e.g., regarding lower triggers for transfusion, lung protective ventilation and management of blood glucose control [29].

**Table 1. Overview of relevant clinical trials with recommendation within the surviving sepsis campaign guidelines 2012 [4] and corresponding numbers needed to treat to save one additional life**

Authors	Patients	Intervention	ARR	NNT (mean, (95%CI))	Grade of evidence [4]	Grade of recommendation [4]
Rivers et al. [10]	patients with severe sepsis, septic shock or sepsis syndrome (n=263)	early-goal-directed-therapy	16% hospital-mortality <sup>1)</sup> (30.5% versus 46.5% p=0.009 <sup>1)</sup> )	6.61 <sup>2)</sup> (3.75-27.60)	1	C
Chinese Group [11]	patients with severe sepsis and septic shock (n=303)	early-goal-directed-therapy	15.7% ICU-mortality <sup>1)</sup> (35.0% versus 50.7% p=0.035 <sup>1)</sup> )	6.38 <sup>2)</sup> (3.74-21.58)	1	C
Kortgen et al. [12]	patients with septic shock in a multi-disciplinary ICU (n=60)	standard operating procedure	26% 28-day-mortality <sup>2)</sup> (53% versus 27% p< 0.05 <sup>1)</sup> )	3.75 <sup>2)</sup> (1.97-35.58)	/	/
Micek et al. [13]	patients with septic shock in emergency department and medical, surgical-trauma ICUs (n=120)	standard operating procedure	18.3% 28-day-mortality <sup>2)</sup> (48.3% versus 30.0% p= 0.04 <sup>1)</sup> )	5.45 <sup>2)</sup> (2.81-84.97)	/	/
Nguyen et al. [14]	patients with severe sepsis and septic shock in an emergency department (n=330)	sepsis bundle	18.7% in-hospital-mortality <sup>2)</sup> (20.8% versus 39.5% p< 0.01 <sup>1)</sup> )	5.33 <sup>2)</sup> (3.37-12.71)	/	/
Gao et al. [15]	patients with severe sepsis and septic shock on medical/surgical wards or	6h sepsis bundle	26% hospital mortality <sup>2)</sup> (23% versus 49% p = 0.01 <sup>1)</sup> )	3.86 <sup>2)</sup> (2.27-12.79)	1	C

	accident/emergency areas (n=101)					
EISolh et al. [16]	patients with septic shock on ICU (n=174)	sepsisbundle	16% 28-day-mortality <sup>1)</sup> (55% versus 39%, p= 0.03 <sup>1)</sup> )	6.21 <sup>2)</sup> (3.25-68.88)	/	/
Suarez et al. [6]	patients with severe sepsis on medical-surgical ICUs (n=2319)	survivingsepsiscamp aignguidelines	4.3% hospitalmortality <sup>2)</sup> (44% versus 39.7%; p = 0.04 <sup>1)</sup> )	23.24 <sup>2)</sup> (11.80-745.80)	/	/
Castellanos-Ortega et al. [5]	patients with septic shock on medical-surgical ICUs (n=480)	survivingsepsiscamp aignguidelines	19.8% hospitalmortality <sup>2)</sup> (57.3% versus 37.5% p= 0.01 <sup>1)</sup> )	5.05 <sup>2)</sup> (3.24-11.39)	/	/
Ferrer et al. [17]	patients with severe sepsis or septic shock from the 77 ICUs contributing to the Edusepsis Study (n=925, subgroup)	antibiotics within 1 h of diagnosis	11.2% hospital mortality <sup>2)</sup> (45.5% versus 34.3% <sup>2)</sup> p< 0.05 <sup>***)</sup> )	8.90 <sup>2)</sup> (5.69-20.37)	1	B*/C**
Puskarich et al. [18]	patients with septic shock in emergency departments (n=291)	antibiotic therapy before shock recognition	12% hospital mortality <sup>2)</sup> (23.8% versus 11.8% <sup>1)</sup> p < 0.05 <sup>***)</sup> )	8.28 <sup>2)</sup> (4.83-28.84)	1	B
Kumar et al. [19]	patients with septic shock on intensive care units of 28 academic and community hospitals in 3 countries (n=2446)	early combination of antibiotic therapy	7.3% 28-day-mortality <sup>2)</sup> (36.3% versus 29.0% <sup>1)</sup> p < 0,05 <sup>***)</sup> )	13.74 <sup>2)</sup> (9.10-28.00)	2	B
Martin-Loeches et al. [20]	patients with severe cap and severe sepsis/septic shock	antibiotic therapy in combination with macrolides	21.2% ICU-mortality <sup>2)</sup> (46.2% versus 25%	4.72 <sup>2)</sup> (2.48-47.99)	2	B

	in 27 ICU's of 9 countries (n=92, subgroup)		p=0.03 <sup>1)</sup>			
Martin et al. [21]	patients with septic shock on a general care ICU of an university hospital (n=97)	use of norepinephrine in treatment	28% 28-day-mortality <sup>2)</sup> (55% versus 82%, p<0.001 <sup>1)</sup> )	3.55 <sup>2)</sup> (2.19-9.41)	1	B

ARR, absolute risk reduction, NNT, number needed to treat, CI, confidence interval, \*= with shock, \*\*=without shock, \*\*\*= p value calculated by the authors of this article, grading system (GRADE): quality of evidence from high "A" to very low "D", and strength of recommendations as strong "1" or weak "2" [4],  
 1)= cited out of publication; 2)= calculated and rounded



**Table 2. Overview of relevant clinical trials out of the surviving sepsis campaign guidelines 2012 [4] with restricted or no recommendation in the guidelines [4] and their numbers needed to treat to save one additional life**

Authors	Patients	Intervention	ARR	NNT (mean, (95%CI))	Grade of evidence [4]	Grade of recommendation [4]
Annane et al. [22]	patients with septic shock and adrenal insufficiency on 19 ICUs in France (n=229)	7-day treatment with low doses of hydrocortisone (50 mg) and fludrocortisone (50 µg)	10.8% 28-day-mortality <sup>2)</sup> (63 % versus 53%, p=0.04 <sup>1)</sup> )	7 <sup>1)</sup> (95% CI, 4-49) <sup>1)</sup>	„We suggest not using intravenous hydrocortisone as a treatment of adult septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability (see goals for Initial Resuscitation). If this is not achievable, we suggest intravenous hydrocortisone alone at a dose of 200 mg per day (grade 2C).“	
Wiedermann et al. [23]	patients with severe sepsis out of the Kyper Sept trial (211 participating centers in 19 countries) (n=302)	high-dose antithrombin III	12% 90-day-mortality <sup>2)</sup> (42.8% versus 55.1% <sup>1)</sup> p<0,05***)	8.27 <sup>2)</sup> (4.29-116.23)	„We recommend against antithrombin administration for the treatment of severe sepsis and septic shock (grade 1B)“	
PontesArrudo et al. [24]	ventilated patients with severe sepsis and septic shock in 3 different brazil ICUs (one medical, one cardiology, one post-surgical) (n=98)	Enteral feeding with eicosapentaenoic acid, gamma-linolenic acid and antioxidants	19.4% 28-day-mortality <sup>1)</sup> (33% versus 52% p=0.037 <sup>1)</sup> )	5.16 <sup>2)</sup> (2.62-180.48)	No recommendation	

ARR, absolute risk reduction, NNT, number needed to treat, CI, confidence interval, \*\*\*= p value calculated by the authors of this article, grading system (GRADE): quality of evidence from high "A" to very low "D", and strength of recommendations as strong "1" or weak "2" [4], 1)= cited out of publication, 2)= calculated and rounded

**Table 3. Important recent studies regarding treatment of sepsis beyond the 2012 SSC publication**

<b>Authors</b>	<b>Patients</b>	<b>Intervention</b>	<b>ARR</b>	<b>NNT (mean, (95%CI))</b>
ARISE Investigators and the ANZICS Clinical Trials Group [28]	Patients with septic shock in emergency department and intensive care units in 51 hospitals mostly in Australia and New Zealand (n=1,600)	early-goal-directed-therapy	There was no significant risk reduction.	/
The ProCESS Investigators [29]	Patients with septic shock in 31 American emergency departments (n=1,341)	early-goal-directed-therapy	There was no significant risk reduction.	/
Levy et al. [30]	Patients with severe sepsis in 218 hospitals worldwide (n=29,470)	Compliance with Surviving Sepsis Campaign resuscitation bundles	21.8 % hospital mortality <sup>2)</sup> (38.6 % versus 29.0%, p<0.001 <sup>1)</sup> )	4.58 <sup>2)</sup> (4.30-4.90)
Bai et al. [25]	Patients with septic shock on two surgical intensive care units (n=213)	Therapy with norepinephrine within the first 2h of onset of septic shock	14.2% 28-day mortality <sup>2)</sup> (29.1% versus 43.3%, p<0.035 <sup>1)</sup> )	7.02 <sup>2)</sup> (3.69-74.70)

ARR, absolute risk reduction, NNT, number needed to treat, CI, confidence interval, 1)= cited out of publication, 2)= calculated and rounded

In this regard, a recent observational trial with 29,470 observed subjects in the years 2005-2012 showed a significant association between lower mortality and higher compliance with the resuscitation bundle and the management bundle of the Surviving Sepsis Campaign Guidelines [30]. High compliance with the resuscitation bundle led to a hospital mortality of 29% in contrast to a hospital mortality of 38.6% in low compliance. This corresponds to an ARR of 21.8 and a NNT of 4.58 [30].

However, it is obvious that distinct interventions have to be done on their time. Dying patients won't benefit from e.g. a certain kind of infection prevention by selective decontamination of the digestive tract to prevent mortality. Thus, interventions which can be done in the first hours of therapy might be the most important ones and have to be done. Further ones also would be with less sense without them.

#### **4.2 Interventions with Marked Reduction of Mortality and Restricted SSC Recommendation or Recommendation Not to Do**

Some trials with significant results led to restricted or no recommendations within the 2012 SSC guidelines (Table 2). The SSC recommendations are based on broader issues around quality of RCTs and generalizability than just NNTs would deliver.

##### **4.2.1 Hydrocortisone**

There is a restricted recommendation in the SSC 2012 guidelines for the therapy with 200 mg hydrocortisone in case of refractory shock, only [4]. Based on the cited studies, it might be an option for an additional treatment in patients with persistent hemodynamic instability, however, it is associated with an unsure NNT. Regarding hydrocortisone, it was not possible to show a benefit in the large European multi-center trial "CORTICUS" [4,31].

##### **4.2.2 AT III and immunonutrition**

Treatment with AT III and immunonutrition with eicosapentaenoic acid, antioxidants and gamma-linolenic acid have shown a benefit in two studies, one for each treatment. However, regarding eicosapentaenoic acid and gamma-linolenic acid, the beneficial effects on mortality were not reproducible [4]. Regarding AT III, no confirma-

tory studies have been performed [4], and the grade of evidence is too low. Thus, it is recommended, not to use ATIII.

##### **4.2.3 Recombinant activated recombinant human protein C (rhAPC)**

Treatment with recombinant activated recombinant human protein C (rhAPC), e.g. in the PROWESS trial, significantly reduced mortality (30.8% versus 24.7%  $p = 0.005$ ) [32]. The ADRESS study with less severe organ dysfunctions required for treatment with rhAPC, even with around 11.000 patients included, demonstrated no difference in mortality, however a significant risk of bleeding [33]. Also, ENHANCE [34], an open-label observational study, revealed a nearly doubled risk of bleeding of 6.5% compared with the PROWESS and the ADRESS trial. rhAPC has been drawn from the market and is no longer recommended in the SSC 2012 guidelines.

##### **4.2.4 Steroids**

Therapy with steroids serves as another example. The trial of Annane et al. was able to show an ARR of 10.8% in mortality by a treatment with hydrocortisone and fludrocortisone in patients with septic shock and adrenal insufficiency [22]. The CORTICUS trial was not able to reproduce this result with hydrocortisone [31]. However, there were essential differences between the Annane vs. the CORTICUS trial: mortality rate in the placebo group 63% vs. 31%, time range for inclusion 8 vs. 72 hours, fludrocortisone yes vs. no, tapering off hydrocortisone no vs. yes, treatment time 7 vs. 11 days, surgical patients 40% vs. 67% and systolic blood pressure  $< 90 \text{ mmHg} > 1 \text{ h}$  vs.  $< 1 \text{ h}$  [22,31].

All in all, the underlying reasons for restricted or even voting against recommendations for some therapeutic actions are low quality of evidence, low magnitude of effects, positive results only in subgroups of patients, conflicting results, availability and costs [4]. If significant results of a study are not reproducible or confirmatory larger studies lead to contradictory results, recommendations may be restricted or even drawn back.

The SSC Guidelines have been the subject of much review and debate [35,36]. Almost all SSC 2012 recommendations were given due to the grading system (GRADE) to guide assessment of quality of evidence from high "A" to very low "D", and to determine the strength of

recommendations as strong “1” or weak “2” [4]. In case that one trial with low number of patients in distinct subgroups revealed a significant effect, however, with a low magnitude of effect, with plausible confounders, could not be reproduced by others or in meta-analyses, could not be generalized to patients with severe sepsis and septic shock, or not provided to many patients due to expensive costs, burden or harm on patients or staff, these procedures were restricted or not recommended in the SSC guidelines [4].

Moreover, the GRADE system itself has also been extensively critiqued, e.g. regarding the reliance on single-center RCTs and the lack of trial data for distinct recommendations [37].

However, if distinct subgroups of patients, physicians want to treat, fulfill the criteria of the patients who have been selected for the studies delivering significant results, the NNTs given in these studies may help the physicians to assess the effectiveness of treatments for reaching distinct aims, such as lowering mortality, days with organ dysfunctions or length of stay.

#### 4.3 Limitations

Our study has several limitations. Firstly, we predominantly reviewed references cited in the actual 2012 SSC guidelines. Secondly, we only took into account publications of original trials. Reviews and meta-analyses were excluded.

Moreover, this paper does not deal with the recommendations based on studies presenting no statistically different results, and, thus, consequently, leading to recommendations not to perform in patients. However, these recommendations are as necessary as the recommendations based on statistically significant beneficial effects. It has to be kept in mind that the degree of adherence to the SSC guidelines is challenged by many confounders, such as severity of organ dysfunctions and disease, and location where septic shock develops (type of ward), limiting the adherence to the complex guidelines [38]. Moreover, not all recommendations are applicable to all patients with severe sepsis and septic shock [38].

Referring to NNT's has one big danger which should be known. NNTs are helpful to assess the effectiveness of an intervention. However, a NNT is specific for a distinct trial and its investigated study population. The population and its

incidence of distinct events (e.g. death) lead to a distinct risk [39]. The difference in the risk between treatment and control group leads to the absolute risk reduction (ARR). If a study investigates a population with a real low incidence of a distinct event, e.g., 2 percent in control group and 1 percent in treatment group, the absolute risk reduction would be 1 percent and the NNT would be 100. If the incidence in the control group would be 50 percent and in the treatment group 25 percent, the absolute risk reduction would be 25 percent, and the NNT would be 4. However, in both examples, the relative risk reduction would be 50 percent. Thus, the knowledge about the investigated population is essential for the rational use of NNTs in clinical practice.

#### 4.4 NNTs under the Scope of Improvements in Standard Care

Underlying the product of the NNTs and the difference in treatment costs per patient, physicians can get aware easily of the costs of the additional treatment success (COATS) [8]. COATS can be calculated as follows [8]:

$$COATS = NNT \times \text{delta costs per patient}$$

Regarding early therapy, screening for severe sepsis and septic shock is inevitable. Consequently, improving the early recognition of septic patients by hospital staff to implement the 2012 SSC guidelines as soon as possible will be a key factor. Both issues could reduce the NNTs, and, thereby, optimize the effectiveness of the diagnostic and therapeutic 2012 SSC recommendations, and help to save resources.

Our examples demonstrate that many aspects should be taken into account if trial results are transferred into the own clinical setting.

Adapting the law of Gossen to guidelines [38], the additional success of every additional treatment is not linear, reaching a saturation where no further additional success is possible or it even runs deleterious. If general improvement in the management of patients with severe sepsis and septic shock has resulted in standard care associated with a low mortality rate, it will be more and more difficult to demonstrate significant results with single interventions leading to NNTs in clinical trials in distinct subgroups of patients. How can these NNTs be transferred to patients treated under real life conditions in different hospitals? One has

to ask: Does the trial fit to my subset of patients in my setting? If resources are limited, one should start with the recommendations which best fit to the own subset of patients with the best effectiveness at the lowest costs. This should be accompanied by a permanent assessment of the quality of all dimensions of medical care: structure, process and outcome [40].

## 5. CONCLUSION

Physicians should critically reflect guidelines and follow new trial results to transfer them to their own patients and setting, should regard to effectiveness using NNTs and assess costs of additional treatment success, to continuously improve management of their patients with sepsis. The aim should be to get NNTs which are as low as possible to effectively benefit as many patients as possible with lowest costs and without doing harm.

## CONSENT

Not applicable.

## ETHICAL APPROVAL

Not applicable.

## COMPETING INTERESTS

The authors declare that they have no competing interests.

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