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**Wiener klinische Wochenschrift**  
The Central European Journal of  
Medicine

ISSN 0043-5325

Wien Klin Wochenschr  
DOI 10.1007/s00508-012-0229-7



Springer Medizin

124. Jahrgang / Heft 9-10, 2012  
www.springer.at  
ISSN Print 0043-5325 / ISSN Electronic 1613-7671  
P. b. h. Verlagspostamt 1201 Wien / 122039287P

9-10/12  
**wiener klinische wochenschrift**

The Central European Journal of Medicine

Offizielles Organ der  
 Österreichischen Gesellschaft für Innere Medizin (OGIM)  Österreichischen Gesellschaft für Pneumologie (OGP)

Gegründet 1888 in Wien

Leitlinie zur Prävention und Früherkennung von Brust- und Eierstockkrebs bei Hochrisikopatientinnen

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# Do clinical guidelines improve management of sepsis in critically ill elderly patients? A before-and-after study of the implementation of a sepsis protocol

Hans Jürgen Heppner, Katrin Singler, Anja Kwetkat, Steffen Popp, Adelheid Susanne Esslinger, Philipp Bahrmann, Matthias Kaiser, Thomas Bertsch, Cornel Christian Sieber, Michael Christ

Received: 21 March 2012 / Accepted: 18 July 2012  
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**Verbessern innerklinische Handlungsanweisungen die Versorgung kritisch kranker älterer Sepsispatienten? Eine vorher-nachher Betrachtung der Einführung eines standardisierten Sepsisprotokolls**

## Zusammenfassung

**Ziel** Leitlinien für die Behandlung der Sepsis sind gut publiziert, aber bisher noch nicht für die alten Patienten speziell betrachtet worden, wenngleich ein rascher Therapiebeginn in dieser Patientengruppe sehr wichtig ist. Die Studie überprüft den Einfluss eines standardisierten Behandlungsablaufes auf eine zeitnahe Therapie und auf die Mortalität.

**Methodik** Alle Patienten, 70 Jahre und älter, mit der Diagnose Sepsis, die während des Beobachtungszeitraumes zur intensivmedizinischen Aufnahme kamen,

wurden in die vorher-nachher-Studie eingeschlossen. Alter, Geschlecht und Qualitätsmerkmale der Therapie wie zeitnahe antiinfektive Behandlung, Entnahme von Blutkulturen vor der Antibiotikaerstgabe, Messung des zentralen Venendruckes, Messung der zentralvenösen Sättigung, Volumenmanagement und Patientenoutcome wurden evaluiert.

**Ergebnisse** Einhundertzweiundzwanzig Patienten konnten in die Studie eingeschlossen werden. Eine Sepsis wurde in 22,9 % der Fälle vor der Einführung des Protokolls und in 57,4 % nach der Einführung dokumentiert. Eine adäquate Volumentherapie wurde bei 63,9 % der Patienten durchgeführt (11,5 % vor Protokolleinführung). Blutkulturen wurden bei 67,2 % der Patienten (4,9 % vor Protokolleinführung) vor der Erstgabe des Antibiotikums abgenommen, und eine zeitnahe Gabe des Antibiotikums erfolgte bei 72,1 % der Patienten (32,8 % vor Protokolleinführung). Die Laktatbestimmung erfolgte bei 77,0 % der Patienten (11,5 % vor Protokolleinführung). Ein zentraler Venenkatheter wurde bei 88,5 % der Patienten (68,9 % vor Protokolleinführung) angelegt, und der vorgegebene zentralvenöse Druck wurde zu 64,3 % (47,2 % vor Protokolleinführung) erreicht. Die Intensivsterblichkeit konnte um 5,2 % und die Krankenhaussterblichkeit um 6,4 % gesenkt werden.

Hans Jürgen Heppner and Katrin Singler contributed equally to this manuscript.

This paper was presented in abstract form at the Weimar Sepsis Update 2011 [Heppner HJ, et al. Sepsis in geriatric patients: Process oriented knowledge management. *Infection*. 2011;39:S127-8] and the 7th Congress of the European Geriatric Medicine Society, Malaga 2011 [Heppner HJ, et al. Sepsis in geriatric patients. *Eur Geriatr Med*. 2011; 2S:S105-6].

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**Schlussfolgerungen** Die Verwendung von standardisierten Konzepten bei der Therapie der Sepsis beim älteren Patienten ist unbedingt zu empfehlen, um bessere Behandlungserfolge zu erzielen. Die konsequente Einhaltung des Protokolls führte zu einer reduzierten Intensivverweildauer, einer reduzierten Sterblichkeit und einer Verbesserung der Initialtherapie.

**Schlüsselwörter:** Sepsis, Protokoll, Behandlungsstandard, Outcome, Intensivmedizin, Geriatrische Patienten

### Summary

**Aim** Guidelines for the management of sepsis have been published but not validated for elderly patients, though a prompt work-up and initiation of appropriate therapy are crucial. This study assesses the impact of a sepsis protocol on timelines for therapy and mortality in standardized management.

**Methods** Consecutive patients aged 70 years and older who were diagnosed with sepsis and admitted during the observation periods were included in this before-and-after study at a medical intensive care unit (ICU). Age, sex, and process-of-care variables including timely administration of antibiotics, obtaining blood cultures before the start of antibiotics, documenting central venous pressure, evaluation of central venous blood oxygen saturation, fluid resuscitation, and patient outcome were recorded.

**Results** A total of 122 patients were included. Sepsis was diagnosed in 22.9 % of patients prior to the introduction of the protocol and 57.4 % after introduction. Volume therapy was conducted in 63.9 % of the patients (11.5 % preprotocol). Blood culture samples were taken prior to the administration of antibiotics in 67.2 % of patients (4.9 % preprotocol), and antibiotics were applied early in 72.1 % of patients (32.8 % preprotocol). Lactate was set in 77.0 % of patients (11.5 % preprotocol). A central venous catheter was inserted in 88.5 % of patients (68.9 % preprotocol), and the target central venous pressure was achieved in 64.3 % of patients (47.2 % preprotocol). ICU mortality was reduced by 5.2 % and hospital mortality by 6.4 %.

**Conclusions** The use of standardized order sets for the management of sepsis in elderly patients should be strongly recommended for better performance in treatment. Compliance with the protocol was associated with reduced length of stay, reduced mortality, and improved initial appropriate therapy.

**Keywords:** Sepsis, Protocol, Standardized order, Outcome, Intensive care medicine, Geriatric patients

### Introduction

Due to the demographic shift, the number of elderly patients treated in intensive care units (ICU) is increasing. Sepsis has a high mortality rate in this patient group. Sepsis is also found among the most frequent leading causes

of overall mortality and the most common cause of shock [1] and a meaningful cause of death [2, 3]. Geriatric patients have not yet been observed in an isolated manner. The care of critically ill elderly patients has become more complex with the number of geriatric patients increasing and more and more clinical information having to be considered within the therapeutic approach. For clinicians, mastering these requirements is difficult and new strategies for managing knowledge are necessary. Therefore, a recent approach is to use protocols, paper based or electronic, to succeed in treatment [4]. As complex the case may be, sepsis patients must be treated fast and effectively to reduce the high case fatality rate [5]. The discussion on the implementation of guidelines is still ongoing, and transferability to everyday clinical practice is frequently questioned [6]. Thus, covering elderly multimorbid patients in guideline recommendations is difficult. Rivers et al.'s [7] study on the early sepsis treatment, specifically the early goal-directed therapy (EGDT) continues to receive attention on this material though sepsis is traditionally viewed as an ICU disease [8]. The different steps in treatment include immediate measures to be completed within the first 6 hours (resuscitation bundle) and a set of targets to be completed within 24 hours (management bundle) to improve patient outcome [9] (Table 1).

Therapy management is driven by the measurement of central venous pressure (CVP), median arterial pressure (MAP), and central venous blood oxygen saturation ( $S_{cv}O_2$ ). This approach led to a significant reduction in the 28-day mortality and was adopted in the American [10] and German [11] guidelines with a specific checklist of targets.

However, the implementation and depth effect of these recommendations is not always quite as trivial as

**Table 1.** Sepsis bundles

Resuscitation bundle	Management bundle
Serum lactate concentration target: < 4 mmol/l	Thrombosis prophylaxis
Obtaining blood cultures before the start of antibiotics	Stress ulcer prophylaxis
Administration of antibiotics within the first hour after the diagnosis	Early enteral nutrition
CVP; target central venous pressure: 8–12 mmHg (mechanical ventilation: 12–15 mmHg)	Control of blood sugar: goal 150 mg/dL
Hypotension (MAP < 65 mmHg) and/or lactate > 4 mmol/L	Mechanical ventilation and deep sedation: RASS < -3
Fluid resuscitation	Lung protective ventilation: tidal volume < 6 ml/kg/KG, $P_{insp}$ < 30 mmHg
Noradrenaline	Hydrocortisone if vasopressors are needed
Central venous oxygen saturation > 70 %	Renal replacement therapy
Hemoglobin > 7–9 g/dL	
<i>CVP</i> central venous pressure, <i>MAP</i> median arterial pressure, <i>RASS</i> Richmond Agitation Sedation Scale	

they appear to be at first glance. For instance, acceptance is not occurring at a considerably high percentage [12], but is clearly in the lower range [13] and far from the status of standardized treatment [14], though compliance in the application of the recommendations has been shown to result in reduced mortality rates [15]. Application of the recommendations in geriatric patients is even rarer, as additional reservations due to multimorbidity and resentment in terms of age rationing come to bear [16]. Thus, showing that a process-orientated course of action is necessary by applying a standardized protocol, which is helpful as patients in the early phase of sepsis particularly benefit from EGDT [17]. The objective of this present study was to apply early stage sepsis treatment in geriatric patients and identify the positive effects.

## Methods

The study is a single-center cohort before-and-after study conducted with medical ICU patients. Consecutive patients aged 70 years and older who were admitted during the observation time period were included. Preprotocol data were collected during the first quarter of 2008, the rollout of the protocol was during the third quarter of 2008, and postprotocol data were collected during the first quarter of 2009. Before implementation, the protocol was discussed with all involved deciders in forefront of implication and was agreed upon by the clinical microbiology department for antimicrobial management and medical ICU staff for step by step implementation. The postprotocol portion was achieved using prospective data collection to evaluate the parameters and the outcomes of protocol-driven elderly patients.

### Patient evaluation

Two thousand patients were retrospectively analyzed. Therefore, clinical histories were reviewed and patients with sepsis were identified if they had a principal discharge diagnosis of sepsis (German-Diagnosis Related Groups [G-DRG] codes). Each chart was reviewed and data were collected by two reviewers using a questionnaire form. Case confirmation required an appropriate G-DRG code based on clinician-documented diagnosis and results of diagnostic tests according to formal sepsis criteria (Table 2). In addition, treatment periods prior and after the introduction of the protocol were compared. Based on the consensus conference recommendations, the predefined sepsis criteria listed in Table 2 were used for patient enrollment. The recommendations included not only the guidelines for adequate fluid resuscitation and empiric antibiotic therapy, but also the diagnostic criteria for sepsis, laboratory orders, and hemodynamic monitoring.

The following characteristics were recorded for all patients: age, sex, and key performance indicators, including administration of antibiotics within the first

**Table 2.** Formal sepsis criteria (modified from [10]) and definition of organ dysfunction (Modified from [7])

SIRS	Temperature > 38 °C or < 35 °C Heartbeat > 90 min <sup>-1</sup> Respiratory rate > 20 min <sup>-1</sup> or p <sub>a</sub> CO <sub>2</sub> < 32 mmHg WBC > 12,000 /μL or WBC < 4,000 /μL	At least 2 criteria
Sepsis	SIRS + focus or bacteremia	
Severe sepsis	Sepsis + organ dysfunction	
Septic shock	BP <sub>systolic</sub> < 90 mmHg more than 1 hour	Despite fluid resuscitation
<i>Organ dysfunction (at least 1 criterion)</i>		
Mental disturbance, acute encephalopathy, delirium		
Thrombopenia < 100,000 /μL (not hemorrhagic)		
Arterial blood gas: p <sub>a</sub> O <sub>2</sub> < 75 mmHg or p <sub>a</sub> CO <sub>2</sub> < 32 mmHg		
Arterial blood gas: metabolic acidosis, BE < 5 mmol/L, lactate > 4 mmol/L		
Renal dysfunction: Diuresis < 0.5 ml/kg/hour despite fluid resuscitation		
SIRS systemic inflammatory response syndrome, WBC white blood cell		

hour, obtaining blood cultures before the start of antibiotics, employing a central venous catheter, documenting the achievement of a CVP > 8 mmHg, evaluating central venous blood oxygen saturation (S<sub>cv</sub>O<sub>2</sub>), and fluid resuscitation. All relevant data were recorded during daily rounds using patient charts, personal notes during treatment, bedside flow sheets, and the hospital's computer database.

### Implementation of the standardized order set

The ICU is a closed unit where patient care is delivered by ICU-resident physicians under the supervision of attending physicians' board certified in critical care. The hospital order set for the management of sepsis on hemodynamic resuscitation and antimicrobial treatment was developed by a committee comprising critical care department nurses, pharmacists, microbiologists, and critical care physicians chaired by two of the authors (M. Christ and H. J. Heppner). The order set was based on recommendations derived from the Surviving Sepsis Campaign [10]. Formal education and clinical training of all physicians, nurses, and patient care technicians in the ICU pertaining to the processes and procedures related to the order set forms was completed in an 8-week period by three of the investigators before the after phase (S. Popp, H. J. Heppner and M. Christ). All educational endeavors included training in sepsis pathophysiology, monitoring of central venous pressures, importance of fluid resuscitation, assessment of central venous blood oxygen saturation and antimicrobial management. After

completing education each member of staff was issued with a personal copy of the standardized order set.

### End points

The endpoints of the study were achieving fluid resuscitation, timelines for taking blood cultures and administering antibiotics, estimating tissue perfusion as measured by serum lactate, and the impact of standardized order sets on mortality.

### Statistical analysis

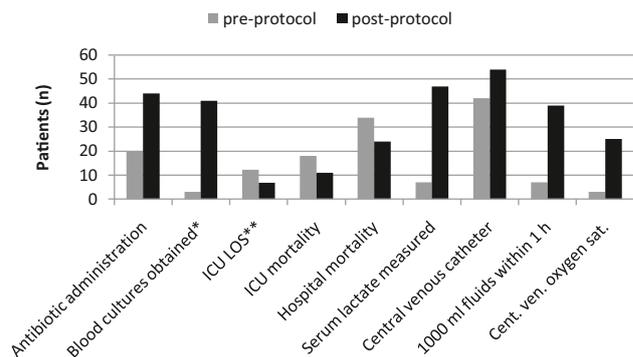
Statistical analysis was performed using SPSS software, version 19.0 (SPSS Inc., Chicago, IL). Bivariate analysis was used to examine differences between pre-protocol and post-protocol groups. The difference in mortality between both groups was illustrated by survival analysis. The study is announced to the local ethics commission approval.

### Results

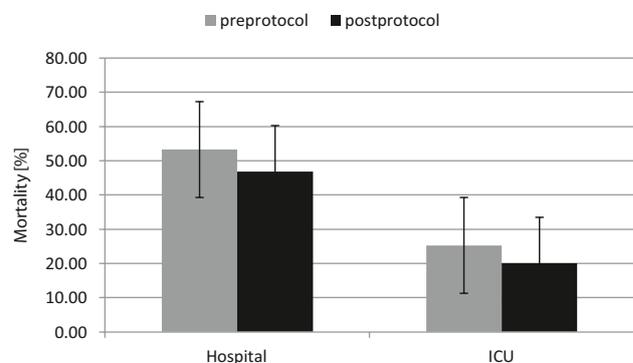
A total of 122 septic patients aged 70 years and older were identified during the observation period. The age distribution was similar in both study groups (average age of 80.3 years prior to and 79.7 years after the introduction of the protocol). Sepsis was diagnosed in 22.9 % of cases prior to introduction of the protocol and 57.4 % after introduction. The diagnosis of severe sepsis declined from 42.6 to 18.0 %. Initial volume therapy was performed in 63.9 % of cases (11.5 % preprotocol); blood culture samples were taken before the first administration of antibiotics in 67.2 % of patients (4.9 % preprotocol). Lactate measurement was documented to evaluate tissue perfusion in 77.0 % of patients (11.5 % preprotocol). A central venous catheter was inserted for volume management and to measure central venous saturation in 88.5 % of patients (68.5 % preprotocol). The target CVP was obtained in 64.3 % of cases (47.2 % preprotocol). In the postprotocol group, 64 % of the patients received intravenous fluids earlier and were more likely to be treated with an appropriate initial antimicrobial regimen within the first few hours than the preprotocol group (32.8 % vs. 72.1 %; Fig. 1). Patients in the postprotocol group had a shorter length of stay (LOS) in the ICU (12.2 days vs. 6.9 days) and a lower risk of mortality (25.3 % vs. 20.1 %) than the preprotocol group (Fig. 2 and Table 3).

### Discussion

Several evidence-based guidelines for the management of sepsis have been published but are yet to be validated for elderly patients, though prompt work-up and initiation of appropriate therapy are crucial in (severe) sep-



**Fig. 1** Medical care processes and key performance indicators (\*) blood cultures were obtained before antibiotic administration. (\*\*) LOS length of stay



**Fig. 2** The probability of ICU and in-hospital survival in elderly patients with sepsis treated in the preprotocol (grey) and post-protocol groups (black)

sis in this age group. Based on complex requirements, medical, administrative, and clinical protocols and their application seem to be prevalent [18], though standardized care may improve a patient's outcome.

Optimization of the processes involved in patient treatment, especially in the sensible field of intensive care medicine, is an indispensable measure for the implementation of modern treatment procedures [19]. Validated quality management instruments are well suited for representing diagnostic procedures and treatment approaches in a process-oriented manner. Structured and standardized treatment paths can be derived from instruments that result in both medically and economically efficient treatment in a patient case group. These paths can be used to achieve a high level of therapeutic and patient safety and improved structural and process quality, which can result in positive effects on illness-related mortality rates. General knowledge regarding sepsis improved over the course of the study. Side effects such as team spirit improved considerably, and the assumption of responsibility over the course of treatment was achieved in all professional groups involved. Allocations for extraclinical staffing, nurses, and physician coverage are not always needed [20], but controlling quality and key performance indicators for monitoring compli-

**Table 3.** Demographics, medical care processes, and key performance indicators

Variable n (%)	Preprotocol (n=61)	Postprotocol (n=61)
Age (year)	80.3	79.7
<i>Sex</i>		
Male	35 (57.4)	36 (59.0)
Female	26 (42.6)	35 (40.9)
<i>Primary dimension</i>		
SIRS	9 (14.8)	3 (4.9)
Sepsis	14 (22.9)	35 (57.4)
Septic shock	12 (19.7)	12 (19.7)
<i>Primary infection site</i>		
Pulmonary	31 (50.8)	33 (54.1)
Intraabdominal	6 (9.8)	5 (8.2)
Urinary tract	21 (34.4)	19 (31.1)
Other	3 (4.9)	4 (6.6)
<i>Key performance indicators</i>		
Antibiotic administration 1 hour	20 (32.8)	44 (72.1)
Blood cultures obtained before antibiotic administration	3 (4.9)	41 (67.2)
ICU LOS, days	12.2	6.9
ICU mortality	15 (25.3)	12 (20.1)
Hospital mortality	32 (53.3)	28 (46.9)
Serum lactate measurement	7 (11.5)	47 (77.0)
Central venous catheter applied	42 (68.9)	54 (88.5)
1,000 ml fluids administered within the first hour	7 (11.5)	39(63.9)
Central venous oxygen saturation assessment	3 (4.9)	25 (40.9)
<i>Chronic comorbid conditions</i>		
Chronic heart failure	19 (31.1)	21 (34.2)
Cerebrovascular disease	17 (27.9)	16 (26.2)
Chronic lung disease	9 (14.8)	12 (19.7)
Chronic renal disease	20 (32.8)	24 (39.3)
Diabetes mellitus	15 (24.6)	17 (27.9)
Charlson comorbidity index >3	17 (27.9)	19 (14.8)

*SIRS* systemic inflammatory response syndrome, *ICU* intensive care unit, *LOS* length of stay

ance with the protocols is necessary for the successful implementation.

Nonetheless, the results of this observation are consistent with other studies, as well as reporting improved patient outcome [21] after implementation of a treatment protocol [1, 22]. Therefore, the initial management of elderly patients with sepsis has an important impact on outcome and reasonable therapeutic approaches. The implementation of the protocol was associated with

an increase in timely antibiotic administration, appropriate fluid resuscitation, and precocious estimation of tissue perfusion to detect septic shock by measuring serum lactate. In addition, the number of central venous catheters inserted, the percentage of correct diagnoses of sepsis, and general awareness were much higher in the postprotocol group. The findings of this study confirm the considerations that patients with sepsis, who are often underserved during the first vulnerable hours, will benefit from a standardized order set including diagnostic criteria, fluid resuscitation, and an antimicrobial pathway [7]. Previous investigations have already shown that a lack of time for initiating antimicrobial regimens is associated with greater mortality [23–25]. In summary, the study demonstrated that sepsis is a disease requiring timely and directed interventions [7]. A positive impact of standard protocols is already documented in pneumonia [26], liberation from mechanical ventilation, sedation administration, and antibiotic treatment of serious infections [27–29]. The use of guidelines was also assessed on fewer days until clinical stability and associated with lower costs [30]. Consistent implementation of the guidelines as well as sustainable and repeated staff training have already had positive successes [31]. Reduced mortality using standardized protocols has already been described on several occasions [31, 32] and was demonstrated here in elderly patients. For example, the early administration of adequate antibiotic therapy is important for sepsis patients' survival [33, 34]. This timeframe was markedly reduced after the sepsis protocol was introduced and initially calculated antibiotic treatment rapidly administered within the first few hours after diagnosis. Evaluation was at the time of antibiotic administration and not the period of prescription, implying that the 'administration times' corresponded to the actual application. With effective transfer of guidelines, end points can be achieved reliably in real-world sepsis resuscitation in critically ill elderly patients after conceptualization of early sepsis therapy [35]. Based on such observations, ICUs currently not using sepsis protocols should consider their implementation in daily clinical practice.

Our conclusions are limited by a few factors. The center involved an acceptable, but not large, sample size. Due to a lack of randomization, bias might exist due to unforeseen individual decisions, making it possible to provide a life-like image of daily clinical practice. However, the use of the protocols can minimize this effect [29]. In addition, diagnosis of sepsis and severe sepsis in the preprotocol group was done without complete adherence to current guidelines, so a shift in numbers does not picture a shift in severity.

The transfer of medical and research innovations into clinical daily practice is historically a complex and hard-bitten process [36, 37]. Implementing new therapeutic methods and strategies in a complex environment such as an ICU is not as simple, especially if different professional categories are involved. Therefore, the overall rate of compliance is sometimes very low [38]. Finding a step-

by-step implementation compatible to the environment is necessary. A variety of reasons lead to noncompliance with the guidelines; some are conceivable, others are not. A lack of knowledge [39] and the feeling of threatened autonomy are common [40], but a general resistance exists toward changes and the various expertise of the parties involved in trying individualized treatment [41]. In addition, system barriers such as a lack of human and material support, poor communication, and difficulty integrating the new procedures into everyday work must not be ignored [41].

## Conclusion

Standardization of evidence-based practices in the care of critically ill patients seems to be the optimal method for patient management. Local consensus directive pathways for implementation are a big step forward in improving treatment. Via this standardized care, clinicians ensure that necessary procedures and therapies are carried out in a timely manner. Clinical protocols significantly improve appropriate therapy in (severe) sepsis and compliance with the protocol, and the management bundle was associated with reduced LOS in the ICU and mortality in old patients. The impact of protocols on morbidity, mortality, and length of ICU stay was clearly shown in this observational study, and significant improvements in process-of-care and outcome were demonstrated.

The guidelines of acute medicine are quite transferrable to geriatric patients. The matrix is suitable for accompanying structural and process quality, as well as the overall constructive change in culture in the treatment of geriatric patients.

## Author contributions

H. J. Heppner: study concept and design, preparation of the manuscript.

A. Kwetkat: preparation of the manuscript.

S. Popp: literature research and design.

K. Singler: acquisition of subjects and data, statistical analysis.

A. S. Esslinger: study concept and health economic aspects.

P. Bahrmann: acquisition of subjects and data.

M. Kaiser: acquisition data.

T. Bertsch: laboratory data.

C. C. Sieber: censorious review of the manuscript.

M. Christ: censorious review of the manuscript.

## Acknowledgments

The authors thank Mrs. Dina Umarov for her expert technical assistance and all physicians, nurses, and administration secretaries involved in the successful implementation of the protocol. This study was sponsored by an unrestricted grant from the Robert-Bosch-Foundation, Germany; "ForschungskollegGeriatric".

## Conflict of interest

The authors affirm that no conflict of interest exist to be declared regarding the content of this article. Hans Jürgen Heppner and Philipp Bahrmann are research fellows of the "ForschungskollegGeriatric" Robert-Bosch-Foundation, Stuttgart, Germany.

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