Pain management in surgical intensive care patients
A retrospective observational research

Christoph Moritz Dinse, MDa–*, Michael Bucher, MDc, Anna-Maria Burgdorff, MDc, Annett Christel, MD, Lilit Flother, MDd

Abstract
Sepsis and septic shock are the most common causes of death in non-cardiac surgical intensive care units (ICU). Adequate analgesia is essential to achieve positive outcomes. There were differences in pain management between patients with and without sepsis or septic shock. The release of inflammatory mediators, especially cytokines, in sepsis or septic shock decreases the pain threshold. Septic intensive care patients probably require higher doses of opioids than do non-septic patients. A retrospective observational study was carried out in an anesthesiologic intensive care unit from January 1, 2014 to June 30, 2016. Patients were divided into 4 groups according to the following criteria: sepsis (“yes/no” and communication ability “yes/no”). After adjusting for the number of cases using the pairing method, a total of 356 patients were recruited. The endpoint of our study was defined as the “total opioid dose”. Statistical evaluations were performed using t tests and 2-factor analysis of variance. There was a significant difference in opioid doses between communicative and non-communicative ICU patients F(1, 352) = 55.102, \( P < .001 \). This effect was observed in the ICU patients with and without sepsis. The mean sufentanil dose was significantly higher in non-communicative patients than in communicative patients group (\( E(1, 352) = 51.435, P < .001 \), partial \( \eta^2 = 0.144 \)). The effect of higher opioid-dose (\( F(1, 352) = 1.941, P = .161 \)) and sufentanil (\( F(1, 352) = 1.798, P = .342 \)) requirement was not statistically significant due to sepsis. The hypothesis that sepsis decreases the pain threshold could not be proven in this study. The effect of a higher opioid requirement is not directly caused by sepsis but by communication ability. Furthermore, we were able to show through our investigations and especially through the data of the pain recording instruments that the septic and non-septic intensive care patients receive sufficient pain therapy treatment in our ICU. Regular pain evaluations should be performed on patients in the ICUs who are able to communicate and those who are not.

Abbreviations: BPS = behavioral pain scale, Ca = communication ability, ICU = intensive care unit, NRS = numerical rating scale, SIRS = systemic inflammatory response syndrome.

Keywords: intensive care patients, opioids, pain management, pain threshold, sepsis

1. Introduction
Sepsis is a complex and severe condition. It is 1 of the most common causes of death in intensive care units.[1] The worldwide incidence of sepsis is approximately 19 million cases per year.[2] Even in high-income countries, the mortality rate is approximately 20% to 30%.[3,4] In Germany, almost 68,000 people died within 1 year of sepsis or as a result of septic shock.[5] According to the most recent studies, the mortality rate of sepsis in Germany was 27%. That of septic shock was 31%. In the case of septic shock, the 90-day mortality in Germany is 39%.[6] Thus, mortality in Germany has declined slightly in the recent years.[7–9] Sepsis is the third most common cause of death in the world. Both diagnosis and therapy are difficult to perform in clinical practice. Intensive care patients are often exposed to pain due to their illness and associated interventions. Sufficient analgesia is essential to achieve positive outcomes in intensive care unit (ICU) patients with sepsis or septic shock.[10,11] The pathogenesis of sepsis is complex and is a central component of sepsis research. This indicates that cytokines influence...

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The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

This study was approved by the Ethics Committee of the Faculty of Medicine of the Martin-Luther-University Halle-Wittenberg (approval number 2015-56.) Patients aged < 18 years were excluded from this study. The ethics committee of the Medical Faculty of Martin Luther University of Halle-Wittenberg works on the basis of German law and in accordance with the ICH-GCP guidelines (Good Clinical Practice). Therefore, the patient’s consent was not required. This was because the retrospectively collected data were sufficiently anonymized as specified in the ICH-GCP guidelines. All methods were performed in accordance with ICH-GCP guidelines.

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Observational Study
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respiratory depression, constipation, nausea, vomiting, and sub-
stance dependence, are observed. [18–20] Regarding the choice of
opioids is based on the interaction between their respective
effects via coupled G-proteins. [15–17] The specific mode of action
of opioids is based on the interaction between their respective
receptor types. Thus, the desired effects, such as analgesia, seda-
tion, and anxiolysis, as well as undesirable side effects, such as
respiratory depression, constipation, nausea, vomiting, and sub-
stance dependence, are observed. [18–20] Regarding the choice of
opioids, the focus was on sufentanil, which is well established in
intensive care.
Sufentanil is 1 of the synthetically produced opioids and the
most potent opioid approved in Germany. [21] Sufentanil binds to
both the µ- and δ-receptor, but with a higher affinity to the µ-opioid receptor. [15,20,22] It is preferred in intensive care medicine
because of its pronounced analgesia and sedation component,
as well as its shorter context-sensitive half-life. [19] The classical
and safest route of medication in intensive care patients is
intravenous.
The aim of the present study was to assess pain management
in patients receiving intensive care for sepsis and non-sepsis.
This study focused on the total opioid dose in patients receiving
intensive care. To check whether septic patients have a higher
consumption of opioids than the non-septic patients, we calcu-
lated by a T test. A 2-factor analysis of variance was used to test
whether sepsis and/or communication skills influence the mean
opioid- and sufentanil dose.
Various studies have shown that sepsis influences the release
of specific cytokines at the cellular level, which, in turn, affects
tolerance. [12,23,24] In their clinical trial, Goeij et al reported
that an iatrogenic induced systemic infection influences the
patient’s pain threshold and causes it to drop. [25] Therefore,
we hypothesized that ICU patients with sepsis or septic shock
would require higher opioid doses than non-septic patients.
This may be an indirect indication of a lower pain thresh-
old. In addition, it should be investigated whether the regular
use of the Behavioral Pain Scale (BPS) and Numerical Rating
Scale (NRS) reflects sufficient pain therapy treatment in ICU
patients.

2. Material and methods
This retrospective observational study was conducted in the
anesthesiologic intensive care unit of University Hospital
Halle (Saale). A total of 1995 patients were admitted to the
intensive care unit during the study period from January 1,
2014 to June 30, 2016. A total of 638 patients from 1995
were recruited. Only patients with a minimum age of 18
years and a minimum length of stay of 3 calendar days were
included in the study. This ensured that the patients were
available for observation for exactly 24 hours on the second
day after admission. They were divided into 4 different groups
according to the criteria: Sepsis “yes/no” and communication
ability (Ca) “yes/no”.
The endpoint of our study was defined as the “total opioid
dose”. It included all parenteral opioids administered within 24
hours and was defined as a unit (mg/kg/24 hour). Individual op-
oid doses were divided by body weight and converted according to
their respective morphine equivalent values.

To show the acuity of the disease, the Simplified Acute
Physiology Score II was also determined in addition to the
American Society of Anesthesiologists classification.

2.1. Inclusions
Sepsis criteria were developed using the surviving sepsis cam-
paign of Dellinger et al (2013) [26] which was originally based
on the Sepsis 2 definition. [27] This includes the systemic inflam-
atory response syndrome (SIRS) criteria for defining sepsis. [28]
Patients diagnosed with sepsis, severe sepsis, or septic shock
were included in the study. Patients who were unable to commu-
nicate were defined by the presence of disorders of conscious-
ness (coma), neurological deficits, and mechanically controlled
ventilation. Patients who needed ventilatory support by venti-
lation modes, such as non-invasive-ventilation continuous pos-
tive airway pressure, were recruited into the group that was
able to communicate. Patients under additional sedation were
included in this study.

2.2. Exclusions
Patients who experienced a change in consciousness during
the 24-hour observation were excluded from the study. This
included delirium, intubation, or extubation. These changes
affect the status of the ability to communicate.
Patients who received ketamine or were supplemented with
regional anesthesia, were excluded from the study. Further
details are presented in Figure 1.

2.3. BPS and NRS
Pain intensity in the intensive care unit of the University
Hospital Halle (Saale) was measured using BPS (Table 1)
and NRS (Fig. 2). The BPS is used for pain assessment and
objectification in patients who are unable to communicate.
Thus, it is possible to assess the efficacy of pain therapy. This
instrument contains 3 parameters, each of which is evaluated
using a point system ranging from 1 to 4. A total value of a
minimum of 3 and a maximum of 12 points was possible. The
higher the total score, the greater is the pain experienced by
the patient. The 3 parameters assess the facial expression, the
upper extremity and additionally the adaptation to the ven-
tilator. [29–31] For better illustration, the BPS is included in the
Figure Legends as Figure 3. Statistical evaluation of the BPS
values was performed descriptively. The NRS describes pain
intensity on a scale of 0 to 10, with 0 representing no pain
and 10 representing the worst pain. A descriptive statistical
evaluation of the NRS values was performed. The results are
shown in Figure 4.
The BPS and NRS were collected purely descriptively. They
are intended to give an overview. No explorative calculation
was made.
The NRS was used for awake, communicative patients, and
BPS for non-communicative patients as is usual in everyday clin-
ical practice.
The NRS was assessed by nursing every 2 to 4 hours. BPS was
assessed every 6 hours. Table 2 presents the modal values and
descriptive results of the study before matching. (Table 2)

2.4. Statistical analysis
To counteract a possible bias due to confounders and to ensure
better comparability between the individual groups by adjust-
ing the number of cases, the 4 groups were paired using the
nearest neighbor method according to the following criteria:
patient age, body size, severity of illness (American Society
of Anesthesiologists classification), and degree of sedation
(Richmond Agitation Sedation Scale). After the successful pairing
of patient data using the statistical program “R”, the number of cases decreased to 356. The data was not normally distributed. Therefore, a bootstrapping procedure was applied in each calculation, because the samples are sufficiently large enough.

The initial statistical evaluation was carried out using a t-test to determine whether septic intensive care patients received a higher opioid dose than non-septic patients did. Differentiation based on the ability to communicate was not initially performed. In further calculation by the 2-fatorial analysis of variance, a differentiation of Ca was carried out. Statistical calculations were performed using SPSS from IBM.
2.5. Limitations

Our study was limited by missing data on the use and dose of benzodiazepines and other sedatives such as propofol. In addition, no medication was documented in the data sets for NRS or BPS elevation, which resulted in pain reduction.

3. Results

3.1. Opioid doses

The initial calculation was performed without differentiation of the Ca. The descriptive data are shown in Table 3. Calculation of the opioid dose between septic and non-septic patients was performed using a t test. The results are presented in Figure 5 and Table 4. Initially, it could be shown that septic ICU patients received a significantly higher mean total opioid dose than non-septic patients by 0.726 mg/kg/24 hour, 95% Bca [−1.425; −0.002], P = .045. This was followed by differentiation according to Ca. All the data are summarized in Table 5. There were no major differences in the biometric data after matching (Table 5). The groups to be compared, sepsis “yes/no” and Ca “yes/no”, are also almost homogeneous in terms of the number of cases. It became apparent that especially the opioids hydromorphone, piritramide and morphine were administered in a negligible dose.

The 2-factorial analysis of variance showed that the effect of higher opioid requirement was not statistically significant due to sepsis (F(1, 352) = 1.941, P = .161). The effect was based on the Ca factor, F(1, 352) = 55.102, P < .001, partial \( \eta^2 = 0.144 \). This effect was statistically significant (Table 6).

In addition, a review of individual analgesics showed that the sufentanil dose was significantly higher in the non-communicative group than in the communicative group (F(1, 352) = 51.435, P < .001, partial \( \eta^2 = 0.144 \)) as the only analgesic. Sepsis had no significant effect on the sufentanil dose (F(1, 352) = 1.798, P = .342, partial \( \eta^2 = 0.003 \)) (Table 6).

3.2. BPS and NRS survey

Table 2 shows the frequency of BPS and NRS use. This demonstrates that the frequency of the BPS survey differed between

| Behavioral pain scale. | Description | Score |
|------------------------|-------------|-------|
| Facial expression      | Relaxed     | 1     |
|                        | Partially tightened | 2     |
|                        | Fully tightened | 3     |
|                        | Grimacing    | 4     |
| Upper limbs            | No movement | 1     |
|                        | Partially bent | 2     |
|                        | Fully bent with finger flexion | 3     |
|                        | Permanently retracted | 4     |
| Compliance with ventilation | Tolerating movement | 1     |
|                        | Coughing but tolerating ventilation for most of the time | 2     |
|                        | Fighting ventilator | 3     |
|                        | Unable to control ventilation | 4     |

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3.2. BPS and NRS survey

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the septic and non-septic groups. The BPS was used in 63% of the non-septic ICU patients. In the septic patients, usable BPS were collected in 48% of all cases. In both groups, a modal value of 3 was chosen most frequently. The range of values in brackets differed minimally between the 2 groups. In non-septic patients, there was a discreetly widened spread of the BPS values (Table 2). It is noticeable that in the 2 columns of intensive care, patients who can communicate BPS values were also determined in the row of BPS frequencies. This is because the BPS was designed specifically for non-communicative patients. To obtain a better overview of the distribution of the individual BPS values, Figure 5 was created.
Figure 5 illustrates the value distribution of individual BPS data for non-communicative intensive care patients. A distinction was made between the septic and non-septic cases. Further scattering of the value distribution was recognizable in patients without sepsis. Values from 3 to 7 were obtained for BPS. The sepsis group had values with a smaller spread of 3 to a maximum of 5.

NRS was documented in 85% of septic and communication patients. In the non-septic patients, it was documented in 92% (Table 2). In both groups, the modal value of zero was chosen most frequently. They differ in the dispersion of modal values. Patients without sepsis had a wider distribution of values than patients with sepsis. Figure 4 provides an overview of the individual values.

### 4. Discussion

Severe sepsis is the most common cause of death in non-cardiac and non-cardiac surgery intensive care units. Adequate pain management can prevent the development of chronic pain and, above all, has a lasting impact on the quality of life even after discharge from the intensive care unit.

Our results showed that septic ICU patients had a higher analgesic requirement than non-septic ICU patients did. This effect is consistent with the results of Goeij et al that septic patients may demonstrate a decreased severity threshold due to an increased need for opioids. In a study by Goeij et al, it was experimentally shown by quantitative sensory testing that intravenously injected endotoxin decreased the pain threshold compared to the control group. A limitation of the study by Goeij et al is that it was published before sepsis-3 definition. This is because the definition of sepsis in 2013 included, in a simplified form, 2 criteria SIRS and a proven infection. Sepsis-3 definition describes sepsis as life-threatening organ dysfunction due to host dysregulation in response to infection. Thus, SIRS is relegated to the background and is currently considered a separate entity. Goeij et al referred to the clinical picture of SIRS, that is not explicitly related to sepsis. However, this clearly shows that the release of inflammatory mediators, especially cytokines decrease the pain threshold.

Huang et al showed that in sepsis, there is also a pathophysiological increase in the release of inflammatory mediators and a cytokine storm at the cellular level. These inflammatory mediators are partly identical to those reported by Goeij et al and the peripheral sensitization of nerve endings. This leads to a consecutive decrease in the stimulus threshold of the nociceptor, and thus, of the pain threshold.

Sufentanil is the most commonly used opioid in non-communicative septic and non-septic ICU patients. We showed that the mean sufentanil dose was significantly higher in non-communicative ICU patients than in communicative ICU patients. This effect could be because sufentanil is used in intensive care both as an analgesic drug and as a sedative drug. The property of reduced context-sensitive half-life and the higher therapeutic breadth make sufentanil a preferred drug in the long-term ventilated and thus in non-communicative ICU patients. During the intensive care stay the opioids hydromorphone, piritramide and morphine were negligible in terms of frequency of use and dose. These data should be critically evaluated because zero values were included in the calculation of the opioid dose. Thus, the mean dose in each group was significantly reduced. Owing to the low average dose of the aforementioned opioids, further statistical evaluation was
not possible. Therefore, we could not prove the hypothesis of decreased pain threshold due to sepsis.

Further exploratory statistical evaluation according to the communication factor showed that the effect of the increased opioid dose was not due to sepsis, but rather to the communication factor. Sepsis had no direct effect on the total opioid dose when the communication factors were considered. This may be because sepsis is complex, severe, and not fully understood. Current studies are looking at a comprehensive pathophysiology, especially at the cellular level, to develop new therapeutic targets. In recent years, new biomarkers have been discovered that will enable new therapeutic approaches in the future.

To ensure sufficient pain management in patients receiving intensive care for sepsis and non-sepsis, the establishment of pain assessment instruments is essential. Our work also showed the successful implementation of BPS and NRS in non-communicative and communicative patients, respectively. The frequency of use was not 100% in all patients. Every patient received a value, but zero values were given, which were excluded from the descriptive analysis. When examining the individual distribution of values, an overall narrower distribution was apparent in patients with sepsis than in those non-septic ICU patients. This does not mean that septic cases have a lower pain intensity than non-septic cases. The BPS and NRS were only included for illustrative purposes and were statistically analyzed in a purely descriptive manner. In addition, the BPS survey must be carried out by a caregiver and not be actively determined by the patient. This could have led to subjective differences in

### Table 4
Results opioid dose in septic and non-septic patients after matching (t-test)*.

|                | T     | df | P-Value | Mean difference | Standard error of difference | Upper value | Lower value |
|----------------|-------|----|---------|-----------------|------------------------------|-------------|-------------|
| Opioids [mg/kg/24 h] | Variances are equal | −1973 | 322 | .045 | −0.72611 | 0.36806 | −1.45022 | −0.00200 |
|                 | Variances are not equal | −1973 | 207,432 | .045 | −0.72611 | 0.36806 | −1.45045 | −0.00177 |

* Bootstrapped Welch-Test.

### Table 5
Opioid dose requirement after matching and separation according to communication ability.

| Communication ability | No Sepsis | Yes Sepsis |
|-----------------------|-----------|------------|
| n (%)                 | Yes 117 (33%) | Yes 61 (17%) |
| Age [years], M (SD)   | 65 (± 14.8)  | 68 (± 11.9)  |
| Gender, female, n (%) | 46 (39%)    | 27 (44%)    |
| Weight [kg], M (SD)   | 83.7 (± 24.1) | 77.7 (± 16.7) |
| Height [cm], M (SD)   | 172 (± 9.1)  | 174 (± 8.5)  |
| BMI [kg/m²], M (SD)   | 28.1 (± 8.2)  | 28.8 (± 7.0)  |
| SAPS II, M, (SD)      | 50.3 (± 14.7)  | 42.7 (± 13.6)  |
| ASA [1 to 6], M (SD)  | 3.43 (± 0.56)  | 3.30 (± 0.59)  |
| ASA [1 to 6], MV (min., max.) | 3 (2 to 5) | 3 (1 to 4) |
| RASS [−5 to 4], M (SD) | −3 (± 0.7) | 0 (± 0.8) |
| RASS [−5 to 4], MV (min., max.) | −3 (−5 to 1) | 0 (−3 to 1) |
| Opioids [mg/kg/24 h], n (%) | 117 (100%) | 61 (100%) |
| M (SD)                | 3.04 (± 0.38)  | 2.22 (± 0.18)  |
| Sufentanil [µg/kg/24 h], M (SD) | <0.01* | <0.01* |
| Hydromorphone [mg/kg/24 h], M (SD) | <0.01* | <0.01* |
| Piritramide [mg/kg/24 h], M (SD) | <0.01* | <0.01* |
| Morphine [mg/kg/24 h], M (SD) | <0.01* | <0.01* |

© Displayed values are < 0.01 and are included for completeness.

ASA = ASA-classification (American Society of Anesthesiologists), BMI = body mass index, M = mean, max. = maximum, min. minimum, MV = modal value, n = number of cases, RASS = Richmond agitation and sedation scale, SAPS = simplified acute physiology score, SD = standard deviation.

### Table 6
Results of opioid dose and sufentanil dose in septic and non-septic intensive care patients by 2-factorial analysis of variance.

| Source                        | Sum of square | df | Mean square | Error | P-Value | Partial $\eta^2$ |
|-------------------------------|---------------|----|-------------|-------|---------|-----------------|
| Communication                 | 545.698       | 1  | 545.698     | 55.102| <.001   | 0.144           |
| Sepsis                        | 19.224        | 1  | 19.224      | 1941  | .161    | 0.006           |
| Communication × Sepsis        | 4087          | 1  | 4087        | 0.415 | .521    | 0.002           |
| Error                         | 3486.010      | 352| 9903        |       |         |                 |
| Total                         | 5341.099      | 356|             |       |         |                 |
| Dependent Sulfantin variable  | 524.909       | 1  | 524.909     | 51.435| <.001   | 0.114           |
| Sepsis                        | 18.352        | 1  | 18.352      | 1798  | .342    | 0.003           |
| Communication × Sepsis        | 7320          | 1  | 7320        | 0.717 | .281    | 0.003           |
| Error                         | 3592.264      | 352| 10.205      |       |         |                 |
| Total                         | 5242.895      | 356|             |       |         |                 |

R$^2$-Square = .144 (corrected R$^2$-Quadrat = .137).

### Table 7
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| Total                         | 5242.895      | 356|             |       |         |                 |

* Determined from robust standard error using HC4-method.
the collection of BPS values. Furthermore, clinical routines are subject to fluctuations among daily staff members. This can also lead to distortions in values. Overall, the modal values of the BPS reflect a very good pain therapy treatment for all intensive care patients who are unable to communicate. NRS also provides an overview of sufficient pain management in patients who can communicate.

5. Conclusion
Our study showed that there were differences in pain management between septic and non-septic intensive care patients in daily clinical practice. The initial calculation showed a higher opioid consumption in the septic group than in the non-septic group. There was a significant difference in opioid doses between the communicative and non-communicative ICU patients. The mean sufentanil dose was significantly higher in the non-communicative patients than in the communicative patients. The current body of evidence supports the hypothesis that sepsis affects the pain threshold. However, we were unable to prove this hypothesis in this retrospective study. This could be because our study was based on a retrospective design and only the dose of opioids was evaluated exploratively. Further prospective studies with specific analgesia in patients receiving septic intensive care should be conducted. In this study, we demonstrated that non-cardiac surgical intensive care patients at the University Hospital Halle (Saale) were treated sufficiently overall in terms of pain therapy. Pain-recording instruments have been successfully implemented.

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Author contributions
CMD helped manage patient data, helped with statistical evaluation, conducted background research, and wrote the manuscript. MB helped manage the patient data and write the manuscript. AMB helped write the manuscript. AC helped in writing the manuscript. LF helped write the manuscript. All the authors have read and approved the final manuscript.
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Writing – review & editing: Michael Bucher, Anna-Maria Burgdorff, Annett Christel, Lilit Flöther.

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