

# Sepsis in the intensive care unit

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## Impact paragraph

### Clinical and societal impact

Sepsis is a life-threatening condition marked by severe organ failure. It is regarded as a worldwide health threat affecting individuals of any age and sex. In fact, it is the costliest healthcare condition, as the average hospital-wide cost of sepsis is estimated at more than US\$ 32 000 per patient.<sup>1</sup> Sepsis is a leading cause of death in Intensive Care Units (ICU's).<sup>2</sup> In 2017, 49 million individuals were affected, and sepsis causes 11 million deaths worldwide.<sup>3</sup> Overall mortality is almost 27%. However, for patients needing ICU treatment, the in-hospital mortality reaches 42%.<sup>3</sup> Furthermore, the epidemiology of sepsis is not well understood and results from existing epidemiologic studies can often not be compared due to heterogeneity of methods and patients.<sup>4</sup> This thesis contributes to gaining more insight into sepsis epidemiology and heterogeneity regarding definition, diagnosis, causes of early death, and development of multi-organ failure and treatment.

**Chapter 3** shows that the Sepsis-3 definition for septic shock defines a more severely ill group of patients with higher mortality than the Sepsis-2 definition. Furthermore, mortality rises significantly when serum lactate levels rise >6 mmol/L. These findings are in line with the purpose of the Sepsis-3 criteria: identifying patients at higher risk of dying than patients with sepsis alone.<sup>5</sup> Consequently, regarding clinical impact, these critically ill patients may be monitored more meticulously and receive more aggressive treatment. As for societal impact, a better discrimination of patients at high risk of dying from septic shock versus patients with an uncomplicated infection may be more cost-effective.<sup>6</sup> For sepsis, however, the added value of Sepsis-3 definition is limited because almost all ICU patients seem to meet these criteria.<sup>7</sup> For the diagnosis of sepsis, application of a SOFA score change of more than 2 points did not result in a more specific criterion, as this resulted in a higher sepsis frequency than the Systemic Inflammatory Response Syndrome criteria.<sup>8</sup> However, the (q)SOFA was never designed as a screening tool for sepsis, as is acknowledged by the authors in the Sepsis-3 definition paper.<sup>9</sup> Indeed, in the latest Surviving Sepsis Guidelines, revised in 2021, usage of the qSOFA as a single screening tool for sepsis and septic shock is not recommended.<sup>10</sup> Furthermore, as a clinician, we should treat the patient and their symptoms (i.e. oliguria, hypoxemia, etc.) and not wait for a score to indicate that the patient is deteriorating.

In **Chapter 4**, we show that early death (<48 hours) in sepsis is common (one in three patients), and flaws in recognition and possible futile treatment are scored in one-third of cases each. Thus, there might be a role for further implementation and optimization of early warning systems. This might have its impact on recognizing patients requiring intensive care monitoring and treatment in an earlier stage and prevent early death. Indeed, early warning systems seem to perform well for prediction of cardiac arrest

and death within 48 hours, but impact on outcome and resource utilization remain to be determined.<sup>11</sup> The careful selection and multi-disciplinary decision-making regarding which patients benefit from an expensive and invasive ICU treatment are relevant. Indeed, this thesis showed a large inter-observer variability between intensivists scoring possible flaws in the recognition and management of early deceased patients. Thus, there seems to be a large variability in clinical judgement regarding these patients, underlining the importance of shared decision-making.

**Chapter 5** underlines the value of an autopsy in early deceased sepsis patients, as discrepancies between clinical diagnoses and postmortem findings are often identified. In addition, these findings encourage clinicians to obtain an autopsy more often, not only from a diagnostic point of view, but also from an educational perspective. Furthermore, the autopsy rate has an impact on society, regarding public health, statistics of diseases, and forensic issues.<sup>12</sup> Moreover, autopsy plays an important role in counseling the families of deceased patients, especially in the intensive care unit. Indeed, it can establish the exact cause of death and help to understand the reason why their relative died. Finally, autopsy can help understand the pathology and the pathogenesis of new diseases, like COVID-19, and this may influence patient management.<sup>13</sup>

In **Chapter 6**, we propose a new possible mechanism contributing to the development of multi-organ failure in inflammation and hypoxia: the detoxifying glyoxalase system that clears dicarbonyl stress. We investigated this mechanism during a highly standardized experiment in a homogeneous population of healthy young males. Although our hypothesis regarding downregulation of glyoxalase-1 (GLO-1) by inflammation was confirmed, the hypothesized increase in methylglyoxal (MGO) was not established. Although the mechanism has potential for intervention by upregulating GLO-1<sup>14</sup> or scavenging MGO<sup>15</sup>, the presumed impact<sup>14</sup> on septic patients remains to be determined. In general, however, investigating possible new mechanisms with a plausible pathophysiological background relating sepsis, may contribute to better patient care and improved outcomes.

**Chapter 7** handles with inappropriateness of antibiotic therapy in septic shock patients with an abdominal, urogenital, or unknown focus. Adequacy of initial empirical antimicrobial treatment is crucial in terms of outcome for ICU patients with sepsis.<sup>16</sup> We found that 14% of patients received inappropriate therapy and 11% of patients had a fungal infection. This might impact patient management as the clinician should still take in account the possibility of inadequate therapy, even in this severely ill patient category with broad antibiotic coverage. Furthermore, the study results indicate a better antibiotic coverage but no earlier shock reversal by adding gentamicin, even in this septic shock population at high risk for extended-spectrum beta-lactamase Gram-negative bacteria and fungal infection. However, in case of unfavourable disease course under antibiotic monotherapy, lowering the threshold for administering

adjunctive aminoglycoside and antifungal therapy should be considered in this high risk patient group.

**Chapter 8** and **Chapter 9** investigate the association of coronary artery calcification (CAC) and serial cardiac biomarkers and electrocardiography with more severe organ failure and survival. Patient selection, clinical decision making, and prognostication is important in mechanically ventilated patients with COVID-19 infection, as a pandemic can stretch intensive care resources. Cardiovascular disease (CVD) has an important impact on fatal outcomes in COVID-19 patients across all ages.<sup>17</sup> Identifying COVID-19 patients at high risk of worse outcome can tailor patient management in these patients and also increase patient awareness regarding risk factors for COVID-19.<sup>18</sup> In patients with known CAC or increased hs-cTnT or NT-pro-BNP, a more thorough diagnostic work-up might be justified. Indeed, transthoracic echocardiography is now performed in a minority of COVID-19 patients and patients with elevated cardiac biomarkers more often had reduced left ventricular function.<sup>19</sup> Patients with CAC or elevated biomarkers might represent a subgroup benefiting from echocardiography early in the disease course to tailor clinical management.

## Scientific impact

Our sepsis database (until 2020) and the *MaastrICht* COVID-19 cohort (up to this day) have included more patients over the years, and the latter database has now included over 500 mechanically ventilated COVID-19 patients with serial measurements during the whole disease course. This provides the opportunity to investigate further additional hypotheses in a more significant number of patients in the future. Thus, the present thesis has multiple implications regarding scientific impact. The sepsis database can be enriched by adding additional measures like ECG, echocardiography, and chest CT scans analyzed in a uniform matter and can be updated and function as an ongoing prospective cohort.

**Chapter 3** points out that the Sepsis-3 definition for septic shock indeed identifies a more severely ill patient population with higher mortality than the Sepsis-2 definition, according to the goal of the guidelines.<sup>9</sup> For future research on septic shock, a clear and uniform definition of septic shock facilitates more standardized reporting on characteristics and outcomes and greater consistency of epidemiologic studies and clinical trials.

Few studies have addressed the temporal relationship between death in sepsis patients. Unfortunately, this is also true for these patients' exact causes of death because autopsy numbers are declining in the Netherlands.<sup>20</sup>

**Chapter 4** confirms that early death is common in sepsis patients and flaws in early recognition and possible futility of treatment are often encountered. This should be considered in future research; for example, research on the effect of early warning systems report inconsistent results regarding health outcomes and resource utilization,

owing to methodological limitations.<sup>11</sup> Furthermore, patients admitted in moribund condition or with pending cardiac arrest might not benefit from an intervention anyway, thereby obscuring potential effectiveness of an intervention for other patients. The latter is important in sepsis research concerning highly heterogenic patients in different stages of the disease process.

The value of reporting autopsy results is confirmed in **Chapter 5** and the fact that clinical causes of death in these patients are confirmed by autopsy findings improves the reliability of these scientific findings. In addition, autopsies can provide material for advancing medical research, in order to study the pathogenesis of different disease processes and their influence on different organ systems.<sup>21</sup> Finally, implementing contemporary approaches to autopsy (post-mortem CT scans and molecular pathology) can lead to improved quality of health care and research.

The study results in **Chapter 6** investigating the effect of hypoxia and inflammation on glyoxalase-1 (GLO-1) as a possible mechanism leading to multi-organ failure urge for further investigation. On the one hand, this study confirmed the hypothesis that inflammation downregulates the protective enzyme glyoxalase-1. However, on the other hand, no significant difference between groups in methylglyoxal (MGO) and methyl-glyoxal derived hydroimidazolone-1 (MG-H1) was observed. The effects of hypoxia and inflammation on the dicarbonyl pathway are performed in a highly homogeneous population of healthy males and in a highly standardized way. The question if the results in healthy males can be extrapolated to sepsis patients remains to be answered. This would be of interest because the dicarbonyl pathway is a mechanism with potential for intervention, either by reducing protein modifications by a combination of trans-resveratrol and hesperitin or by GLO-1 induction by isothiocyanates.<sup>14</sup>

**Chapter 7** handled the appropriateness of antibiotic therapy in septic shock patients, reporting inappropriate therapy in 14% of septic shock patients. It also investigates the effect of adjunctive aminoglycoside treatment and compares monotherapy and combination therapy groups. Although inappropriate treatment is more common in the monotherapy group versus the combination group (17% vs. 10%), there was no association between aminoglycoside administration and the occurrence of shock reversal in these patients. This study extends the findings of two other studies<sup>22,23</sup> to an underinvestigated septic shock population at high risk for extended-spectrum beta-lactamase Gram-negative bacteria and fungal infection.

**Chapter 8** and **Chapter 9** investigate the association between CAC and organ failure and the value of serial assessment of cardiac biomarker and electrocardiography in mechanically ventilated COVID-19 patients. A higher degree of CAC on chest CT scans is linked to more severe organ failure development over time. Furthermore, higher hs-cTnT at admission and an increase in NT-proBNP over time were associated with lower survival. These findings are scientifically relevant and might be used for future prognostication in patients. The latter seems feasible to investigate in our *MaastricCcht*

COVID-19 cohort, as this cohort now included over 500 mechanically ventilated COVID-19 patients. Moreover, because cardiac events like myocardial infarction, also occur more often during or after non-COVID related infections<sup>24</sup>, the value of CAC detection and serial cardiac biomarkers and ECGs might also apply to these patient populations. This is a possible future research question to investigate in a larger prospective cohort of sepsis patients.

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