Early detection of patient deterioration in patients with infection or sepsis

Quinten, Vincent

Chapter 1

Introduction and aims of the thesis

Sepsis

Sepsis is a syndrome encompassing a multifaceted aberrant or dysregulated host response to an infecting pathogen. Sepsis can be identified by a constellation of clinical signs and symptoms in patients with suspected infection[1]. There is no gold standard diagnostic test for sepsis or infection[1-3]. Sepsis was originally defined as an suspected infection in the presence of at least two systemic inflammatory response syndrome (SIRS) criteria: (1) a body temperature >38°C or <36°C; (2) a heart rate >90 beats per minute; (3) tachypnea, manifested by a respiratory rate >20 breaths per minute, or hyperventilation indicated by a PaC02 of <4.3 kPa (<32 mm Hg); (4) white blood cell count >12·10^9/ L, < 4·10^9/ L, or >10% immature neutrophils (*'bands'*)[4]. The illness severity can be further classified into three categories: sepsis, severe sepsis and septic shock. Severe sepsis is sepsis associated with organ dysfunction, hypoperfusion or hypo-tension. Septic shock is defined as sepsis-induced hypo-tension persisting despite adequate fluid resuscitation[4]. These original criteria and categories are now known as the Sepsis-2 criteria. More recent, the Sepsis-3 criteria have redefined sepsis as: a life-threatening organ dysfunction caused by a dysregulated host response to infection[1]. The Sepsis-3 criteria redefined the Sepsis-2 severity categories as follows: sepsis became infection and severe sepsis became sepsis. It should be noted that patients meeting the Sepsis-3 criteria have signs of organ failure by definition. In the remainder of this thesis, we will use the Sepsis-2 criteria. We chose to use the Sepsis-2 criteria, since the designs of the studies described in this thesis originate from before the introduction of the Sepsis-3 criteria, and furthermore, we are especially interested in patients that progress from infection into (multiple) organ failure.

Patient deterioration in sepsis

Sepsis is responsible for 2% of hospitalizations and 17% of in-hospital deaths[5-8]. Conservative estimates indicate that sepsis is the leading cause of death and critical illness worldwide, with around 1400 sepsis-related deaths every day. The incidence of sepsis increases annually, likely reflecting aging populations with more comorbidities, greater recognition and (sometimes) reimbursement-favorable coding[1,5,9,10]. Sepsis-related mortality is still around 20%, although prognosis is better than a decade ago. Survivors have a persistent decrement in their quality of life, sustain some degree of neuromuscular, functional, and/or neuropsychologic morbidity and have an increased mortality risk for more than a year after the sepsis episode[11]. Up to half of all patients with sepsis are admitted through the emergency department (ED)[6]. The patient population is very heterogeneous, since patients with sepsis present to the ED at various stages of the disease and sepsis often is a complication of life-limiting comorbidities[7,8].

In 2002, the Surviving Sepsis Campaign (SSC) launched guidelines for the treatment of sepsis to reduce sepsis-related mortality worldwide[12]. Recent studies have shown that early and aggressive resuscitation is more important than the specific kind of treatment provided[13-16]. However, one in five patients presenting to the ED with infection or sepsis, deteriorate within 48 hours after hospital admission, despite treatment[7,17]. Deterioration can be defined as a move from one clinical state to a worse clinical state which increases the patient's individual risk of morbidity, including organ dysfunction, protracted hospital stay, disability or death[18]. How to monitor patients for early signs of deterioration and response to treatment remains unclear[12,19]. When not properly responded to, deterioration can result in mortality and/or morbidity, including (multiple) organ failure or progression into septic shock[18].

Clinical scoring systems and biomarkers for sepsis

Multiple attempts have been made to effectively stratify patients with sepsis, by using sepsis severity categories, clinical judgment, clinical scoring systems, and biomarkers[4,20-23]. Stratification based on sepsis severity is not as accurate as clinical judgment or an adequate scoring system[24]. There are numerous scoring systems available; most predict sepsis-related mortality and/or sepsis severity. These include the Predisposition, Infection, Response and Organ dysfunction (PIRO) score[25], the Mortality in Emergency Department Sepsis (MEDS) score[26], the Sequential Organ Failure Assessment (SOFA) score[27] and the recent quick SOFA (qSOFA) score introduced with the Sepsis-3 definition[1]. However, not all scoring systems are specifically designed for the ED and they may not be the most practical bedside tool as they may require information that is not readily available on ED admission, such as biomarker levels, patient history and living situation. There are also numerous sepsis-related biomarkers, however, almost all available biomarkers lack the required sensitivity and specificity to be of real clinical value[19,22,23].

Vital signs in sepsis

A thorough re-evaluation of available physiological variables, including routine vital signs, is suggested by the latest SSC guidelines as they may describe the patient's clinical state and response to treatment[12]. Sepsis is traditionally diagnosed and monitored based on infrequently measured discrete absolute values of vital signs using thresholds derived from epidemiological research[28]. However, thresholds for the *'average'* patient may not apply or be beneficial for individual patients because of the heterogeneous nature of the patient population and unpredictable individual's response to treatment[28]. In the ED or intensive care unit (ICU), vital signs are mostly measured continuously, however, most data is discarded by using only discrete values at specific points in time[28,29]. Surprising little is known about the relation between vital signs and clinical outcomes, especially in the ED setting and despite the relative ease of measurement[30-33]. In addition, how to monitor and identify deteriorating patients in the ED is also largely unknown[34]. Patient deterioration was preceded by changes in vital signs, often hours before it was clinically noticed, in 80% of cases as shown by some small studies mainly in the ICU and on the nursing wards[18,35-42]. Additional information about response to treatment of (early) signs of patient deterioration may be provided by monitoring changes in vital signs over time, this process is called variability analysis[29].

Variability analysis

The host response to infection is a complex non-linear system[28,29]. Complex non-linear systems are composed of a virtually infinite number of interconnected variables. Although different variables and their interactions are seemingly chaotic and constantly changing, the system as a whole will naturally settle into a stable state configuration. Complex systems have emergent properties that none of the individual parts have and that disappear on decomposition of the system into smaller parts. Small perturbations of individual variables in the system may be magnified or dampened depending on the state of the system, which may cause unpredictably large changes (*'Butterfly effect'*)[43,44]. These properties explain why chaotic dynamics may lead to unexpected rapid deterioration or clinical improvement without identifiable cause[28]. Using

continuous variability analysis over time the state of the system can be tracked over time. Applied to patients continuous variability analysis has the potential to determine whether an individual patient is progressing towards a state of health or towards deterioration[29]. Many types of signals and vital signs can be analyzed using variability analysis, however, heart rate variability (HRV) is the most studied[29,43].

Heart rate variability

HRV analysis examines the beat-to-beat variation in heart rate. HRV can be measured readily, easily and non-invasively using equipment available in every ED[43]. Reduced or decreasing HRV is associated with the diagnosis of sepsis, reflects greater severity of illness and predicts subsequent deterioration, impending shock and mortality in ICU patients[28,36,37]. Although a couple of studies have been performed on HRV in adults with sepsis, HRV is most studied and applied in neonates to predict an increased likelihood of deterioration in the subsequent 24 hours[28,45]. Patients presenting to the ED with infection or sepsis are generally less severely ill than ICU patients, therefore the question remains whether reduced HRV can be used as an early warning signal for impending patient deterioration in the ED population.

Modeling

One of the main challenges for the physician in the ED remains to determine the risk of deterioration for the individual patient[28]. A model could help the physician with the clinical decision making. Traditional models should be easy to use, and therefore have only a few variables that do not require complex calculations[46,47]. However, because of the complex non-linear behavior of the host response to infection (described above), it is unlikely that this can be captured in a simple model with only a few variables. Therefore, more complex analysis techniques are required, which can perform non-linear analyses and deal with missing data. These models may also reveal surprising relationships that challenge conventional knowledge[46,48]. For example, variability patterns are hidden in the data generally produced by monitoring vital signs, by applying more advanced techniques these non-linear hidden patterns could be revealed. These patterns may provide valuable information on the host response to infection and for the early detection of patient deterioration. Early detection of deterioration could help to recognize patients at risk and potentially provide an opportunity to anticipate on or even prevent deterioration. This would potentially reduce mortality, morbidity and increase the quality of life.

General aims and outline of this thesis

The general aim of this thesis was to gain insight into the different factors involved with deterioration of patients with infection or sepsis, in order to create a model for early detection of patient deterioration.

PART I: PREDICTION OF SEPSIS OUTCOMES OF SEPSIS IN THE EMERGENCY DEPARTMENT

CHAPTER 2 focuses on clinical scoring systems to predict in-hospital mortality and ICU admission. The predictive value of the clinical impression of the nurse and attending physician are compared with the PIRO and qSOFA scores for these outcomes.

In **CHAPTER 3**, relatively new biomarkers for sepsis and multiple organ failure are investigated. The biomarkers tissue inhibitor of metalloproteinase-2 (TIMP-2), angiopoietin-2 (Ang-2), neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1) and insulin-like growth factor-binding protein-7 (IGFBP-7) were investigated together with routine biomarkers. The aim was to determine whether these new biomarkers help to identify severity of infection, need for ICU admission and organ failure.

PART II: TRENDS AND VARIABILITY IN VITAL SIGNS AS PREDICTORS OF DETERIORATION IN SEPSIS

CHAPTER 4 describes why it is time for sepsis research to move its focus from mortality to the occurrence and prevention of organ failure in sepsis.

CHAPTER 5 describes a pilot study aimed at detecting trends in vital signs (heart rate, blood pressure, respiratory rate, temperature and oxygen saturation) and routine biomarker levels during resuscitation of patients with sepsis in the ED. In this study, vital sign measurements and the routine blood draw were repeated after 3 hours in the ED.

CHAPTER 6 focuses on the additional value of repeated vital signs (heart rate, blood pressure, respiratory rate, temperature) in 30-minute intervals during the patient's stay in the ED. The aim of this study was to determine whether there is a relation between trends in vital signs and patient deterioration (mortality, ICU admission or development of organ failure).

CHAPTER 7 describes the protocol of the SepsiVit study. The aim of this study is to determine whether continuous HRV measurement in patients presenting to the ED with suspected infection or sepsis during their first 48 hours of hospitalization can provide an early warning signal for patient deterioration within 72 hours from admission. The preliminary results of the SepsiVit study are described in **CHAPTER 8**.

CHAPTER 9 summarizes the main findings of the studies presented in this thesis and puts them into a broader context, together with the vision and directions for future research.

Finally, **CHAPTER 10** provides a summary of this thesis in Dutch.

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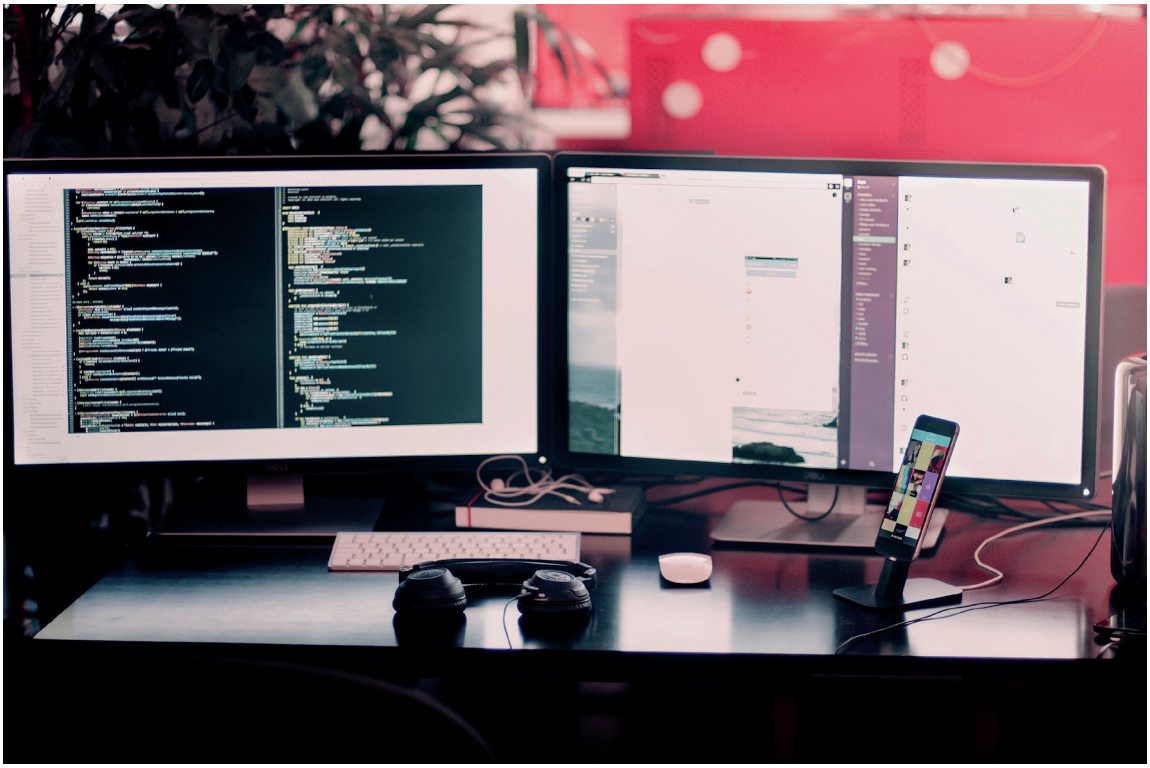

PART I

PREDICTING OUTCOMES OF PATIENTS WITH INFECTION OR SEPSIS IN THE EMERGENCY DEPARTMENT