Infection and sepsis in the Dutch acute care chain

INFECTION AND SEPSIS IN THE DUTCH ACUTE CARE CHAIN:

OPPORTUNITIES FOR OPTIMISATION OF CARE

GIDEON LATTEN

Infection and sepsis in the Dutch acute care chain:

opportunities for optimisation of care.

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G.H.P. Latten

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Infection and sepsis in the Dutch acute care chain: opportunities for optimisation of care.

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Promotores

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‘We cannot solve our problems with the same thinking we used when we created them’

Albert Einstein

Voor Evi, Siem en Jip

Terms and definitions

Both in daily practice, as well as in the literature, a plethora of terms are used to describe patients with a suspected or proven infection. Professionals in the acute care chain often mention a probability diagnosis (e.g. pneumonia) and sometimes describe the disease severity (e.g. severe or serious infection, severe sepsis, shock). Although understandable, this harms the clarity of research manuscripts. Therefore, effort was made to provide clear definitions throughout this thesis. It is nevertheless unavoidable that different terms are sometimes used. The most frequently used terms within the acute care chain are summarised below.

Vital signs (or parameters): clinical measurements that indicate the state of a patient's essential body functions. Values vary between individuals and can be influenced by, among others, disease processes and medication. Examples of measurable vital signs include blood pressure, heart rate, respiratory rate, level of consciousness, temperature and peripheral oxygen saturation.

Infection: a pathologic process caused by the invasion of normally sterile tissue or fluid or body cavity by pathogenic or potentially pathogenic microorganisms. In the acute care chain, the (probability) diagnosis of an infection is usually made based on a patient's history and physical evaluation.

Common (or uncomplicated) infection: an infection that is either self-limiting or resolves with oral antibiotics.

Severe (or serious) infection: in general, this term is used to describe an infection that requires evaluation and/or treatment in the hospital.

Sepsis: a life-threatening organ dysfunction caused by a dysregulated host response to infection.

Septic shock: a subset of sepsis in which underlying circulatory and cellular metabolism abnormalities are profound enough to substantially increase mortality.

Clinical rule: a model in which the values of vital signs are entered, after which they add up to a sum score, providing information on diagnosis and/or prognosis. For this, most clinical rules use cut-off points. Some clinical rules are not useable on the bedside, as they incorporate one or more laboratory results.

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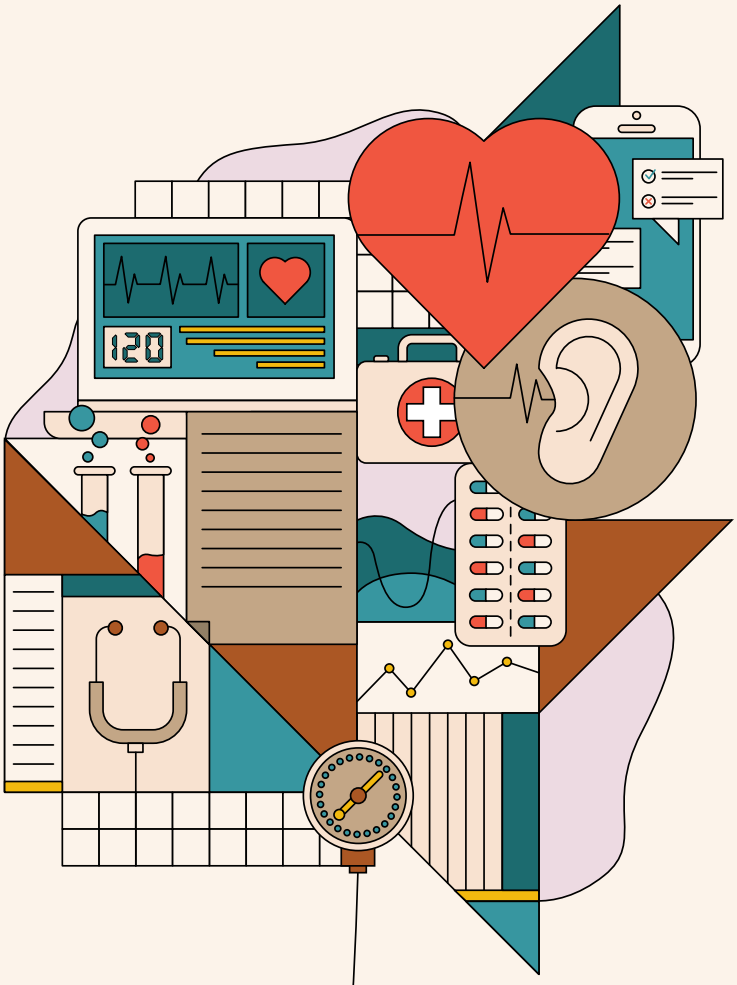
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CHAPTER 1

GENERAL INTRODUCTION

Introduction

Infections are among the most common reasons for people to visit a healthcare provider. The majority of infections are self-limiting or resolve with oral antibiotics. Sometimes, however, patients need to visit a hospital for diagnostics and/or treatment. Examples include surgery in case of an acute appendicitis or intravenous antibiotics when an infection does not resolve with oral treatment. A small proportion of patients become so seriously ill that they require an even higher level of care. These patients have sepsis, a syndrome that is considered to be the most important complication of an infection.[1]

Sepsis has a high mortality rate, comparable with that of myocardial infarction and stroke.[2,3] The incidence of sepsis and its mortality depend on the definition used, but estimates are that approximately 48.9 million incident cases of sepsis occurred worldwide in 2017, with 11 million (22.5%) sepsis-related deaths.[4,5] People who survive sepsis often have a persistent decrease in quality of life, with physical impairments and/or emotional complaints.[6,7]

Timely treatment of patients with sepsis improves prognosis. Treatment protocols of sepsis include administration of oxygen, intravenous fluids and broad spectrum antibiotics.[1,8-10] Databases such as PubMed are filled with articles on optimal treatment of sepsis, but for many professionals, the greatest challenge of sepsis lies in its diagnosis. The 16th century quote from Nicholas Machiavelli still seems strikingly accurate.[11]

"…as the physicians say it happens in hectic fever, that in the beginning of the malady is easy to cure but difficult to detect, but in the course of time, not having been either detected or treated in the beginning, it becomes easy to detect but difficult to cure"

The syndrome of sepsis

There is no definite diagnostic test that can prove or rule out sepsis. Contrary to other acute illnesses, sepsis cannot be 'diagnosed'; it can only be suspected and be made more or less probable. Nonetheless, in order to achieve uniformity on the question 'does this patient have sepsis?', standardised definitions have been in use since the early nineties of last century (Table 1). These definitions consist of a combination of vital signs and laboratory values.

Table 1 – Sepsis-related definitions throughout the years

Year	1991	2001	2016
Consensus	ACCP/SCCM consensus conference	SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference	The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)
Infection	Microbial phenomenon characterised by an inflammatory response to the presence of microorganisms or the invasion of normally sterile host tissue by those organisms.	Pathologic process caused by the invasion of normally sterile tissue or fluid or body cavity by pathogenic or potentially pathogenic microorganisms. In essence unchanged definition.	No specific definition
Sepsis	Infection plus a systemic inflammatory response (SIRS ≥2).	Infection plus a systemic inflammatory response.	A life-threatening organ dysfunction caused by a dysregulated host response to infection.
Severe sepsis	Sepsis + organ dysfunction, hypoperfusion, or hypotension.	Unchanged definition	Term no longer advised
Septic shock	Sepsis-induced with hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities.	Acute circulatory failure characterised by persistent arterial hypotension (Psyst <90, MAP <60, or reduction in Psyst of >40mmHg from baseline), despite adequate volume resuscitation.	Subset of sepsis in which circulatory and cellular metabolism substantially increase mortality.
Organ dysfunction	Altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention.	Based on either MOD Score or SOFA score	An acute change in total SOFA score ≥2 points consequent to the infection.
Advised clinical rule	SIRS criteria	SIRS criteria, list of possible signs of sepsis was expanded	Bedside: qSOFA score Organ dysfunction: SOFA score.

Abbreviations: ACCP – American College of Chest Physicians, SCCM – Society of Critical Care Medicine, ESICM – European Society of intensive Care Medicine, ATS – American Thoracic Society, SIS – Surgical Infection Society, Psyst – systolic blood pressure, MAP – Mean Arterial Pressure, MOD – Multiple Organ Dysfunction, SIRS - Systemic inflammatory response syndrome, SOFA - Sequential Organ Failure Assessment, qSOFA – quick Sequential Organ Failure Assessment

Since 1990, sepsis was defined as the presence of both (a suspected or proven) infection and two or more systemic inflammatory response syndrome (SIRS) criteria. These criteria included (1) temperature >38.0°C or <36.0°C, (2) heart rate >90/min, (3) respiratory rate >20/min or $PaCO_2$ <32 mmHg (4.3 kPa) and (4) white blood cell count >12,000/mm^3 or <4,000/mm^3 or >10% immature bands.[12]

In 2001, the definition of sepsis was updated to 'a clinical syndrome combined with organ injury'. Despite evidence that the SIRS criteria offered suboptimal accuracy, the diagnostic criteria for sepsis remained unchanged.[13]

The biggest change in definition happened in 2016 when the SEPSIS-3 working group published the latest update of the definitions of sepsis and septic shock.[1] Sepsis has since then been defined as '**life-threatening organ dysfunction caused by a dysregulated host response to infection**'. It was found that previous definitions focused too much on inflammation, and the SIRS criteria were no longer advised to be used for diagnosing sepsis. Instead, they recommended to use the Sequential Organ Failure Assessment (SOFA) score as a measure of organ dysfunction (Table 2). Although the SOFA score has been shown to accurately predict mortality, it is not meant to be a stand-alone diagnostic test for sepsis.[14] To date, such a definite diagnostic test is still lacking.

Table 2 – Sequential Organ Failure Assessment (SOFA) Score

System	Score 0	1	2	3	4
Respiration PaO_2/FiO_2, mmHg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation Platelets, x103/µL	≥150	<150	<100	<50	<20
Liver Bilirubin, mg/dL (µmol/L)	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-104)	>12.0 (204)
Cardiovascular	MAP ≥70 mmHg	MAP <70 mmHg	Dopamine <5 or dobutamine (any dose)[a]	Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1[a]	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[a]
Central nervous system – GCS	15	13-14	10-12	6-9	<6
Renal Creatinine, mg/dL (µmol/L) Urine output, mL/day	<1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440) <500	>5.0 (440) <200

Abbreviations: GCS – Glasgow Coma Scale a Catecholamine doses are given as µg/kg/min for at least 1 hour

Sepsis is a medical emergency

Patients with sepsis should be identified and treated as soon as possible, as this can improve prognosis.[9,15] The goal of the treatment is to prevent progression from sepsis to septic shock, which is associated with high morbidity and mortality.[1] The cornerstone of sepsis treatment is considered to be timely intravenous administration of antibiotics, if necessary paired with targeted treatment of the source of the infection. Currently, there are still ongoing discussions on patient selection for aggressive treatment, the timing of antibiotics and the benefit or harm of aggressive fluid resuscitation and oxygen therapy.[8,16-20] However, despite these controversies, the general opinion remains that a patient with sepsis should be treated with intravenous antibiotics without unnecessary delay.[19,21]

Clinical rules

In order to make timely treatment possible, sepsis first and foremost has to be recognised as soon as possible. In the absence of a definite diagnostic test, clinical rules have been developed that can help professionals identify patients with, or at risk for, sepsis. The aforementioned SOFA score quantifies a patient's degree of organ dysfunction (Table 2). This score is not well known and hardly used outside the critical care setting, likely due to its extensive nature and need for multiple laboratory investigations. The SOFA score is therefore not practically useable outside the hospital, nor during a patient's stay in the emergency department (ED).

Some clinical rules are however suited to be used at the bedside. Specific examples for sepsis include the quick Sequential Organ Failure Assessment (qSOFA) score and the previously mentioned Systemic Inflammatory Response Syndrome (SIRS) criteria.[1] In addition, there are clinical rules such as the Modified Early Warning Score (MEWS) and the National Early Warning Score (NEWS), which were developed to be used for all patients (Table 3).[22,23]

Table 3 – Clinical rules used for sepsis

qSOFA – quick Sequential Organ Failure Assessment

	Points
Respiratory rate ≥22/min	1
Altered mental state	1
SBP ≤100mmHg	1

Score: 0-3 points, positive/abnormal when score ≥ 2 points

SIRS – Systemic Inflammatory Response Syndrome

	Points
Temperature >38°C or <36°C	1
Heart rate >90 bpm	1
Respiratory rate >20 /min or $PaCO_2$ <32mmHg/4.3kPa	1
White blood cell count >12,000/mm^3 or <4,000/mm^3 or >10% immature bands	1

Score: 0-4 points, positive/abnormal when score ≥ 2 points

MEWS – Modified Early Warning Score

	Points						
	3	2	1	0	1	2	3
SBP (mmHg)	<70	71-80	81-100	101-199		≥200	
Heart rate (bpm)		<40	41-50	51-100	101-110	111-129	≥130
Respiratory rate (/min)		<9		9-14	15-20	21-29	≥30
Temperature (°C)		<35.0		35.0-38.4		≥38.5	
Level of consciousness				A	V	P	U

Score: 0-14 points, positive/abnormal when score ≥ 4 points

NEWS – National Early Warning Score

	Points						
	3	2	1	0	1	2	3
Respiratory rate (/min)	≤8		9-11	12-20		21-24	≥25
Oxygen saturation (%)	≤91	92-93	94-95	≥96			
Supplemental oxygen		Yes		No			
Temperature (°C)	≤35.0		35.1-36.0	36.1-38.0	38.1-39.0	≥39.1	
SBP (mmHg)	≤90	91-100	101-110	111-219			≥220
Heart rate (bpm)	≤40		41-50	51-90	91-110	111-130	≥131
Level of consciousness				A			V-U

Score: 0-20 points, positive/abnormal when score ≥ 5 points

Abbreviations: SBP – systolic blood pressure, bpm – beats per minute; AVPU score: A = Alert, V = reacting to voice, P = reacting to pain, U = unresponsive

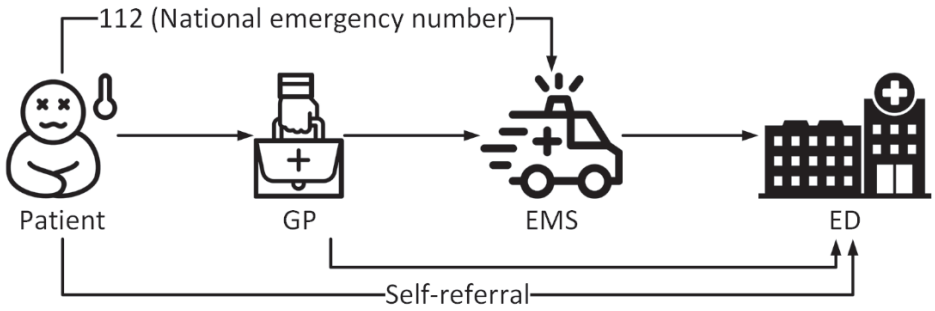
These four rules are practically useable, as they are mainly composed of vital signs. Cut-off points of the total scores of these rules are used for diagnosis (qSOFA and SIRS) or as warning triggers to escalate care (MEWS and NEWS). Although they have almost exclusively been developed, and subsequently widely implemented, in hospital settings, these clinical rules could theoretically be used by general practitioners (GPs) and in the ambulance (i.e. by emergency medical services (EMS)). However, evidence on their diagnostic value in these settings is lacking.

The Dutch acute care chain and infections

When a patient presents with an infection, healthcare providers have to differentiate between common infections with an expected uncomplicated recovery (either self-limiting or requiring antibiotic treatment), and severe infections/sepsis. How professionals approach this challenge depends on several factors, and not in the least place on their task within the acute care chain. The organisation of acute care differs around the world and the unique approach in the Netherlands requires some explanation.

The Dutch acute care chain covers the entire trajectory from the patient at home to the ED and there are several possible routes and stops in between (Figure 1). The primary goal of this system is to provide appropriate care for acute medical problems by the person best suited for the task at hand, as close to home as possible. When patients are in need of health care, they are urged to primarily contact their GP, who fulfils a prominent role by acting as a gatekeeper for hospitals.

Figure 1 – The acute care chain in the Netherlands



Abbreviations: GP – General Practitioner, EMS – Emergency Medical Services, ED – Emergency Department

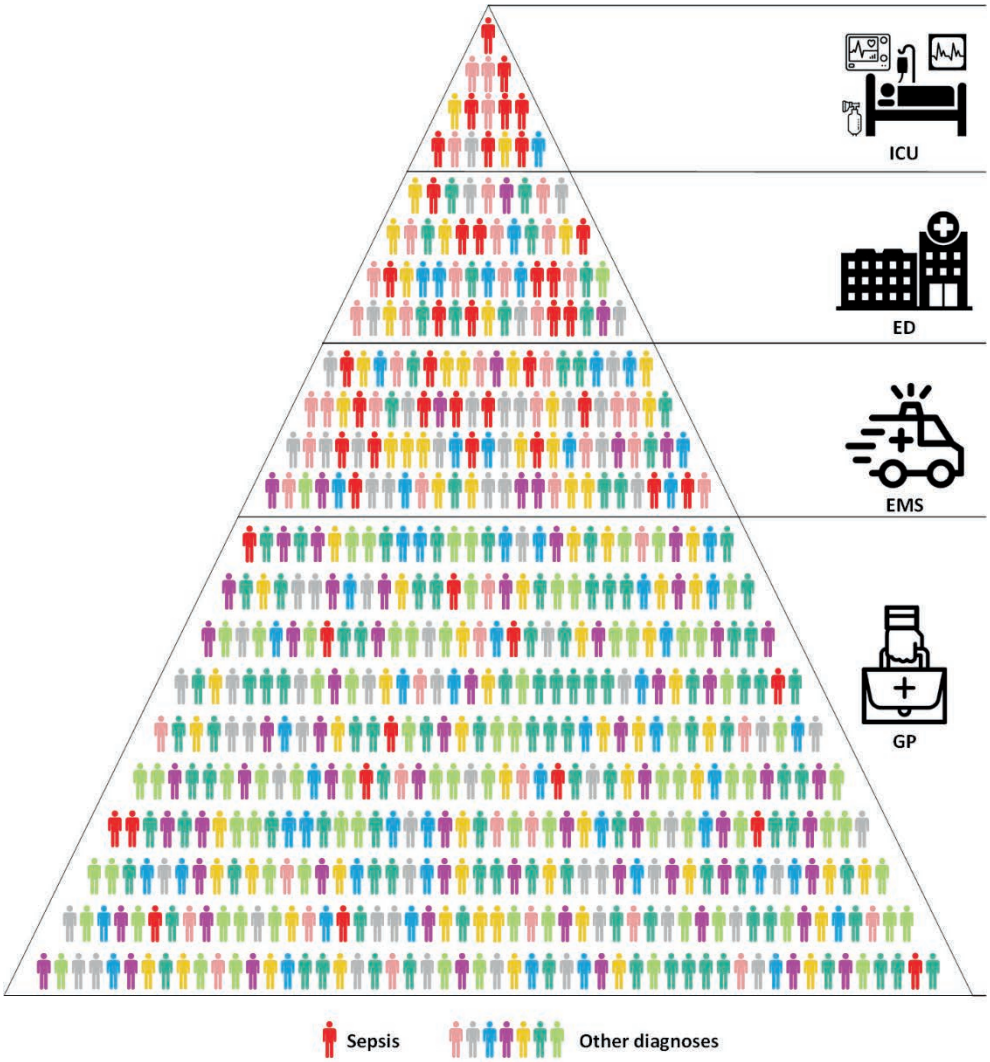
During office hours, patients contact their own GP practice, after which they receive self-care advise over the phone or e-consultation, are called in for a face-to-face consultation with the GP, or are visited at home by the GP. During out-of-hours, patients call their nearby general practitioner cooperative (GPC), which is often co-located with an ED. At these GPCs, 50-150 GPs take rotating shifts.[24] Nurses initially triage the patient by telephone or video consultation, using the Netherlands Triage System (NTS).[25] If physical assessment by a GP is deemed necessary, patients can get a GP appointment at the cooperative's facility, or be scheduled for a home visit by a GP. After assessment by a GP, only the minority of patients are referred to the ED. Reasons to refer are among others diagnostic uncertainty or the need for hospital care.

If a life threatening situation is suspected during triage, GPs can – at all times – order immediate assessment, help and/or transportation by emergency medical services (EMS). The same applies when patients themselves or their caregivers, family members or bystanders suspect a life-threatening situation. In such cases, it is advised to call the national emergency number (112) and ask for immediate assessment by EMS. EMS nurses in the Netherlands are highly trained, usually with experience in acute clinical and/or intensive care (ICU). They treat the patient and, if necessary, provide transport to the ED. Similar to the GPCs' triage, EMS dispatch codes are assigned by the ambulance dispatch centre, using NTS.[25] Due to the abovementioned organisation of acute care, patients are kept from receiving unnecessary investigations, such as laboratory investigations or imaging, and ED crowding is manageable.[26] In case of sepsis, however, GPs' task can be difficult.

Common infections account for the largest proportion of GPs' workload albeit with seasonal differences. In patients with a severe infection and thus a complicated course GPs need to decide whether or not he/she should be referred, and with what urgency. How GPs make these decisions without a definite diagnostic test for sepsis is largely unknown and several factors complicate this task.

First, the majority of patients who visit a GP are not seriously ill and do not have sepsis. Low exposure to patients with sepsis may cause GPs to have suboptimal awareness and a diminished sense of urgency. Although there are no exact incidence numbers for sepsis, infections account for over 25% of GPs' consultations, which translates to >11 million consultations annually in the Netherlands.[27,28] Simultaneously, 140,000 patients were admitted to a hospital with an infection and 'only' 3,980 patients (2.8%) were admitted to an ICU with a diagnosis of sepsis in 2018.[29] These numbers show that the majority of primary care patients with an infection are not referred to the ED, nor are they admitted to the ICU. They recover without intervention or with a short course of antibiotics. Figure 2 shows a proposed model of the incidence of sepsis within the Dutch acute care chain. Although the exact shape of the pyramid is largely unknown, GPs' annual exposure to patients with fulminant sepsis is likely to be low.

Figure 2 – Proposed model of distribution of sepsis patients through the acute care chain



Abbreviations: GP – General Practitioner, EMS – Emergency Medical Services, ED – Emergency Department

A second factor that may impair GPs' ability to identify sepsis is that sepsis does not always present with a distinct set of symptoms. Although some patients show clear signs of sepsis, and are therefore easy to recognise, many patients present without textbook signs of sepsis. In these cases, disease severity is likely one of the factors a GP takes into account when deciding whether or not to refer a patient, and with what urgency. Previous

retrospective research has shown that general appearance, gut feeling and history are most often indicated as important for the decision to refer patients with possible severe infections to the hospital.[30] Whether and how GPs specifically assess disease severity and how this is subsequently communicated throughout the acute care chain is largely unknown. It is, however, indispensable to communicate the severity of a patient's illness, as not all patients are equally ill and physicians in (crowded) EDs need to prioritise.

Third, outside hospital settings, physicians usually do not have access to immediate laboratory results. As shown in the SOFA score, organ dysfunction is often discovered by laboratory tests. Prehospital healthcare providers are therefore dependent on abnormal vital signs only and limited in their ability to 'diagnose' sepsis.

Fourth, the presence of organ dysfunction does not equal the presence of sepsis. Organ dysfunction can be caused by a variety of diseases, of which sepsis is only one. Studies show that approximately 1 in 2 patients treated for sepsis in the ED have negative blood cultures and 1 in 5 eventually have a non-infectious diagnosis that mimics sepsis.[31] Examples include, but are not limited to, pancreatitis, diabetic ketoacidosis and exacerbations of chronic obstructive pulmonary disease.

Finally, establishing whether vital signs are normal or abnormal is not as straightforward as it may seem. Not only age and sex, but also comorbidities and medication can influence an individual's baseline vital signs. What a patient's baseline values are is often unknown and changes herein can be subtle and difficult to recognise. Clinical rules generally do not take these individual factors into account and simplify the value of vital signs by using cut-off points. A risk could lie in the assumption that when a vital sign does not score points on a specific rule, it is considered to be normal, although in reality, a patient could be slowly deteriorating. The effect of small changes in vital signs on the scores of clinical rules has not been investigated.

Strengthening the chain

It is clear that timely and adequately selecting patients with, or at risk for, sepsis is no easy task. It is, however, a task that deserves attention from *all* professionals within the acute care chain. Only few studies have investigated the phase prior to an ED visit, although there is an abundance of sepsis research in hospitals. A patient's journey, however, does not start in the hospital, nor at the moment of arrival in the ED. It starts at home. Little is known about this prehospital phase during which a patient can meet several healthcare providers. Optimisation of care could be achieved by strengthening the acute care chain as a whole, in addition to strengthening each 'station'.

Aim of this thesis and main research questions:

This thesis aims to provide more insight into the trajectory of patients with a severe infection through the Dutch acute care chain, with specific attention to possible targets for optimisation of care.

Our main research questions therefore are:

1. How do patients with a severe infection or sepsis 'travel' through the acute care chain, how long is their journey and who do they meet whilst in transit?
2. How do GPs approach patients with fever during out-of-hours, with a specific focus on vital signs and gut feeling?
3. Do professionals within the acute care chain agree on and document the disease severity of patients with an infection?
4. How reliable are measurements of clinical rule scores, and how does the respiratory rate contribute to these scores?

THESIS OUTLINE

Severe infections – from home to hospital

- **Chapter 2**

Research on severe infections and sepsis has focused mainly on the hospital environment and the time-sensitive treatment from the moment a patient arrives in the ED. Little is known about the course of the disease prior to the hospital visit, although this phase could be a window of opportunity for optimisation of care. In this prospective cohort study we will investigate the prehospital phase of a cohort of ED patients with an infection, specifically focusing on duration of symptoms before ED arrival, primary care health seeking behaviour, use of oral antibiotics, and referral pathway.

- **Chapter 3**

GPs are key players in the Dutch acute care chain. They have the difficult task of differentiating an uncomplicated infection from sepsis. In the absence of a diagnostic test for sepsis, adequate patient selection for ED referral is difficult. In this prospective cohort study, we will investigate how many adult primary care patients with fever, presenting during out-of-hours, are referred to the hospital, and whether (measurement of) vital signs, SIRS/qSOFA scores, or gut feeling are associated with referral. In addition, we will investigate how many patients are admitted to the hospital or intensive care unit (ICU) and how many die within 30 days.

- **Chapter 4**

Throughout the acute care chain, patients with possible sepsis encounter GPs and/or EMS, followed by physicians working in the ED. Communication of the severity of a patient's illness is indispensable, as not all patients are equally ill and physicians in (crowded) EDs need to prioritise. In this prospective cohort study, we will investigate how often sepsis and a sense of urgency are documented throughout the acute care chain. In addition, we will examine whether sepsis and a sense of urgency are documented in the same patients and whether there is an association between documentation of sepsis or a sense of urgency and adverse outcomes.

Severe infections – vital signs and clinical rules

- **Chapter 5**

For ED patients with a suspected infection, a single set of vital signs is measured shortly after the patient arrives. Their values are often subsequently incorporated in clinical rules, which provide information on diagnosis and/or prognosis. Since vital signs vary over time, the scores of these rules can change as well. Information on this topic is lacking and could be used to optimise monitoring, prioritisation and decision making. In this prospective multicentre cohort study, we explore how the variation in vital signs during the ED stay of patients with suspected infection affects the following 4 clinical rules: qSOFA, SIRS, MEWS and NEWS. In addition, we will investigate which vital signs cause most changes in the clinical rule scores.

- **Chapter 6**

The respiratory rate is an important predictor of deterioration of a patient. Nevertheless, it is the least measured vital sign. In clinical rules aimed at early detection of critically ill patients, the respiratory rate has a prominent role. Inaccuracy in respiratory rate measurements could cause a delay in diagnosis and treatment of critically ill patients. In this questionnaire-based study, we use 5 videos to investigate the accuracy and interobserver-agreement of respiratory rate measurements by healthcare providers, and the potential effect of incorrect measurements on the scores of 4 common clinical rules: qSOFA, SIRS, MEWS and NEWS.

General discussion

- **Chapter 7**

In the general discussion of this thesis, the results of all chapters will be put into perspective, compared to existing literature, and recommendations for clinical practice and research are formulated.

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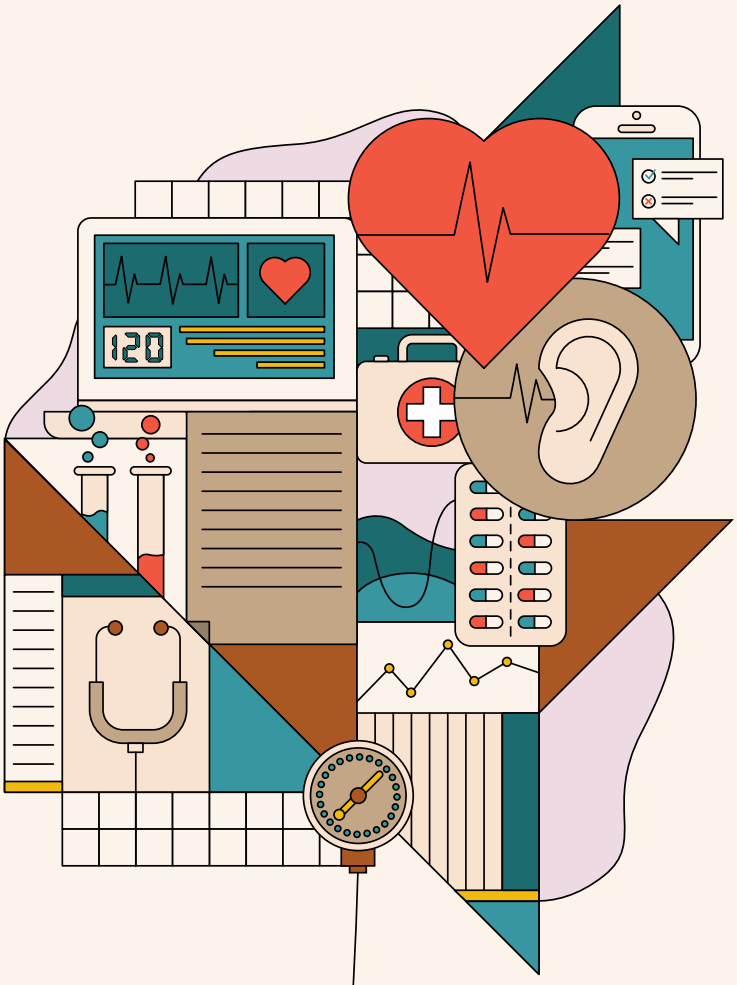
PART I

Severe infections – from home to hospital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CHAPTER 2

CHARACTERISTICS OF THE PREHOSPITAL PHASE OF ADULT EMERGENCY DEPARTMENT PATIENTS WITH AN INFECTION: A PROSPECTIVE PILOT STUDY.

Gideon H.P. Latten

Lieke Claassen

Marnix Jonk

Jochen W.L. Cals

Jean W.M. Muris

Patricia M. Stassen

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ABSTRACT

Objective

Research on serious infections/sepsis has focused on the hospital environment, while potentially the most delay, and therefore possibly the best opportunity to improve quality of care, lies in the prehospital setting. In this study we investigated the prehospital phase of adult emergency department (ED) patients with an infection.

Methods

In this prospective pilot study all adult (≥18y) patients with a suspected/proven infection, based on the notes in the patient's ED chart, were included during a 4-week period in 2017. Prehospital course, ED findings, presence of sepsis and 30-day outcomes were registered.

Results

A total of 440 patients were identified, with a median symptom duration before ED visit of 3 days (IQR 1–7 days). Before arrival in the ED, 23.9% of patients had used antibiotics. Most patients (83.0%) had been referred by a general practitioner (GP), while 41.1% of patients had visited their GP previously during the current disease episode. Patients referred by a GP were triaged as high-urgency less often, while vital parameters were similar. Emergency Medical Services (EMS) transported 268 (60.9%) of patients. Twenty-two patients (5.0%) experienced an adverse outcome (30-day all-cause mortality and/or admission to intensive care).

Conclusions

Patients with a suspected infection had symptoms for 3 (IQR 1–7) days at the moment of presentation to the ED. During this prehospital phase patients often had consulted, and were treated by, their GP. Many were transported to the ED by EMS. Future research on severe infections should focus on the prehospital phase, targeting patients and primary care professionals.

INTRODUCTION

One of the challenges for physicians is to timely recognise patients with an infection who are at risk of developing sepsis. Similar to myocardial infarction and stroke, mortality in sepsis patients increases with delayed treatment.[1,2] Early recognition and treatment of patients at risk therefore provide an opportunity to improve outcome.

Over the past years, timely recognition and treatment of patients with sepsis has improved. However, research has focused on sepsis within the hospital and not on the prehospital professionals: emergency medical services (EMS) and general practitioners (GPs).[3,4] To our knowledge, the prehospital phase of ED patients with a suspected infection has not yet been investigated before. This phase however, could potentially include most delay and may therefore be the best phase to focus on when aiming to improve quality of care for sepsis patients.

In this prospective pilot study, we investigate the prehospital phase of adult ED patients with a suspected infection. We specifically aim to investigate the duration of symptoms, number of GP contacts in the current disease episode, use of antibiotics, adverse outcomes (30-day all-cause mortality and/or intensive care unit (ICU) admission) and referral pathway (involvement of GP and/or EMS).

METHODS

Design and setting

This prospective pilot study took place during a 4-week period between 23 January and 19 February 2017 in Zuyderland Medical Centre, a large teaching hospital located in Heerlen, the Netherlands. Yearly, approximately 35,000 patients are assessed and treated in our ED by either emergency physicians or residents of other specialties. The majority of patients are referred by a GP. In the Netherlands, these are well trained primary care physicians, who provide the first step in emergency care 24/7 from their practices or out-of-hours services. The remaining patients contact the EMS or visit the ED on their own initiative. All patients are triaged by a dedicated triage nurse, using the Manchester Triage System.[5] After diagnosis and treatment in the ED, patients are either discharged home, or admitted to the hospital (regular wards, specific medium care units (e.g. brain care unit, cardiac care unit), or ICU).

We used the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for reporting this observational study.[6] The study was reviewed and approved by the medical ethics committee of Zuyderland (METC-Z nr. 16-N-202).

Patients

All ED patients aged 18 years or older were included if they had a suspected or proven infection, based on signs and symptoms mentioned in the referral letter and/or the patients' ED chart. All charts were checked manually to find evidence of suspicion of infection. One investigator (MJ) screened all patients for inclusion in the study. If it was unclear whether a patient should be included, a second investigator (GL or LC) was consulted and consensus was reached. To avoid any errors, a random sample of 10% of all data were double-checked by a second investigator. Patients visiting the ED more than once during the study period were included at their initial visit only.

Data collection

Patient data were collected using a Case Report Form (CRF) comprising data from the patient chart, including the referral letter and EMS notes. Additional information from GP or patient was requested by telephone, if necessary (i.e. use of antibiotics, previous GP

consultation, and outcome). Table 1 shows the variables that were retrieved and the definitions that were used.

Table 1 – Documented variables and used definitions	
Documented variables	
General	
Age	
Sex	
Comorbidities	Quantified using the Charlson Comorbidity Index (CCI)[7]
Number of medications	
Prehospital phase	
Duration of symptoms	In days
Use of antibiotics	At moment of presentation to the ED and in the preceding 30 days
Previous GP consultation	During current disease episode, starting from the first day of symptoms and not including GP consultation on the day of ED referral
Ambulance phase	
Mode of transportation to hospital	Ambulance or other means of transportation
EMS urgency	Assigned by the ambulance dispatch centre following the Netherlands Triage Standard (NTS).[8] A1: most urgent category, life-threatening situation; A2: urgent but not life-threatening; B: non-urgent conditions.
ED phase	
Referral to ED	Current visit: referred by GP or not?
Level of triage	Determined using the Manchester Triage System (MTS).[5] Assessment necessary: Red: immediately, orange: ≤10 minutes, yellow: ≤60 minutes, green: ≤120 minutes and blue: ≤240 minutes. We combined the red and orange urgency as 'high urgency' and the yellow, green and blue urgency as 'low urgency'.
ED vital parameters	Lowest systolic blood pressure (mmHg) Lowest diastolic blood pressure (mmHg) Mean arterial pressure (MAP, mmHg) Highest heart rate (beats per minute, bpm) Lowest oxygen saturation (%) Highest respiratory rate (/minute) Most abnormal temperature (°C) Lowest Glasgow Coma Scale (GCS)
Patient outcomes	
Focus of infection	Respiratory, urogenital, abdominal, skin, cardiovascular, central nervous system, unknown
Admission to hospital	all departments
ICU admission	
Length of stay in the hospital (LOS)	
30-day all-cause mortality	

Table 1 – continued	
Definitions	
Sepsis	Suspected or proven infection and the presence of two or more Systemic Inflammatory Response Syndrome (SIRS) criteria and/or quick Sepsis-related Organ Failure Assessment (qSOFA) criteria. We choose to use both the old (systemic inflammation (≥2 SIRS criteria) and infection) and the new definition of sepsis (qSOFA ≥2 or SOFA score>2), because the new definition has just been introduced and research comparing both is still ongoing. Primary care and ED professionals can use SIRS and qSOFA as screening tools for sepsis in contrast to the SOFA score.[9-13]
SIRS	Temperature >38°C or <36°C, heart rate >90/min, respiratory rate >20/min or $PaCO_2$ <4.3kPa (32 mmHg), white blood cell count >12000/mm^3 or <4000/mm^3 or >10% immature bands
qSOFA	Respiratory rate ≥22/min, altered mentation, systolic blood pressure ≤100 mmHg[9]
SOFA	0-24 points, depending on PaO_2/FiO_2 ratio, platelet count, bilirubin, MAP, administration of vasopressors (type and dose), Glasgow Coma Scale and serum creatinine or urine output[10]
Sepsis severity	Sepsis: sepsis in the absence of severe sepsis or septic shock Severe sepsis: sepsis complicated by organ failure Septic shock: sepsis with a mean arterial pressure (MAP) <60 mmHg, despite adequate fluid resuscitation
Adverse outcomes	All-cause mortality within 30 days and/or admission to ICU
Focus of infection at discharge	Focus at the moment of discharge from the hospital or from the ED (not-admitted patients)

Analysis

Descriptive analysis was performed, using the variables in Table 1, to provide insight in the prehospital and ED phase of patients with an infection. GP-referred patients were compared with unreferred patients, regarding prehospital and ED characteristics, presence of sepsis and outcome. In addition, patients with an adverse outcome (30-day all-cause mortality and/or ICU admission) were compared with those without adverse outcome.

Statistical methods

All statistical analyses were performed using IBM SPSS statistical software version 21 (Chicago, Illinois, USA). Continuous data were reported as means with standard deviation (SD) and compared using Students' T test, or as medians with interquartile ranges (IQR) and compared using the Mann Whitney U test. We reported categorical data as absolute

numbers and as valid percentages (to correct for missing data); they were compared using chi-square or Fisher exact tests. Differences in mortality were calculated using the Kaplan-Meier method and the log-rank test. A P value <0.05 was considered statistically significant.

RESULTS

Participants

During the inclusion period, 2,163 adult patients visited our ED; 440 patients (20.3%) had a suspected or proven infection.

Characteristics of patients with a proven/suspected infection

The mean age was 67 years and median CCI score was 2 (IQR 1–3, Table 2). The median duration of symptoms before ED arrival was 3 days (IQR 1–7 days) and 83.0% of patients were referred by a GP. In the period preceding the ED visit, 41.1% had already consulted their GP at least once, while 32.7% had used antibiotics in the preceding 30 days. Patients were transported by ambulance in 60.9%, most commonly as EMS urgency A2 (45.9%). Patients were triaged as high urgency in the ED in 25.9%. A positive (≥2) SIRS score was present in 58.9%, and a positive (≥2) qSOFA score in 12.3% of patients. Eighty percent of patients were admitted to the hospital.

Comparison of referred with unreferred patients

In total, 365 (83.0%) patients had been referred by a GP (Table 2). General characteristics did not differ between the two groups. Median duration of symptoms was 3 days in both groups, but referred patients more often had visited their GP earlier during the current disease episode (43.6 vs. 29.6%, p=0.03) and more often had used antibiotics, although this difference was not significant (34.5 vs. 23.9%, p=0.08). Referred patients were less often triaged as high urgency by the EMS (A1 18.5 vs. 52.1%, p<0.001) and by the ED (23.8 vs. 35.2%, p<0.05) than unreferred patients.

Vital parameters and the proportion of patients with SIRS or (q)SOFA scores ≥2 did not differ between the two groups. Referred patients were admitted to the hospital and ICU less often (77.8 vs. 90.1%, p<0.05 and 1.9 vs. 11.3%, p<0.001). All-cause 30-day mortality was lower in the referred group, although this difference was not significant (1.9 vs. 4.2%, p=0.24).

Table 2 – Baseline characteristics and outcomes of ED patients with a suspected/proven infection and a comparison between GP-referred and unreferred patients

	Total (n=440)	n	GP-referred[a] (n=365, 83.0%)	Unreferred[a] (n=71, 16.1%)	p
General					
Age – years	67 (±18)	440	67 (±18)	66 (±15)	0.63
Male	218 (49.5%)	440	178 (48.8%)	37 (52.1%)	0.61
CCI	2 (1-3)	440	2 (1-3)	2 (0-4)	0.29
Number of medications	6 (±4)	440	5 (±4)	6 (±4)	0.71
Prehospital phase					
Duration of symptoms – days	3 (1-7)	440	3 (1-7)	3 (2-4)	0.41
Previous GP consultation	181 (41.1%)	440	159 (43.6%)	21 (29.6%)	0.03
Antibiotics in past 30 days	144 (32.7%)	440	126 (34.5%)	17 (23.9%)	0.08
Current use of antibiotics	105 (23.9%)	440	92 (25.2%)	12 (16.9%)	0.13
Ambulance phase					
Transport by ambulance	268 (60.9%)	440	216 (59.2%)	48 (67.6%)	0.18
EMS urgency		268			<0.001
A1	65 (24.3%)		40 (18.5%)	25 (52.1%)	
A2	123 (45.9%)		104 (48.1%)	18 (37.5%)	
B	73 (27.2%)		68 (31.5%)	2 (4.2%)	
Emergency department phase					
High urgency triage	114 (25.9%)	440	87 (23.8%)	25 (35.2%)	0.04
Systolic BP – mmHg	135 (±28)	410	135 (±28)	135 (±27)	0.93
Diastolic BP – mmHg	74 (±17)	410	74 (±18)	74 (±17)	0.87
MAP – mmHg	94 (±18)	410	94 (±18)	94 (±18)	0.97
Heart rate - bpm	97 (±23)	429	97 (±23)	100 (±24)	0.25
Oxygen saturation - %	95 (92-97)	426	95 (92-97)	95 (91-97)	0.31
Respiratory rate – /min	20 (16-24)	434	20 (16-24)	20 (16-24)	0.51
Temperature - °C	37.5 (37.0-38.3)	432	37.5 (37.0-38.2)	37.7 (36.9-38.7)	0.40
Glasgow Coma Scale	15 (15-15)	440	15 (15-15)	15 (15-15)	0.82
SIRS ≥2	259 (58.9%)		209 (57.3%)	47 (66.2%)	0.16
qSOFA ≥2	54 (12.3%)		43 (11.8%)	10 (14.1%)	0.59
SOFA ≥2	240 (54.5%)		202 (55.3%)	38 (53.5%)	0.78
SOFA score	2 (1-3)		2 (1-3)	2 (0-3)	0.82
Sepsis severity					0.41
Sepsis (no severe sepsis/shock)	102 (23.2%)		79 (21.6%)	21 (29.6%)	
Severe sepsis	158 (35.9%)		131 (35.9%)	26 (36.6%)	
Septic shock	5 (1.1%)		4 (1.1%)	1 (1.4%)	
No sepsis	175 (39.8%)		151 (41.4%)	23 (32.4%)	

Table 2 - continued	Total (n=440)	n	GP-referred (n=365, 83.0%)	Unreferred (n=71, 16.1%)	p
Outcome					
Hospital admission	352 (80.0%)	440	284 (77.8%)	64 (90.1%)	0.02
ICU admission	15 (3.4%)	440	7 (1.9%)	8 (11.3%)	<0.001
LOS – days	6 (4-11)	440	6 (4-11)	6 (3-11)	0.65
30-day mortality	10 (2.3%)	440	7 (1.9%)	3 (4.2%)	0.95
Focus of infection at discharge		440			0.44
Respiratory	269 (61.1%)		229 (62.7%)	38 (53.5%)	
Urogenital	55 (12.5%)		39 (10.7%)	14 (19.7%)	
Abdominal	46 (10.5%)		39 (10.7%)	7 (9.9%)	
No infection[b]	11 (2.5%)		10 (2.7%)	1 (1.4%)	
Skin	9 (2.0%)		7 (1.9%)	2 (2.8%)	
Cardiovascular	4 (0.9%)		4 (1.1%)	0	
CNS	1 (0.2%)		1 (0.3%)	0	
Other or focus unknown	45 (10.2%)		36 (9.9%)	9 (12.7%)	

Values: n (%), mean (±SD), or median (IQR)
Abbreviations: GP – General Practitioner, CCI – Charlson Comorbidity Index, EMS – Emergency Medical Services, BP – blood pressure, MAP – Mean Arterial Pressure, SIRS – Systemic inflammatory response syndrome, qSOFA – quick Sequential Organ Failure Assessment, SOFA – Sequential Organ Failure Assessment, ICU – Intensive Care Unit, LOS – length of stay, CNS – central nervous system
a for 4 patients referral pathway could not be retrieved (GP-referred or unreferred)
b patients who had a suspected infection in the ED, but were diagnosed with other pathology after admission (e.g. pancreatitis, intoxication)

Comparison of patients with and without adverse outcomes

Twenty-two (5.0%) patients experienced in total 25 adverse outcomes: 15 (3.4%) were admitted to the ICU and 10 (2.3%) patients died (Table 3). There were no significant differences in general characteristics, but patients with an adverse outcome were less often referred by a GP (59.1 vs. 84.2%, p=0.001) and were considered more urgent by both EMS (A1: 52.6 vs. 22.1%, resp., p<0.05) and ED (highly urgent in 72.7 vs. 23.4%, resp., p<0.001). The number of patients with ≥2 SIRS criteria and vital parameters did not differ, except for the respiratory rate, which was higher in the adverse outcome group (22.5 vs. 20.0, p=0.02). In patients with adverse outcomes, both qSOFA and SOFA scores were more often ≥2 than in the adverse outcome group (qSOFA 36.4 vs. 11.0%, p<0.001; SOFA 81.1 vs. 53.3%, p=0.01).

Table 3 – Comparison between patients with and without an adverse outcome				
	Adverse outcome[a] (n=22)	**No adverse outcome[a] (n=418)**	**n**	**p**
General				
Age – years	70.1 (±13.7)	67.1 (±17.9)	440	0.44
Male	10 (45.5%)	208 (49.8%)	440	0.69
CCI	2 (1-3)	2 (1-3)	440	0.38
Number of medications	7 (±3)	5 (±4)	440	0.17
Prehospital phase				
Duration of symptoms – days	2.5 (1-4)	3 (1-7)	440	0.23
Previous GP consultation	9 (40.9%)	172 (41.1%)	440	0.98
Antibiotics in past 30 days	6 (27.3%)	138 (33.0%)	440	0.58
Current use of antibiotics	5 (22.7%)	100 (23.9%)	440	0.90
Ambulance phase				
Transport by ambulance	19 (86.4%)	249 (59.6%)	440	0.01
EMS urgency			440	0.01
A1	10 (52.6%)	55 (22.1%)		
A2	7 (36.8%)	116 (46.6%)		
B	2 (10.5%)	71 (28.5%)		
Emergency department phase				
Currently referred by GP	13 (59.1%)	352 (84.2%)	440	0.001
High urgency triage	16 (72.7%)	98 (23.4%)	440	<0.001
Systolic BP – mmHg	127.6 (±43.7)	134.9 (±26.6)	410	0.47
Diastolic BP – mmHg	67.9 (±22.3)	74.0 (±16.7)	410	0.23
MAP – mmHg	87.8 (±27.5)	94.3 (±17.7)	410	0.30
Heart rate - bpm	102.6 (±36.6)	97.2 (±21.8)	429	0.52
Oxygen saturation - %	92.0 (90.0-97.0)	95.0 (92.0-97.0)	426	0.09
Respiratory rate – /min	22.5 (19.0-30.5)	20.0 (16.0-24.0)	434	0.02
Temperature - °C	37.4 (36.2-38.0)	37.6 (37.0-38.4)	432	0.23
Glasgow Coma Scale	15.0 (12.8-15.0)	15.0 (15.0-15.0)	440	<0.001
SIRS ≥2	11 (50.0%)	248 (59.3%)		0.39
qSOFA ≥2	8 (36.4%)	46 (11.0%)		<0.001
SOFA ≥2	18 (81.8%)	223 (53.3%)		0.01
SOFA score	4 (3-5)	2 (0-3)		<0.001
Sepsis severity				<0.001
Sepsis (no severe sepsis/shock)	0	102 (24.4%)		
Severe sepsis	9 (40.9%)	149 (35.6%)		
Septic shock	3 (13.6%)	2 (0.5%)		
No sepsis	10 (45.5%)	165 (39.5%)		

Table 3 - continued	Adverse outcome[a] (n=22)	No adverse outcome[a] (n=418)	n	p
Outcome				
Hospital admission	22 (100%)	330 (78.9%)	440	0.02
LOS – days	10 (5.8-13.3)	6 (4-11)	440	0.03

Values: n (%), mean (±SD), or median (IQR)
Abbreviations: GP – General Practitioner, CCI – Charlson Comorbidity Index, EMS – Emergency Medical Services, BP – blood pressure, MAP – Mean Arterial Pressure, GCS – Glasgow Coma Scale, SIRS – Systemic inflammatory response syndrome, qSOFA – quick Sequential Organ Failure Assessment, SOFA – Sequential Organ Failure Assessment, ICU – Intensive Care Unit, LOS – length of stay, CNS – central nervous system
a Adverse outcome defined as 30-day all-cause mortality and/or ICU admission

DISCUSSION

To the best of our knowledge, no other study has prospectively investigated the prehospital phase of ED patients with a suspected infection. In a median period of 3 days before visiting the ED, many (41.1%) patients had prior contact with their GP, and 23.9% had already used antibiotics. For the actual ED visit, GPs referred most patients (83.0%) and many were transported by ambulance (60.9%). Between referred and unreferred patients, no differences in general characteristics, vital parameters or sepsis criteria were found. However, referred patients were less often placed in a high triage category or admitted to either the hospital (77.8 vs. 90.1%, p=0.02) or ICU (1.9 vs 11.3%, p<0.001). Patients who experienced an adverse outcome (5.0%) had the same duration of symptoms, number of GP contacts and prior use of antibiotics as those without an adverse outcome.

Our study shows that for most ED patients with an infection, the acute care chain starts with a contact with the GP and transport by EMS. These findings suggest that the acute care chain offers a window of opportunity that allows for a good start of treatment. It is probable that the prehospital phase is important and that it influences choices that are made in the ED, although no studies have taken this phase into account when evaluating sepsis.

Selecting those in need of hospital care is one of the challenges GPs have to deal with. In our study, the majority (83.0%) of patients was referred by a GP. These patients were considered less urgent by the EMS and the ED than unreferred patients. An explanation could be that unreferred patients accurately assessed their situation as highly urgent and called for help (EMS). One study investigated why GPs refer patients with an infection. General patient appearance, gut feeling and patient history turned out to be most important for the decision whether or not to refer.[14] Our finding that the respiratory rate was higher in patients with an adverse outcome may suggest that including this vital parameter in this decision-making process could be useful. In 2016, a NICE guideline provided recommendations for GPs when to refer patients with suspected sepsis to the hospital.[15] The guideline committee has recommended that an evaluation of implementation of the guideline should be performed.[16] As far as we know, this has not been done yet. It would be interesting to investigate whether the selection process and the treatment started by GPs is optimal. For this analysis, data on symptoms, vital signs and treatment in the GP-phase must be retrieved. Further, a way of assessing the accuracy of the referral policy and prehospital treatment must be developed: just right/too early/too late. Consensus meetings could contribute to this assessment, but interviewing patients should also be considered. Their behaviour probably influences treatment of the infection (e.g. patient delay) and their assessment of care is important.

It should be noted that EMS are a key player in the acute care chain as well. EMS staff decide what route their patients follow. This is important since documentation of sepsis by EMS could be further improved, especially since patients who are recognised receive appropriate care sooner when they subsequently arrive in the ED.[3,4,17-19]

Future research may focus on patient education, appropriate triage, early treatment, including ED referral, and the use of point-of-care testing (POCT), such as lactate and/or CRP.

Limitations

Patients were included when an infection was suspected/proven. It is possible that some patients were missed when an infection was not appropriately documented or recognised in the ED. Also, vital signs were sometimes missing. Most missing data were however retrieved by asking patients and retrieving referral handover information. Information may have been incomplete, but this loss of information was random and therefore has not influenced our results. In addition, the organization of acute health care in the Netherlands probably differs from that in other countries. Specifically, the (Dutch) low number of self-referrals can make extrapolation to other countries difficult. Finally, our cohort was included during a flu episode, which may have influenced our patient characteristics: 20% of patients with an infection seems high. We therefore evaluated ED visits in other months of 2017 and found an equal number of ED visits because of infections. An explanation for this high proportion of infections is that our GPs prevent ED visits for minor complaints, like small trauma.

In conclusion, patients with an infection in our ED had a median symptom duration of 3 days, regardless of the way of referral. Almost half of all patients visited their GP once or more before they were referred and one in four patients already used antibiotics. Future research should further investigate the prehospital pathway and outcomes of sepsis patients.

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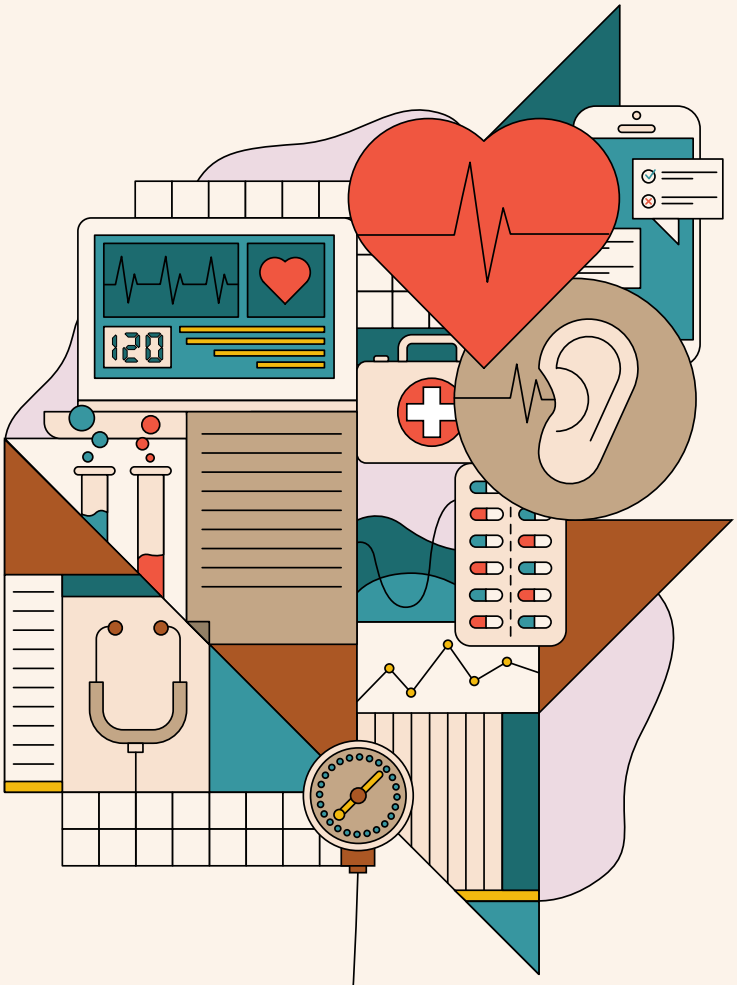
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CHAPTER 3

VITAL SIGNS, CLINICAL RULES, AND GUT FEELING: AN OBSERVATIONAL STUDY AMONG PRIMARY CARE PATIENTS WITH FEVER DURING OUT-OF-HOURS.

Gideon H.P. Latten

Lieke Claassen

Lucinda Coumans

Vera Goedemondt

Jean W.M. Muris

Jochen W.L. Cals

Patricia M. Stassen

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ABSTRACT

Background

GPs decide which patients with fever need to be referred to the emergency department (ED). Vital signs, clinical rules, and gut feeling can influence this critical management decision.

Aim

To investigate which vital signs are measured by GPs, and whether referral is associated with vital signs, clinical rules, or gut feeling.

Design & setting

Prospective observational study at two out-of-hours GP cooperatives in the Netherlands.

Methods

During two 9-day periods, GPs performed their regular work-up in patients aged ≥18 years with fever (≥38.0°C). Subsequently, researchers measured missing vital signs for completion of the systemic inflammatory response syndrome (SIRS) criteria and the quick Sequential Organ Failure Assessment (qSOFA) score. Associations between the number of referrals, positive SIRS and qSOFA scores, and GPs' gut feelings were investigated.

Results

GPs measured and recorded all vital signs required for SIRS criteria and qSOFA score calculations in 24 of 108 (22.2%) assessed patients, and referred 45 (41.7%) to the ED. Higher respiratory rates, temperatures, clinical rules, and gut feeling were associated with referral. During 7-day follow-up, nine (14.3%) of 63 patients who were initially not referred were admitted to hospital.

Conclusion

GPs measured and recorded all vital signs for SIRS criteria and qSOFA score in one-in-five patients with fever, and referred half of 63 patients who were SIRS positive and almost all of 22 patients who were qSOFA positive. Some vital signs and gut feeling were associated with referral, but none were consistently present in all patients who were referred. The vast majority of patients who were not initially referred remained at home during follow-up.

INTRODUCTION

GPs have the difficult task of deciding whether or not to refer a patient with fever to the ED. This decision can be critical, as delay in the treatment of those with a serious infection, such as sepsis, is associated with increased morbidity and mortality.[1,2] Unfortunately, there is no gold standard for diagnosing sepsis, which makes adequate patient selection for ED referral difficult.

Professionals are encouraged to measure vital signs, in order to pick up potential signs of organ failure and diagnose sepsis.[3,4] Two clinical rules have been developed to aid in the detection of sepsis: the SIRS criteria and the qSOFA score.[3,5] These simple rules are often recommended as screening tools for sepsis, but it is unknown whether GPs actually measure the vital signs required for calculation of these scores.

In a retrospective survey-based study, GPs indicated that they measure vital signs in the majority of patients with a possible serious infection.[6] However, for making the decision to refer these patients, vital signs were not considered as important as general appearance, gut feeling, and medical history of the patient. Gut feeling may be especially important, as it has been shown to play a considerable role in the diagnostic reasoning of GPs.[7,8] To the authors' knowledge, no study has prospectively investigated the measurement of vital signs, SIRS and qSOFA scores, and gut feeling in primary care patients with fever.

In this prospective study, we investigated which vital signs were measured by GPs in out-of-hours (OOH) primary care patients with fever, and how often SIRS and qSOFA were calculated. In addition, we investigated how many patients were referred to hospital, and whether vital signs, SIRS and qSOFA scores, and gut feeling were associated with referral. In addition, it was investigated how many patients were admitted to hospital (ward or intensive care unit [ICU]) and how many died within 30 days. It was expected that vital signs would not be measured in all patients and that the decision to refer would be multifactorial.

METHODS

Design and setting

In this prospective observational study, adult patients with fever (≥38.0°C) were included at two GP cooperatives (GPCs) in Heerlen and Maastricht, the Netherlands. In these GPCs, medical care is provided by GPs. Dutch GPs are obliged to work both in- and out-of-hours. Patients who need medical care out-of-hours have to contact their nearby GPC first, after which nurses initially perform triage by telephone, using the computer-assisted triage method of the Netherlands Triage System. If physical assessment by a GP is deemed necessary, patients can get an appointment at the cooperative's facility, or be scheduled for a home visit.[9]

The participating cooperatives in this study provide OOH primary care for 430 000 inhabitants of the region and are both — as is customary in the Netherlands — located adjacent to an ED, which subsequently receive less than 3% walk-ins.[10]

The Strengthening the Reporting of Observational Studies in Epidemiology guidelines were used for reporting this observational study.[11]

Patients

Patients eligible for inclusion were adults (aged ≥18 years) with a documented body temperature of ≥38.0°C (measured at home or by a GP), who were triaged to a face-to-face GP consultation at the GPC or a GP home visit. Refusal of written informed consent and a language barrier were exclusion criteria, as was a second presentation within the study period, since it is likely that these patients are treated differently. Owing to the labour-intensive design of the study, it was decided to include patients during two specific periods, mentioned below. A sample size calculation was not performed.

Data collection

This study was conducted during two 9-day periods (1–9 September 2018 and 12–20 January 2019) including eight weekend days from 08.00 to 23.30 hours and 10 weekdays from 17.00 to 23.30 hours. The GPs initially assessed and treated every eligible patient as they normally would. Immediately after the GP's assessment, well-instructed research students included patients. As not all patients were expected to be included, age and sex

of all eligible patients of one GPC were retrieved in order to investigate possible inclusion bias.

Immediately after inclusion, data on sex, age, duration of symptoms, and use of antibiotics during the current disease period were collected, as well as the following vital signs measured by the attending GP: blood pressure, heart rate, respiratory rate, temperature, and a Glasgow Coma Scale (GCS). Research students only measured missing vital signs required for SIRS criteria and qSOFA score calculations following a strict protocol. Blood pressure was measured electronically, heart and respiratory rate manually for 1 minute, temperature using an ear thermometer, and the GCS manually (normal or abnormal). Not considered essential for completeness were the two SIRS criteria leucocyte count and partial pressure of carbon dioxide (pCO2). In order to avoid influence of the study on the GP's treatment plan, only abnormal measurements were reported back to the GP.

During the second 9-day period, the Gut Feelings Questionnaire (GFQ), a validated 10-item questionnaire, was used (see Appendix 2).7 This questionnaire evaluates what level of a sense of alarm doctors feel when treating. GPs were asked to fill in the questionnaire after complete evaluation of the patient and after deciding whether or not the patient needed referral.

Follow-up data included hospital admission within 7 days and 30-day ICU admission and all-cause mortality.

Analysis and statistics

Descriptive analyses were performed to evaluate the prevalence of fever, baseline characteristics, and the measurement of vital signs by GPs. The number of positive (≥2) SIRS and qSOFA scores was calculated using the GPs' measurements alone and using all vital signs (after students had completed the additional measurements).

Next, the authors compared (the measurement of) vital signs by the GP and the number of positive SIRS and qSOFA scores (using all measurements performed) in patients who were referred and those who were not.

Descriptive analyses were performed regarding ED (re)visit, hospital and/or ICU admission, and mortality for all patients.

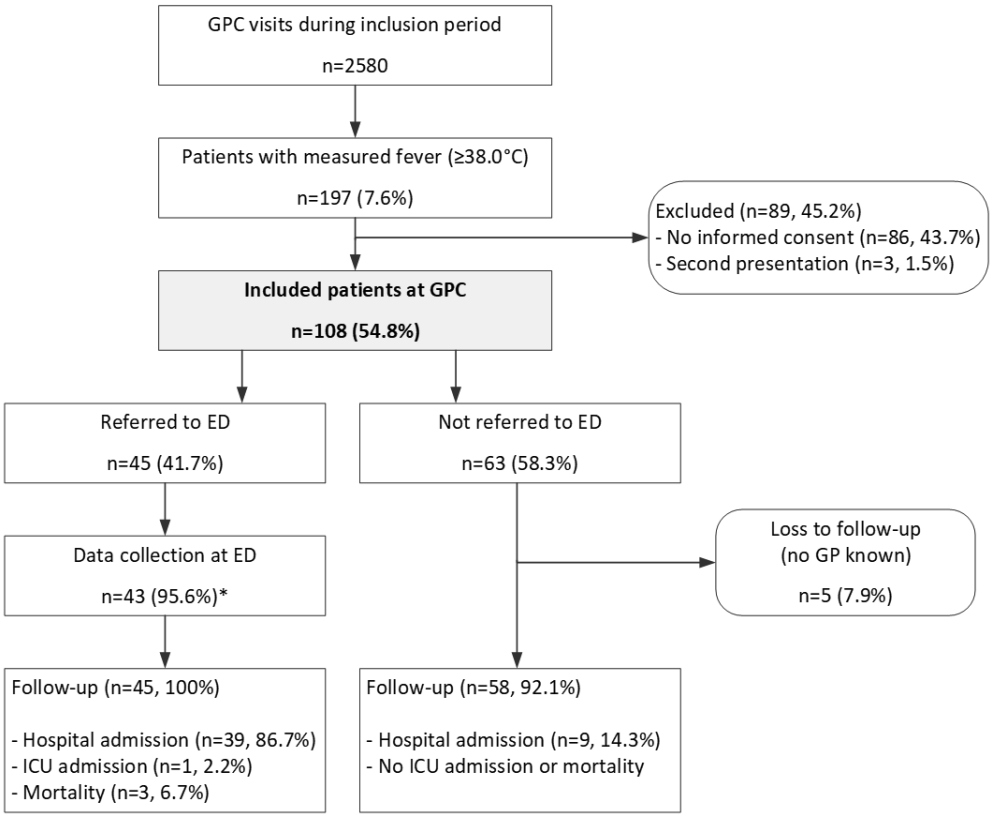
Statistical analyses were performed using IBM SPSS Statistics (version 26). Continuous data were reported as means with standard deviation (SD) and compared using Student's

t-test, or as medians with interquartile ranges (IQR) and compared using the Mann-Whitney U test. Categorical data were reported as absolute numbers and as valid percentages; these were compared using $\chi 2$ or Fisher's exact tests. A P-value <0.05 was considered statistically significant.

RESULTS

During the study period, 2580 adult patients visited the two GPCs (Figure 1). Of these, 197 had a temperature ≥38.0°C, resulting in a fever prevalence of 7.6%. Of these, 89 (45.2%) were excluded because of no informed consent (n=86) or a second presentation in the study period (n=3). In total, data of 108 (54.8%) patients were available for analysis. Excluded patients were younger than those included (median 58 years vs. 72 years, P<0.001) (see Appendix 1). There was no difference in sex between excluded and included patients (43.1% vs. 39.7% male, P = 0.15).

Figure 1 – Flowchart of study population



Abbreviations: GP – General Practitioner, ED – Emergency Department, ICU – Intensive Care Unit

Baseline patient characteristics and vital sign measurements

Of 108 included patients, 38.0% (n=41) were male and median age was 69 years (IQR 49–80 years) (Table 1). Median duration of symptoms was 1 day (IQR 0–3 days) and 13.9% (n=15) of patients were already using antibiotics.

GPs measured a complete set of vital signs required for SIRS criteria and qSOFA score calculations in 24 (22.2%) patients. The respiratory rate was measured least (n=34, 31.5%), while the temperature was measured most frequently (n=99, 91.7%). Positive (≥2) SIRS scores were present in 53 (49.1%) patients and positive (≥2) qSOFA scores in 6 (5.6%) patients, based on the GPs' measurements. These numbers increased to 69 (63.9%) for SIRS and 11 (10.2%) for qSOFA after adding missing vital signs.

In total, researchers performed 146 additional measurements. Of these, 40 (27.4%) were abnormal (mostly the respiratory rate [80.0%]) and therefore reported back to the GP (Table 2). Not once did these abnormal findings change the decision whether or not to refer a patient.

Table 1. Baseline characteristics and measurements of vital signs (n=108)*				
Baseline characteristics				
Male	41 (38.0%)			
Age (years)	69 (49-80)			
Home visit	61 (56.5%)			
Current disease period				
Duration of symptoms (days)	1 (0-3)			
Use of antibiotics before GPC visit	15 (14.2%)			
Vital signs	GP		GP + investigator	
	Measured	Median (IQR)	Measured	Median (IQR)
Systolic blood pressure (mmHg)	94 (87.0%)	130 (118-140)	107 (99.1%)	130 (117-140)
Diastolic blood pressure (mmHg)	94 (87.0%)	79 (70-81)	107 (99.1%)	70 (70-81)
- Heart rate (bpm)	87 (80.6%)	97 (85-115)	106 (98.1%)	95 (84-113)
- Respiratory rate (/min)	34 (31.5%)	22 (18-28)	104 (96.3%)	20 (18-26)
- Temperature (°C)	99 (91.7%)	38.5 (38.1-39.2)	107 (99.1%)	38.5 (38.1-39.2)
- Abnormal GCS – n (%)	71 (65.7%)	17 (23.9%)[a]	107 (99.1%)	21 (19.6%)[a]
Clinical rules				
Complete set of vital signs[b]	24 (22.2%)		99 (91.7%)	
All SIRS parameters measured	29 (26.9%)		101 (93.5%)	
SIRS ≥2	53 (49.1%)		69 (63.9%)	
All qSOFA parameters measured	27 (25.0%)		102 (94.4%)	
qSOFA ≥2	6 (5.6%)		11 (10.2%)	

Numbers are N (%) or median (IQR), unless stated otherwise
Abbreviations: GP – General Practitioner, GPC – General Practitioner Cooperative, GCS – Glasgow Coma Scale, SIRS – Systemic Inflammatory Response Syndrome, qSOFA – quick Sequential Organ Failure Assessment
a Number of patients with GCS <15
b Complete set of vital signs = blood pressure (BP), heart rate (HR), respiratory rate (RR), temperature (T) and a Glasgow Coma Scale (GCS)

Table 2 – Abnormal vital signs reported back to GPs				
Vital sign	**Cut-off value for back-reporting to GP**	**Reported back to treating GP – n**	**Referred to ED – n (%)**	**Change in referral strategy – n**
Systolic blood pressure	<90 mmHg	0	-	-
Heart rate	>100 bpm	4	3 (75%)	0
Respiratory rate	>20/minute	32	17 (53%)	0
Glasgow coma scale	<15	4	3 (67%)	0
Temperature	>40°C	0	-	-

Abbreviations: GP – General Practitioner, ED – Emergency Department, bpm – beats per minute

Comparison between referred patients and patients who were not referred

GPs referred 45 (41.7%) patients to the ED (Table 3). These patients had higher respiratory rates (24 vs. 18, P<0.001) and temperatures (38.6°C vs. 38.3°C, P = 0.02) and more often an abnormal GCS (31.1% vs.11.3%, P = 0.01) than patients who were not referred. Positive SIRS and qSOFA scores were more prevalent in the referred group (75.6% vs. 55.6%, P = 0.03 and 22.2% vs. 1.6%, P = 0.001, respectively), as was a sense of alarm (76.5% vs. 14.7%, P<0.001). Of the patients who were not referred, 35 (55.6%) had SIRS ≥2 and one (1.6%) qSOFA ≥2.

Table 3. Comparison between referred patients and not referred patients

		Referred patients	Not referred patients	
	N	Value	Value	P
Baseline characteristics		n=45	n=63	
Male	108	19 (42.2%)	22 (34.9%)	0.44
Age (years)	108	69 (56-81)	65 (40-79)	0.16
Home visit	108	29 (64.4%)	32 (50.8%)	0.16
Vital signs at GPC		n=45	n=63	
- SBP (mmHg)	107	128 (110-140)	130 (120-140)	0.26
- HR (bpm)	106	100 (87.8-120.0)	95 (83.5-104.3)	0.15
- Respiratory rate (/min)	104	24 (19-30)	18 (16-24)	<0.001
- Temperature (°C)	107	38.6 (38.2-39.4)	38.3 (38.0-39.3)	0.02
- GCS <15 (n (%))	107	14 (31.1%)[a]	7 (11.3%)[a]	0.01
Complete set of vital signs measured by GP	108	13 (28.9%)	11 (17.5%)	0.16
Clinical rules		n=45	n=63	
SIRS ≥2	108	34 (75.6%)	35 (55.6%)	0.03
qSOFA ≥2	108	10 (22.2%)	1 (1.6%)	0.001
Gut feeling		n=17	n=34	
Sense of alarm present	51*	13 (76.5%)	5 (14.7%)	<0.001

Numbers are N (%) or median (IQR)
a Number of patients with GCS <15
b Complete set of vital signs = blood pressure (BP), heart rate (HR), respiratory rate (RR), temperature (T) and a Glasgow Coma Scale (GCS)
* Gut feeling questionnaires were only filled in during the second inclusion period of the study
Abbreviations: GP – General Practitioner, GPC – General Practitioner Cooperative, SBP – Systolic Blood Pressure, DBP – Diastolic Blood Pressure, HR – Heart Rate, bpm – beats per minute, GCS – Glasgow Coma Scale, ED – Emergency Department

Follow-up

In total, one (2.2%) patient was admitted to ICU and three (6.7%) patients died within 30 days (Figure 1). All of these patients were primarily referred to the ED. Nine (14.3%) of 63 patients who were initially not referred were admitted to hospital within 1 week after the GPC visit. Six (66.7%) of these nine patients already had a positive SIRS score based solely on the GP's measurements, while none were qSOFA positive (Appendix 1).

DISCUSSION

Summary

In the study, GPs measured a complete set of vital signs for SIRS criteria and qSOFA score calculations in only 22.2% of patients. With their measurements, GPs could have calculated positive SIRS and qSOFA scores in 49.1% and 5.6% of patients, respectively. After missing vital signs were measured, these numbers increased to 63.9% and 10.2%. Patients who were referred had higher respiratory rates and temperatures, and more often an abnormal GCS than patients who were not referred. In addition, positive SIRS and qSOFA scores and a sense of alarm were more prevalent in patients who were referred. Of patients who were not referred, 14.3% were admitted to hospital (ward) within 7 days of the consultation. ICU admission and mortality happened in patients who were referred only.

Strengths and limitations

To the authors' knowledge, this is the first prospective study investigating the measurement of vital signs, gut feeling, and referral strategies of primary care patients with fever. The unique study design allowed the authors to investigate the real-world approach of GPs and still use complete sets of vital signs. This resulted in almost no missing vital signs and complete follow-up. Both summer and winter were included to consider seasonal differences. Nonetheless, an important limitation of the labour-intensive design is the achieved sample size. Despite placing maximum effort on patient inclusion, 89 patients were not included mainly owing to refusing informed consent (n = 86). The fact that included patients were older than excluded patients may have inflated referral rates. More precise information to investigate possible selection bias was not available. Owing to these limitations, it is concluded that this study must be seen as a pilot study that justifies further and larger investigations into the decision-making process of GPs in patients with fever. In these studies, moving consent and measurement of the vital signs forward (that is, to the waiting time) could result in partial improvement of the inclusion rates.

Comparison with existing literature

In this study, GPs measured a complete set of vital signs in only one-fifth of patients. The respiratory rate was measured least (31.5%) and less often than in other studies, but

blood pressure, heart rate, and temperature were measured more frequently.[6,12] A possible explanation lies in the study design. Although GPs were asked to perform their work-up as they normally would, they may have measured more vital signs than usual owing to the presence of research students (Hawthorne effect).[13] This overestimation might also have occurred in other studies, as GPs were asked to recall their last-referred patient with a serious infection, causing possible recall bias.[6,12] How GPs decide if and which vital signs they measure in a patient is not known, but may depend on habit or ritual, or even a patient's expectations. In addition, GPs' association of some vital signs with disease severity may play a role (for example, blood pressure in relation to shock). One could argue that GPs sometimes decide to refer a patient on the basis of one or two vital signs, and measuring the others is therefore redundant. The authors, however, would like to argue against this. Although measuring all vital parameters may not necessarily affect the referral decision, complete information on a patient's current vital sign status is indispensable for identifying trends and urgency throughout the acute care chain.

The respiratory rate was measured in only a minority of patients. Explanations include the fact that the respiratory rate is mostly measured manually and the belief measuring it wastes valuable time.[14-19] Not only was it measured least, but also the respiratory rate was most frequently reported back to the GP after it was found to be abnormal by the research students (n = 32). Not once did this change the decision whether or not to refer the patient; almost half (46.9%) of these patients were not referred to the ED. The most likely explanation is that the respiratory rate does not solely determine the decision to refer. Some patients may always have an elevated respiratory rate or their other vital signs are reassuring. Another possibility is that GPs underestimate the prognostic value of an elevated respiratory rate, but the extensive attention this specific vital sign has received over the past years makes this less likely. Finally, the cut-off point of >20/min could be inadequate for primary care settings. It is likely that GPs assess many patients with an elevated respiratory rate who recover without complications, making them less aware of mild elevations. The true value of the respiratory rate in primary care settings can only be determined once accurately measured in all patients.

Another important finding is that 35 patients with positive SIRS scores and one patient with a positive qSOFA score were not referred to the ED. In general, this turned out to be a safe approach, as none of these were admitted to the ICU or died. However, 14.3% of the initially not referred patients were admitted to the hospital within 7 days of the primary consultation. In a recent survey, GPs' knowledge of the SIRS criteria was substantially higher than of the qSOFA.[20] It is therefore somewhat surprising that the majority (66.7%) of patients who were admitted to the hospital within 7 days after the initial GPC visit had a positive SIRS score using the vital signs initially measured by the GP.

This shows that positive SIRS scores do not automatically trigger a specific assessment or treatment protocol. The probability of finding a patient with sepsis differs substantially between the primary care and hospital setting. Since GPs do not measure all vital signs needed to calculate these scores and not all patients with positive scores are referred, it is likely that SIRS and qSOFA scores alone do not determine the decision to refer a patient with fever to the ED.

To further investigate GPs' referral strategies, GPs were asked to complete the GFQ.[7] Like others, an association was found between the presence of a sense of alarm and referral.[7,8] Five (14.7%) of the patients who were not referred raised a sense of alarm. A possible explanation may be that the GFQ does specify why there is a sense of alarm, which could be caused, for example, by the suspicion of an underlying malignancy. As with vital signs, referral decisions could not be explained by gut feeling alone.

Implications for research and practice

In the present study, GPs measured a complete set of vital signs in one-in-five patients with fever. Although associations were found between some vital signs, clinical rules, gut feeling, and ED referral, the decision to refer a patient is probably multifactorial. Future research may focus on the diagnostic and prognostic value of vital signs, the use of point-of-care tests, such as lactate and/or C-reactive protein, and gut feeling in primary care to help develop diagnostic algorithms for GPs that aid in the decision to refer. For these algorithms to work adequately, systematic measurement and recording of vital signs is indispensable, either manually or by using electronic devices.

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APPENDIX

Appendix 1

Appendix 1. Patients admitted within 7 days after initial GPC visit		
Baseline characteristics (n=9)		
Male	2 (22.2%)	
Age, years	73 (45-86)	
Clinical rules (n=9)	GP	GP + investigator
Complete set of vital signs[a]	1 (11.1%)	9 (100%)
SIRS ≥2	6 (66.7%)	7 (77.8%)
qSOFA ≥2	0	0
Gut feeling (n=5)		
Sense of alarm present	2 (40.0%)	

Values presented as n (%) or median (IQR)
a Complete set of vital signs = blood pressure, heart rate, respiratory rate, temperature, and GCS
Abbreviations: GPC – General Practitioner Cooperative, GP – General Practitioner, SIRS – Systemic Inflammatory Response Syndrome, qSOFA – quick Sequential Organ Failure Assessment

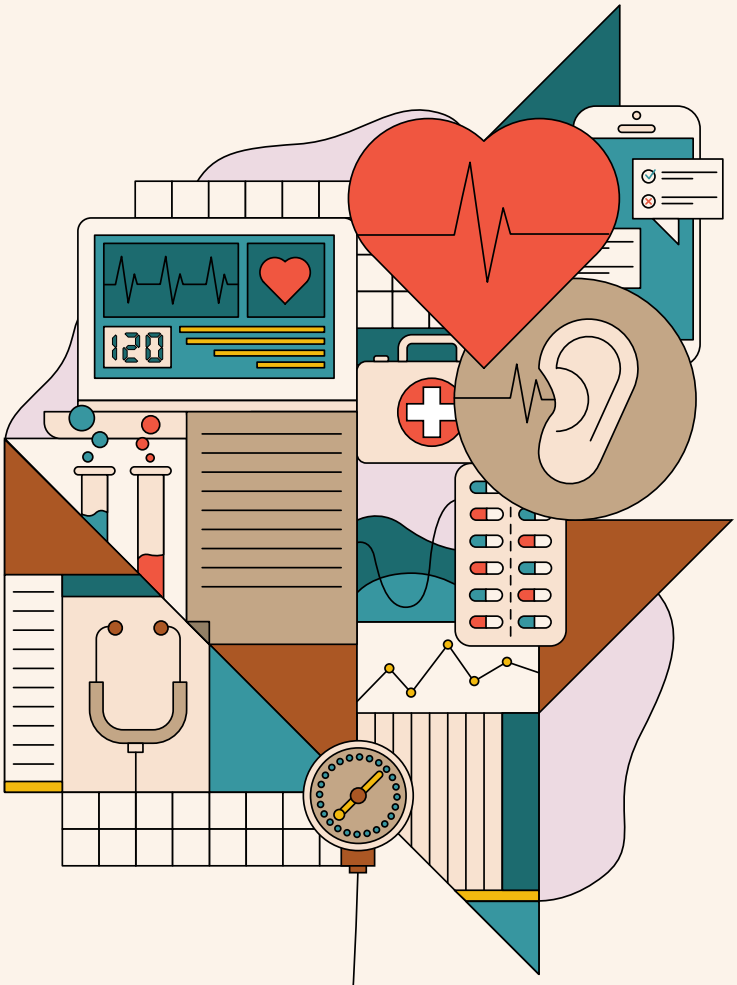
Appendix 2

Gut Feelings Questionnaire	Completely disagree	Disagree	Neutral	Agree	Completely agree
	1	2	3	4	5
1. Please indicate what kind of gut feeling you have at the end of the consultation. If you cannot answer this question now, please answer the following nine questions, then give your answer to question 1, which is repeated at the end of the questionnaire. O something is wrong with this picture. O everything fits. O impossible to say, or not applicable.					
2. It all adds up. I feel confident about my management plan and/or about the outcome.	O	O	O	O	O
3. Something does not add up here. I am concerned about this patient's state of health.	O	O	O	O	O
4. In this particular case, I will formulate provisional hypotheses with potentially serious outcomes and weigh them against each other.	O	O	O	O	O
5. I have an uneasy feeling because I am worried about potentially unfavourable outcomes.	O	O	O	O	O
6. To prevent any (further) serious health problems this case requires specific management.	O	O	O	O	O
7. This patient's situation gives me reason to arrange a follow-up visit sooner than usual or to refer him or her more quickly than usual to a specialist.	O	O	O	O	O
8. What diagnoses (or diagnosis) do you have in mind? (max. 3) …….. …….. ……..					
9. What management have you chosen? (Please tick one answer.) I will… O not yet take action; wait and see. O not yet take action, but advise the patient to come back if the problem persists. O not yet take action, but invite the patient for a follow-up appointment. either face-to-face or by phone. O order further testing (laboratory tests, X-rays, etc.). O order further testing, and in the meantime, I will start treatment (medicinal or other). O start treatment, but will not arrange a follow-up. O start treatment and give the advice to the patient to come back if the problem persists. O start treatment and invite the patient for a follow-up appointment. either face-to-face or by phone. O refer the patient.					
10. Which diagnosis has determined your management? …….					
11. This question is the same as question 1. If you have already given an answer, there is no need to answer this question again. Please indicate what kind of gut feeling you have at the end of the consultation: O something is wrong with this picture. O everything fits. O impossible to say, or not applicable. If you want to share some thoughts about your diagnostic reasoning, please use the back of this questionnaire.					

Gut Feeling Questionnaire Cut-off points

To determine when there is a sense of alarm, a sense of reassurance or gut feelings are not applicable, the COGITA group found consensus about cut-off values:

- A sense of alarm is considered to be present when the answer to item 1 or 11 indicates a sense of alarm or when the answer to item 1 or 11 indicates that it is not applicable and at least one of the scores of items 3-7 is higher than 3/5.
- A sense of reassurance is considered to be present when the answer to items 1 or 11 indicates a sense of reassurance or when the answer to items 1 or 11 indicates that it is not applicable and the score for item 2 is higher than 3/5.
- It is considered that there has not been any type of gut feeling when the answer to items 1 or 11 indicates that it is not applicable, none of the scores of items 3-7 is higher than 3/5 and the score for item 2 is lower than 4/5.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CHAPTER 4

HOW WELL ARE SEPSIS AND A SENSE OF URGENCY DOCUMENTED THROUGHOUT THE ACUTE CARE CHAIN IN THE NETHERLANDS? A PROSPECTIVE OBSERVATIONAL STUDY.

Gideon H.P. Latten

Kirsten Hensgens

Eefje G.P.M. de Bont

Jean W.M. Muris

Jochen W.L. Cals

Patricia M. Stassen

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ABSTRACT

Objective

To investigate the documentation of sepsis and a sense of urgency throughout the acute care chain.

Design

Prospective cohort study.

Setting

Emergency department (ED) in a large district hospital in Heerlen, The Netherlands.

Participants

Participants included patients ≥18 years with suspected sepsis who visited the ED during out-of-hours between September 2017 and January 2018 (n=339) and had been referred by a general practitioner and/or transported by ambulance. We defined suspected sepsis as suspected or proven infection and the presence of ≥2 quick Sepsis-related Organ Failure Assessment and/or ≥2 Systemic Inflammatory Response Syndrome criteria.

Outcome measures

We analysed how often sepsis and a sense of urgency were documented in the prehospital and ED medical records. A sense of urgency was considered documented when a medical record suggested the need of immediate assessment by a physician in the ED. We described documentation patterns throughout the acute care chain and investigated whether documentation of sepsis or a sense of urgency is associated with adverse outcomes (intensive care admission/30-day all-cause mortality).

Results

Sepsis was documented in 16.8% of medical records and a sense of urgency in 22.4%. In 4.1% and 7.7%, respectively, sepsis and a sense of urgency were documented by all involved professionals. In patients with an adverse outcome, sepsis was documented

more often in the ED than in patients without an adverse outcome (47.9% vs 13.7%, p<0.001).

Conclusions

Our study shows that in prehospital and ED medical records, sepsis and a sense of urgency are documented in one in five patients. In only 1 in 20 patients sepsis or a sense of urgency is documented by all involved professionals. It is possible that poor documentation causes harm, due to delayed diagnosis or treatment. Hence, it could be important to raise awareness among professionals regarding the importance of their documentation.

INTRODUCTION

Sepsis is a potentially lethal syndrome, and its incidence is still rising.[1] Prior to emergency department (ED) arrival, many patients with sepsis have one or more contacts with a general practitioner (GP) and/or emergency medical services (EMS).[2,3] As early recognition and treatment can improve outcome, prehospital professionals are key players in the recognition and management of patients with sepsis.[4,5] This is especially true during out-of-hours (OOH), when patients are assessed by GPs on duty, who most often do not know the patient and his or her history and comorbidities.

To date, it is not exactly known how well sepsis is recognised and documented by healthcare professionals working in acute care during OOH. A few studies, mainly focusing on EMS, have found documentation rates between 10% and 40%.[3,6,7] In addition, the urgency with which patients need to be treated is often not mentioned.[8] Possible explanations for these low rates include the absence of a gold standard for sepsis and a lack of awareness that adequate documentation of both the diagnosis and the urgency of sepsis is important.

In other time-dependent conditions such as stroke or acute coronary syndrome (ACS), early recognition and interventions to increase awareness among health professionals on the importance of timely diagnosis and treatment have been shown to improve survival substantially.[9-11] Due to improved awareness and specific care systems, patients with a possible stroke or ACS immediately raise a sense of urgency. Taking the similar mortality rates of stroke, ACS and sepsis into account, one could assume that documenting sepsis when referring or transporting a patient to the hospital will also directly generate a sense of urgency. It is likely, however, that physicians in (crowded) EDs will prioritise patients, even across those meeting sepsis criteria, as not all patients with sepsis are equally ill. To our knowledge, no studies have investigated the documentation of a sense of urgency in acute care chain medical records, in relation to documentation of 'sepsis'.

In this prospective, observational study of ED patients with suspected sepsis, we investigated (1) how often the suspicion of sepsis is documented throughout the acute care chain during OOH, (2) how often a sense of urgency is documented throughout the acute care chain, and (3) the association between documentation of sepsis and the documentation of a sense of urgency. Fourth, we investigated the association of documentation of sepsis or a sense of urgency with adverse outcomes (intensive care admission and/or 30-day mortality).

METHODS

Design and setting

In this study, ED patients with suspected sepsis were enrolled prospectively, after which their medical records (i.e. GP referral letters, EMS charts and ED charts) were reviewed retrospectively. We included patients at the ED in a large district hospital providing care to a region with 260,000 inhabitants (Zuyderland Hospital Heerlen, the Netherlands), during OOH (Monday through Friday from 17:00 to 08:00, and during weekends) between 2 September 2017 and 6 January 2018. The ED in Heerlen provides general and specialised acute medical care to the region, including patients referred by GPs and EMS. Less than 3% of ED patients are walk-ins (i.e. unreferred, without involvement of GP and/or EMS), which is a common percentage in the Netherlands.[12] We focused on patients during OOH as the co-located GP cooperative provides a digital referral for nearly 100% of patients.

OOH primary care in the Netherlands is organised in large-scaled GP cooperatives, which serve as the first step in emergency care. At these cooperatives, 50–150 GPs take rotating shifts during OOH. For OOH medical complaints, patients have to contact their nearby GP cooperative by telephone. If physical assessment by a GP is deemed necessary based on the telephone triage system (Netherlands Triage Standard, NTS), they can either get a GP appointment at the cooperative's facility or be scheduled for a home visit by a GP.[13] GPs have a gate-keeping function in the Netherlands, which means that most patients are seen by a GP before they are referred to an ED. The location of the participating cooperative in this study – adjacent to the ED – is customary in the Netherlands.[14]

For life-threatening complaints, patients are supposed to call the national emergency telephone number (112). If a patient inadvertently calls the GP cooperative and life-threatening complaints are suspected, immediate assessment by EMS is ordered. EMS nurses in the Netherlands are highly trained, usually with experience in acute and/or intensive care. They treat and, if necessary, transport the patient to the ED. Similar to the GP cooperatives' triage, EMS dispatch codes are assigned by the ambulance dispatch centre, using NTS.[13] A1 is the most urgent category, indicated for life-threatening situations. A2 is urgent but not life-threatening, and B is for non-urgent conditions.

When a GP refers a patient to the ED, he/she informs the receiving physician – usually a senior staff member – by telephone, and writes a (digital) referral letter from the patient's medical record, which includes the reason for referral, vital signs, and relevant comorbidities and medication. This letter is immediately available for the treating physician in the ED, but not always for the EMS. They rely on a summary of information, supplied by the EMS dispatch centre and the GP on site. In our ED, triage levels are determined using the Dutch version of the Manchester Triage System.[15-17]

We used the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for reporting this observational study.[18]

Patients

All patients ≥18 years old with suspected sepsis who visited the ED during OOH and had been referred by a GP and/or transported by EMS were included. We defined suspected sepsis as suspected or proven infection and the presence of ≥2 quick Sepsis-related Organ Failure Assessment (qSOFA) and/or ≥2 Systemic Inflammatory Response Syndrome (SIRS) criteria, based on the vital signs and laboratory results measured in the ED.[1,19] We included patients who had been referred by a GP and/or transported by EMS. We used qSOFA, as it is considered a risk stratification tool for adverse outcomes in patients with an infection.[1] However, the sensitivity of qSOFA has been found to be low when used as a screening tool for sepsis.[20,21] We therefore included patients with ≥2 SIRS criteria as well.

Patients were excluded if they were walk-ins or had been referred by a different physician than a GP (e.g. elderly care physician), in case of an ED diagnosis of sterile inflammation (e.g. pancreatitis, pericarditis), and when a patient visited the ED for a second time during the inclusion period. The screening process for eligibility was conducted by two independent researchers, according to an established protocol. Follow-up data (30 days after hospital discharge) were obtained by retrieval of hospital records or by telephone contact with the patient's GP.

Data collection

Patient data were collected using a case report form, comprising data from the patient's medical records. We retrieved general patient information, as well as information regarding the patient's referral pathway (GP, EMS, ED, hospital).

Definitions

Comorbidities were quantified using the Charlson Comorbidity Index.[22] For the calculation of SIRS and qSOFA, the most abnormal vital parameters (blood pressure, heart rate, respiratory rate, oxygen saturation, Glasgow Coma Scale, temperature) in the ED were used. Adverse outcomes were defined as intensive care unit (ICU) admission, 30-day all-cause mortality or both.

We retrieved the documentation of the word 'sepsis' (literally) and the documentation of a sense of urgency. The documentation of a sense of urgency (yes/no) was based on the complete text in each medical record (i.e. not on the documentation of 'sepsis' alone). This was judged by an assessment panel of three acute healthcare professionals (a GP, an acute internist and an ED consultant) who independently assessed patients' medical records. The medical records were anonymised and randomly shuffled in such a way that the assessors could not match (GP, EMS, ED) records of a patient in the acute care chain.

In addition, the assessors were blinded to the clinical outcomes of patients after the ED visit. A record was considered to have documented a sense of urgency when it suggested that the patient was in need of immediate assessment by a physician in the ED. No specific cues were provided to the panel, as their judgement regarding the sense of urgency reflects daily practice. In case of disagreement, the panel discussed the case face-to-face, aiming to reach consensus. In case of persistent disagreement, the majority rule was applied.

Analyses

Descriptive analysis was performed in order to provide insight into the baseline patient characteristics and referral pathways. We analysed how often sepsis and a sense of urgency were documented in the medical records. We described the patterns of documentation of both sepsis and a sense of urgency throughout the acute care chain. In order to test the hypothesis that 'sepsis' is documented more often in patients with a documented sense of urgency, we analysed the association and agreement between these two. Finally, we investigated whether there was an association between the documentation of sepsis or a sense of urgency and adverse outcomes (ICU admission and/or 30-day mortality).

Statistical methods

All statistical analyses were performed using IBM SPSS V.25 statistical software. Continuous data were reported as mean with SD and compared using Student's t-test, or as median with IQR, and compared using the Mann-Whitney U test. We reported categorical data as absolute numbers and as valid percentages (to correct for missing data); these were compared using $\chi 2$ or Fisher's exact tests. A p value <0.05 was considered statistically significant.

Regarding the documentation of a sense of urgency, we calculated the number of medical records in which there was immediate agreement between the three professionals and the proportion in which there was agreement after face-to-face discussion. Fleiss kappa values were calculated to determine the level of agreement.

To investigate the association between the documentation of sepsis and a sense of urgency, we calculated OR with 95% CI. We reported kappa values for the agreement between the documentation of sepsis and a sense of urgency. Kappa values of 0.6–0.8 represent moderate, values of 0.8–0.9 strong, and values >0.9 almost perfect agreement.[23]

For this study, we calculated the minimum sample size to be able to detect a difference in sepsis documentation of 25% between patients with and without an adverse outcome. With an estimated adverse event rate of 12.5%, and documentation of sepsis at least once in 50% of patients with and in 25% of patients without an adverse outcome, we required 35 patients with an adverse outcome and 280 without one, resulting in a target sample size of 315 patients.

RESULTS

Patients and referral pathways

We recruited 339 patients with (suspected/proven) infection and ≥2 SIRS and/or qSOFA criteria who visited the ED during OOH, with a median age of 68 years (Table 1). Of all patients, 269 (79%) were referred by the GP and 193 (57%) were assessed and transported by EMS. The included 339 patients had a total of 800 medical records: 268 GP referral letters, 193 EMS charts and 339 ED charts. Of these, 16 GP referral letters and 2 EMS charts could not be retrieved, leaving 782 complete medical records available for analysis.

Table 1 – Baseline patient characteristics (n=339)

General	
Age – years	68 (53-78)
Male	151 (44.5%)
Comorbidities (CCI)	1 (0-2)
Referral pathway	
Referred by GP	268 (79.1%)
Transport by EMS	193 (56.9%)
Referral pathway, contact with:	
GP+EMS+ED	122 (35.6%)
GP+ED	146 (43.1%)
EMS+ED	71 (20.9%)
EMS dispatch code (n=185)[a]	
A1	77 (41.6%)
A2	83 (44.9%)
B	25 (13.5%)
Emergency department	
qSOFA ≥2	47 (13.9%)
SIRS ≥2	336 (99.1%)

Values are n (%) for ordinal variables and median (IQR) for continuous variables.
Abbreviations: CCI – Charlson Comorbidity Index, ED – emergency department, EMS – emergency medical services, GP – general practitioner, qSOFA – quick Sepsis-related Organ Failure Assessment, SIRS – Systemic Inflammatory Response Syndrome.
a Eight missing.

Documentation of sepsis

Sepsis was literally documented in 131 (16.8%) of the 782 records (Figure 1). GP referral letters contained the word 'sepsis' in 35 (13.9%), EMS charts in 33 (12.3%) and ED charts in 63 (18.6%) cases. In 92 (27.1%) patients, sepsis was documented by at least one healthcare professional in the acute care chain.

The different patterns of sepsis documentation in the acute care chain are illustrated in Figure 2. In 14 (4.1%) patients, all involved professionals documented sepsis, while in 247 (72.9%) none mentioned it. In all other cases (n=78, 23.0%), sepsis was documented at least once, but not by all professionals.

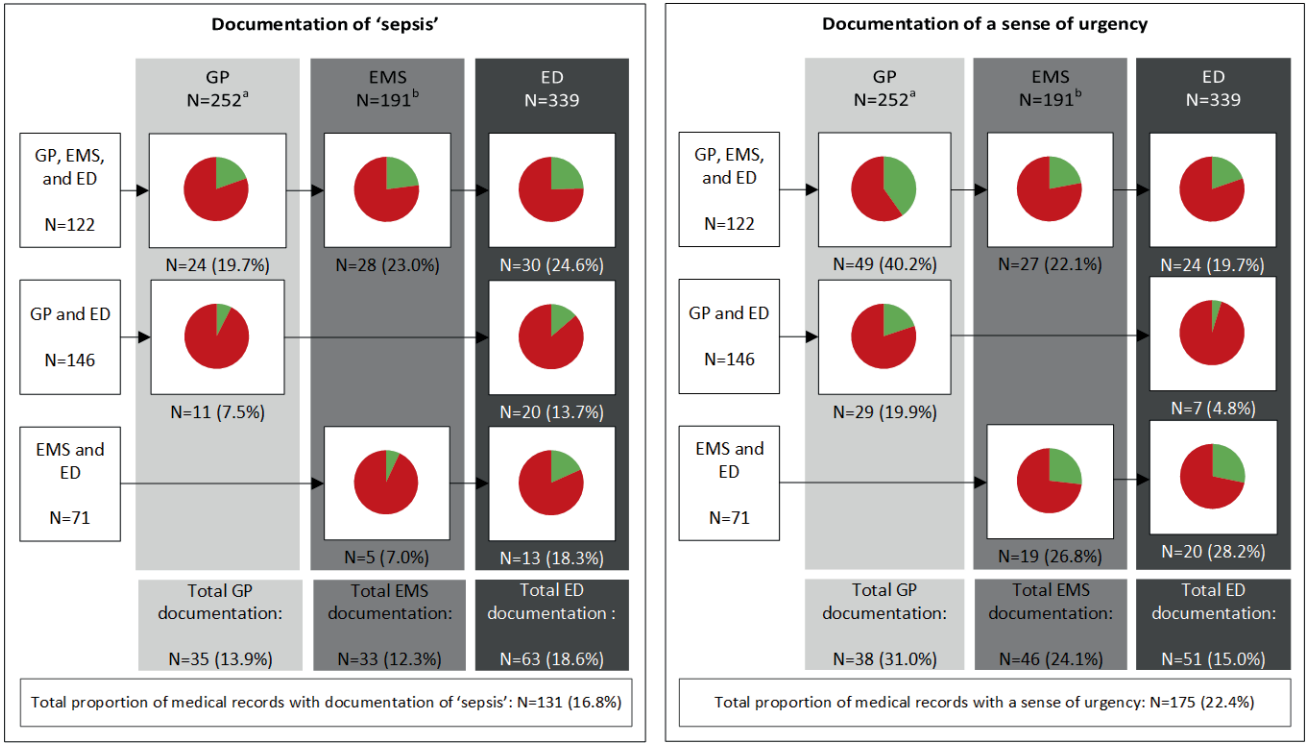
Sense of urgency

The assessment panel agreed on the sense of urgency being present or absent in 515 (65.9%) cases (Appendix 1). Face-to-face discussion was necessary for 267 (34.1%) medical records. After discussion, agreement was reached for 90.5% of records. Fleiss kappa values varied between 0.36 and 0.43 before discussion, and between 0.71 and 0.91 after discussion.

In the end, the panel agreed that in 175 (22.4%) medical records, a sense of urgency was documented (Figure 1). GPs documented a sense of urgency in 38 (31.0%), EMS in 46 (24.1%) and ED physicians in 51 (15.0%) cases. In 123 (36.3%) patients, a sense of urgency was documented in at least one record within the acute care chain.

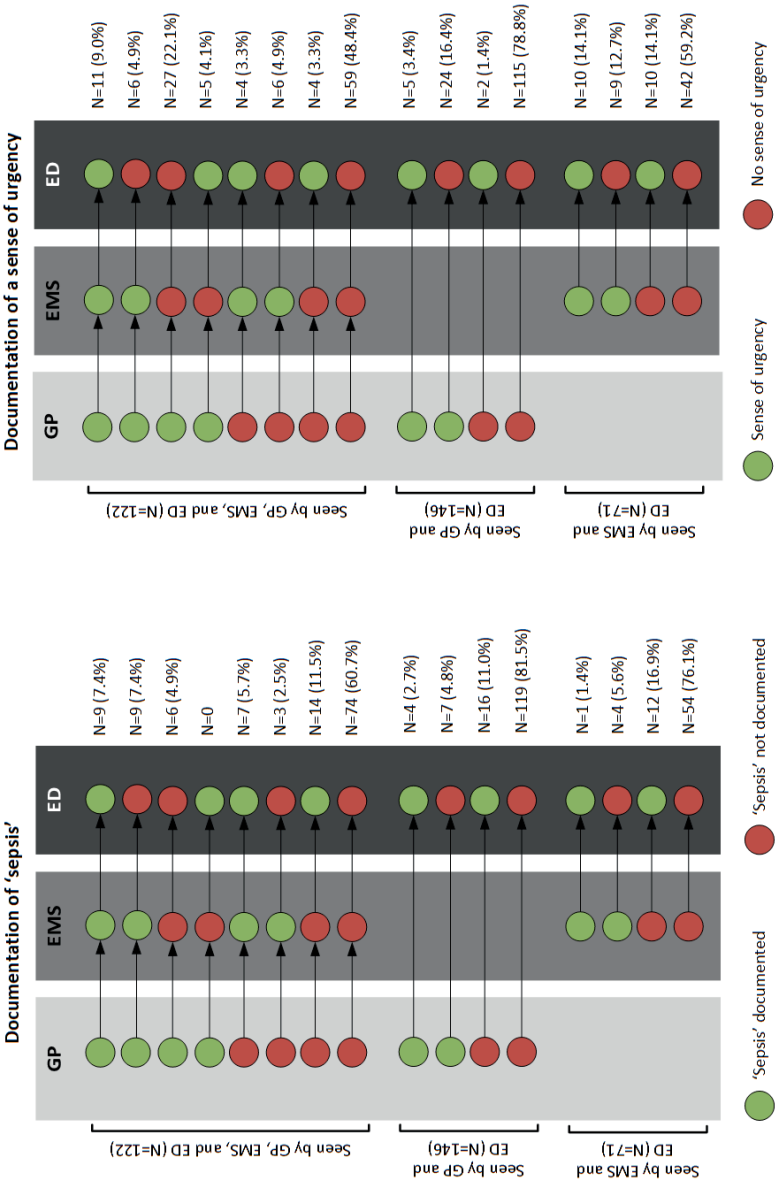
Figure 2 shows the different patterns in the acute care chain of the documented sense of urgency in medical records. In 26 (7.7%) patients, all medical records contained a sense of urgency, and in 216 (63.7%) none did.

Figure 1 – Documentation of sepsis and of a sense of urgency in medical records



Values are n (%)
a 16 missing; b 2 missing
Left figure – documentation of sepsis: green = sepsis documented, red = sepsis not documented.
Right figure – documentation of a sense of urgency: green = sense of urgency documented, red = no sense of urgency documented.
Abbreviations: ED – emergency department, EMS – emergency medical services, GP – general practitioner

Figure 2 - – Patterns of documentation of sepsis and of a sense of urgency



Values are n (%)
Abbreviations: ED – emergency department, EMS – emergency medical services, GP – general practitioner

Association and agreement between the documentation of 'sepsis' and a sense of urgency

In 71 (9.1%) medical records, 'sepsis' as well as a sense of urgency were documented (Table 2). In 547 (69.9%) records, neither was documented.

We found a significant association between the documentation of sepsis and the documentation of a sense of urgency. ORs varied between 2.9 for EMS charts and 16.6 for GP referral letters. Kappa values for the agreement between the documentation of 'sepsis' and a sense of urgency were 0.40 for GP referral letters, 0.19 for EMS charts and 0.39 for ED charts.

Table 2 –Association and agreement between the documentation of sepsis and of a sense of urgency

			Sense of urgency documented		OR (95% CI)	p	kappa
			Yes	No			
GP referral letters	Sepsis documented	Yes	29	6	16.6 (7-42)	<0.001	0.40
		No	49	168			
EMS charts	Sepsis documented	Yes	14	19	2.9 (1-6)	0.007	0.19
		No	32	126			
ED charts	Sepsis documented	Yes	28	35	8.8 (5-17)	<0.001	0.39
		No	23	253			

Abbreviations: OR – odds ratio, GP – general practitioner, EMS – emergency medical services, ED – emergency department

Comparison between patients with and without an adverse outcome

In total, 48 (14.2%) patients experienced an adverse outcome. ICU admission was necessary for 36 (10.6%) patients and 16 (4.7%) died within 30 days (Table 3). In patients with an adverse outcome, 'sepsis' was more often documented at least once in the acute care chain (54.2% vs. 22.7%, p<0.001). We found 'sepsis' to be documented more often in ED records of those with than in those without an adverse outcome (47.9% vs. 13.7%, p<0.001), but this pattern was not found in GP and EMS medical records. Throughout the acute care chain, a sense of urgency was documented more often in patients with an adverse outcome than in patients without one (Table 3).

Table 3 – Comparison between patients with and without an adverse outcome			
	Adverse outcome (n=48, 14.2%)	No adverse outcome (n=291, 85.8%)	p
General			
Age – years	68 (60-82)	68 (52-77)	0.35
Male	21 (43.8%)	130 (44.7%)	0.91
Comorbidities (CCI)	2 (1-3)	1 (0-2)	0.08
Referral pathway			
Referred by GP	35 (72.9%)	233 (80.1%)	0.26
Transport by EMS	35 (72.9%)	158 (54.3%)	0.02
Referral pathway, contact with:			0.05
GP+EMS+ED	22 (45.8%)	100 (34.4%)	
GP+ED	13 (27.1%)	133 (45.7%)	
EMS+ED	13 (27.1%)	58 (19.9%)	
EMS dispatch code (n=185)[a]			0.88
A1	15 (45.5%)	62 (40.8%)	
A2	14 (42.4%)	69 (45.4%)	
B	4 (12.1%)	21 (13.8%)	
Emergency department			
qSOFA ≥2	20 (41.7%)	27 (9.3%)	<0.001
SIRS ≥2	48 (100%)	288 (99.0%)	0.48
Sepsis documentation			
Documentation of sepsis in:			
GP letter	6/31 (19.4%)	29/221 (13.1%)	0.35
EMS chart	6/35 (17.1%)	27/156 (17.3%)	0.98
ED chart	23/48 (47.9%)	40/291 (13.7%)	<0.001
Sepsis documented in ≥1 record	26 (54.2%)	66 (22.7%)	<0.001
Sense of urgency documentation			
Sense of urgency documented in:			
GP letter	17/31 (54.8%)	61/221 (27.6%)	0.002
EMS chart	17/35 (48.6%)	29/156 (18.6%)	<0.001
ED chart	27/48 (56.3%)	24/291 (8.2%)	<0.001
Sense of urgency documented in ≥1 record	35 (72.9%)	88 (30.2%)	<0.001

Values are n (%) for ordinal variables and median (IQR) for continuous variables, unless otherwise specified.
Abbreviations: CCI – Charlson Comorbidity Index, ED – emergency department, EMS – emergency medical services, GP – general practitioner, qSOFA - quick Sepsis-related Organ Failure Assessment, SIRS – Systemic Inflammatory Response Syndrome
a 8 missing
b 16 missing
c 2 missing

DISCUSSION

Main findings

In this prospective observational study, we found that in ED patients with suspected sepsis, the word 'sepsis' was literally documented in 16.8% of all prehospital and ED medical records. In only 4.1% of patients 'sepsis' was documented by all professionals involved in the acute care chain. We found similar results for the documentation of a sense of urgency. Despite a significant association between the documentation of 'sepsis' and of a sense of urgency, agreement between these two was low (kappa 0.19–0.40). In patients with an adverse outcome, sepsis and a sense of urgency were documented more often than in patients without an adverse outcome.

Comparison with existing literature

In our study, 'sepsis' was documented at least once in the acute care chain in 27.1% of patients. Previous studies found similar results, with prehospital documentation rates between 10% and 40%.[3,6,7] A likely contributor to poor recognition is the absence of a gold standard test for sepsis. Furthermore, loss of information and semantics (e.g. documenting pneumonia instead of pneumosepsis) are possible explanations. It is also possible that the term 'sepsis' does not cover the severity of the disease or the professional's sense of urgency.

An important finding in our study is the fact that 'sepsis' was documented by all professionals in only 4.1% of patients. Poor handover strategies, disagreement between professionals and varying vital signs over time are possible explanations. In our region, GPs and EMS use digital handovers. These are transmitted directly to the ED (and are thus immediately available), but EMS personnel cannot see the complete GP's handover. Therefore, they rely on a summary of information, supplied by the EMS dispatch centre, supplemented by an analogue letter supplied by the GP. Direct verbal handover may reduce loss of information in these situations, but an adequate written handover is still necessary, as previous research has shown that a substantial amount of information is lost in verbal handovers.[8,24]

In addition to documentation of 'sepsis', we were, to our knowledge, the first to also investigate the documentation of a sense of urgency in medical records. In only 7.7% of patients all medical records of the same patient documented a sense of urgency. When we compared the documentation of 'sepsis' with the documentation of a sense of urgency in the medical records, we found a significant association between these two (OR 6.2). However, agreement was low with kappa values of 0.40 for GP referral letters, 0.19 for EMS charts and 0.39 for ED charts. This may suggest two things. First, mentioning 'sepsis' in a medical record does not automatically generate a sense of urgency. Possibly,

professionals use the word 'sepsis' when a patient meets a specific set of criteria (e.g. SIRS criteria), even when they do not consider the patient to be severely ill. Second, patients who do not appear severely ill are not considered to be 'septic'. Either can be caused by professionals not considering sepsis as the most important differential diagnosis, the lack of a gold standard test and the belief documenting sepsis is not useful.[8]

When comparing patients with and without an adverse outcome, we found that ED charts of patients with an adverse outcome more often contained the word 'sepsis' (47.9% vs. 13.7%, $p<0.001$), which is in line with previous studies.[25] We did not find this difference in prehospital (GP, EMS) documentation, possibly due to the fact that the suspicion of sepsis can be made more definite once diagnostics—leucocytes or partial pressure of carbon dioxide, both SIRS criteria—are performed in the ED. Noteworthy is that we found that GP and EMS medical records of patients with an adverse outcome significantly more often documented a sense of urgency than those without an adverse outcome (GP 54.8% vs. 27.6%; EMS 56.3% vs. 8.2%). This suggests that these professionals acknowledged the urgency with which these patients needed to be treated, but that they did not document sepsis or did not consider this as a differential diagnosis. Half of the medical records of those with an adverse outcome, however, still did not contain a sense of urgency. This suggests there is still room for improvement.

Strengths and limitations

Our study has two major strengths. First, to our knowledge, this is the first study comparing OOH documentation of 'sepsis' with the presence of a sense of urgency in acute care chain medical records. Second, our study had only 2.3% missing medical records. Our results therefore reflect a best-case scenario. It is likely that in daily practice, there is more missing information due to lost records, causing poorer results than found in our study. A limitation could be that we investigated written documentation without taking verbal handovers into account. It is possible that GPs mentioned sepsis over the phone, but did not document it, especially in patients requiring urgent care. Prehospital medical records, however, should be an adequate representation of the information that needs to be communicated, especially since there can be loss of information within the hospital as well. Second, we defined 'sepsis' based on vital signs in the ED. It is possible that prior to ED arrival, patients did not meet sepsis criteria, or that laboratory results—available only in the ED—made the diagnosis of sepsis more likely.[7] Finally, the subjectivity in judgement of handovers by three healthcare professionals may be a limitation. After discussion, there was still disagreement in 9.8% of the records by the assessment panel, showing how difficult it is to adequately judge documented information on this topic.

Conclusion and implications

In conclusion, our study shows that in prehospital and ED medical records, sepsis and a sense of urgency are documented in one out of five patients. In only 1 out of 20 patients sepsis or a sense of urgency is documented by all involved professionals in the acute care chain. It is possible that poor documentation causes harm, due to delayed diagnosis or treatment. Hence, it could be important to raise awareness among healthcare professionals regarding the importance of their documentation. Our study provides a basis for future, preferably qualitative, research investigating why 'sepsis' and a sense of urgency are documented so infrequently in handovers; is it uncertainty about the diagnosis, lack of knowledge or disagreement regarding the severity of illness? If it is found that professionals are hesitant to mention 'sepsis', since they are not certain of the diagnosis, this should be a target for future interventions. Similar to myocardial infarction and stroke, patients are sent to the ED with a probability diagnosis, and once a prehospital professional suspects sepsis this suspicion should be carried on throughout the acute care chain.

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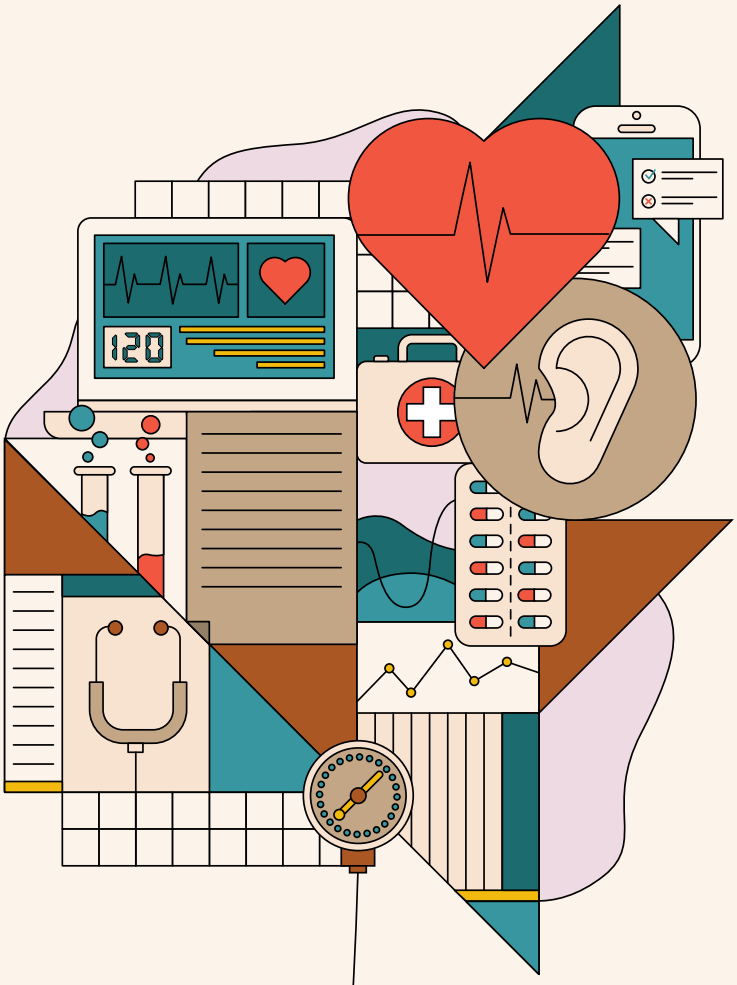
APPENDIX

Appendix 1 – Agreement between professionals regarding sense of urgency					
Medical records	Immediate agreement	k	Agreement after discussion	k	Majority rule applied
GP referral letters (n=252)	144 (57.1%)	0.36	226 (89.7%)	0.83	26 (10.3%)
EMS charts (n=191)	121 (63.4%)	0.43	181 (94.8%)	0.91	10 (5.2%)
ED charts (n=339)	250 (73.7%)	0.43	301 (88.8%)	0.71	38 (11.2%)

Values are n (%), unless otherwise specified
Abbreviations: GP – general practitioner, EMS – emergency medical services, ED – emergency department

PART II

Severe infections – vital signs and clinical rules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CHAPTER 5

FREQUENCY OF ALTERATIONS IN QSOFA, SIRS, MEWS AND NEWS SCORES DURING THE EMERGENCY DEPARTMENT STAY IN INFECTIOUS PATIENTS: A PROSPECTIVE STUDY.

Gideon H.P. Latten

Judith Polak

Audrey H.M. Merry

Jean W.M. Muris

Jan C. Ter Maaten

Tycho J. Olgers

Jochen W.L. Cals

Patricia M. Stassen

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ABSTRACT

Background

For emergency department (ED) patients with suspected infection, a vital sign-based clinical rule is often calculated shortly after the patient arrives. The clinical rule score (normal or abnormal) provides information about diagnosis and/or prognosis. Since vital signs vary over time, the clinical rule scores can change as well. In this prospective multicentre study, we investigate how often the scores of four frequently used clinical rules change during the ED stay of patients with suspected infection.

Methods

Adult (≥ 18 years) patients with suspected infection were prospectively included in three Dutch EDs between March 2016 and December 2019. Vital signs were measured in 30-min intervals and the quick Sequential Organ Failure Assessment (qSOFA) score, the Systemic Inflammatory Response Syndrome (SIRS) criteria, the Modified Early Warning Score and the National Early Warning Score (NEWS) score were calculated. Using the established cut-off points, we analysed how often alterations in clinical rule scores occurred (i.e. switched from normal to abnormal or vice versa). In addition, we investigated which vital signs caused most alterations.

Results:

We included 1,433 patients, of whom a clinical rule score changed once or more in 637 (44.5%) patients. In 6.7–17.5% (depending on the clinical rule) of patients with an initial negative clinical rule score, a positive score occurred later during ED stay. In over half (54.3–65.0%) of patients with an initial positive clinical rule score, the score became negative later on. The respiratory rate caused most (51.2%) alterations.

Conclusion

After ED arrival, alterations in qSOFA, SIRS, MEWS and/or NEWS score are present in almost half of patients with suspected infection. The most contributing vital sign to these alterations was the respiratory rate. One in 6–15 patients displayed an abnormal clinical rule score after a normal initial score. Clinicians should be aware of the frequency of these alterations in clinical rule scores, as clinical rules are widely used for diagnosis and/or prognosis and the optimal moment of assessing them is unknown.

BACKGROUND

Measuring vital signs is indispensable when assessing patients with suspected infection in the emergency department (ED), as their values provide information on patients' current disease status. Vital signs are often incorporated in clinical rules, which can help establish a diagnosis and/or prognosis. Four well-known and frequently used clinical rules for medical patients in the ED are the quick Sequential Organ Failure Assessment (qSOFA) score, the Systemic Inflammatory Response Syndrome (SIRS) criteria, the Modified Early Warning Score and the National Early Warning Score (NEWS).[1-3]

In many EDs, a clinical rule score is calculated with a single set of vital signs, measured shortly after arrival. Depending on the ED's protocol, a positive – or abnormal – score can have important implications, either by triggering specific treatment protocols (e.g. for sepsis in case of qSOFA and SIRS), or by prioritising patients in crowded settings. Although these protocols are all aimed at early detection of deteriorating patients, it is known that vital signs change during a patient's ED stay, due to natural fluctuation, clinical deterioration, or improvement as a result of prehospital or ED treatment. It has not been investigated how often the scores of clinical rules change after a patient's arrival in the ED.[4]

For physicians in the ED, it would be insightful to know the frequency of these changes, specifically taking cut-off points for treatment protocols or warning triggers for escalation of care into account. This information could be used to optimise monitoring, prioritisation and decision making.

In this prospective multicentre study, we therefore aim to investigate how often the scores of four frequently used clinical rules (qSOFA, SIRS, MEWS and NEWS) change during the ED stay of patients with suspected infection and which vital signs cause most alterations.

METHODS

Design and setting

This prospective multicentre study included patients in three EDs in the Netherlands: Zuyderland Heerlen (large teaching hospital, > 30,000 ED visits/year), Maastricht University Medical Centre (MUMC+, university secondary and tertiary care teaching hospital, > 20,000 visits/year) and University Medical Centre Groningen (UMCG, university tertiary care teaching hospital, > 30,000 visits/year).

Study population

Data were collected in three inclusion periods, based on the availability of research staff per inclusion site (centre 1: 26 March 2018 – 28 April 2018, centre 2: 25 June 2018 – 3 August 2018, centre 3: 2 March 2016 – 11 December 2019). Patients visiting the ED between 8 a.m. and 11 p.m. were screened for eligibility. We included adult patients (≥ 18 years), who presented to the ED with fever (≥3 8.0 °C) and/or suspected infection and who were able to provide informed consent. The clinical suspicion of infection was judged by the staff member on duty, either an emergency physician or internist acute medicine. The judgement was based on information provided by the referring physician and information available immediately after ED triage. Examples of signs suggestive of an infection included localised signs of an infection (e.g. erythema) or specific complaints (e.g. chills and/or coughing).

Participation in the study did not alter the treatment of patients, which was at the physician's discretion. All three hospitals have a protocol for sepsis, which includes intravenous antibiotics, fluid resuscitation and oxygen supplementation.

The Institutional Review Boards of Zuyderland, The Maastricht University Medical Centre and The University Medical Centre Groningen ruled that the Dutch Medical Research Involving Human Subjects Act is not applicable and granted waivers (METCZ20180022, METC 2018-0420, METC 2015/164). All participants provided written informed consent. We used the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for reporting this observational study.[5]

Data collection

For this study, we retrieved data on age, sex and triage urgency (determined using the Dutch version of the Manchester Triage System (MTS)).[6,7]

In intervals of approximately 30 min during the patient's ED stay (T0-T3), we measured the following six vital signs: blood pressure (mmHg), heart rate (beats per minute – bpm), respiratory rate (/min), level of consciousness (Glasgow Coma Scale, GCS), temperature (°C) and peripheral oxygen saturation (%). A complete set of vital signs was defined as measurement of all six parameters. A maximum of four sets were measured (T0-T3), depending on the patient's length of ED stay. Patients with less than two complete sets were excluded from analysis, since it is not possible to investigate variation over time in these patients.

Definitions

In order to improve clarity throughout the remainder of the manuscript, we provide some additional details on the definitions used. In this study, four vital-sign based clinical rules were investigated (SIRS, qSOFA, MEWS, NEWS) (Table 1). When the values of a patient's vital signs are entered in one of these rules, they add up to a numeric value. Depending on the established cut-off points, a clinical rule can be normal (i.e. negative) or abnormal (i.e. positive). This is called the clinical rule score. As stated, these scores (normal or abnormal) can have important implications by triggering specific treatment protocols or by escalating care. Cut-off points for abnormal clinical rule scores were ≥ 2 points for qSOFA and SIRS, ≥ 4 points for MEWS and ≥ 5 points for NEWS.[1-3]

Table 1 – Clinical rules				
Clinical rule	**Included vital signs**	**Possible values**	**Normal score**	**Abnormal score**
qSOFA	Respiratory rate Level of consciousness Systolic blood pressure	0-3 points	0-1 points	≥ 2 points
SIRS	Temperature Heart rate Respiratory rate White blood cell count	0-4 points	0-1 points	≥ 2 points
MEWS	Systolic blood pressure Heart rate Respiratory rate Temperature Level of consciousness	0-14 points	0-3 points	≥ 4 points
NEWS	Respiratory rate Oxygen saturation Supplemental oxygen Heart rate Level of consciousness	0-20 points	0-4 points	≥ 5 points

Abbreviations: qSOFA, quick Sequential Organ Failure Assessment; SIRS, Systemic Inflammatory Response Syndrome; MEWS, Modified Early Warning Score; NEWS, National Early Warning Score

Statistical analysis

Descriptive analyses were performed for age, sex, triage urgency and the values of the measured vital signs. We calculated the scores of qSOFA, SIRS, MEWS and NEWS and the corresponding clinical rule score (normal/abnormal) at the different intervals (T0-T3). We analysed how often the clinical rule score changed from normal to abnormal or vice versa, and we examined whether these alterations represented a switch from an abnormal to a normal score or from a normal to an abnormal score. In addition, we investigated the different patterns in clinical rule scores that occurred during the patients' ED stay and analysed which vital signs caused most alterations. We specifically chose to perform analyses based on cut-off points, as these represent daily practice.

All statistical analyses were performed using IBM SPSS statistical software version 26 (Armonk, 2019). Continuous data were reported as means with standard deviation (SD) and compared using Students' T test or as medians with interquartile ranges (IQR) and compared using the Mann-Whitney U test. We reported categorical data as absolute

numbers and as valid percentages (to correct for missing data); they were compared using chi-square or Fisher exact tests. A P value < 0.05 was considered statistically significant.

Based on an expected proportion of patients in whom the qSOFA score changed from positive to negative or vice versa at least once being 15%, a desired precision of estimate of 2% and a confidence level of 95%, we found the minimum sample size to be 1,225 participants. Since qSOFA is currently recommended as the bedside tool for identifying poor clinical outcome in patients with (suspected) infections, we used this clinical rule to calculate the required sample size.[3]

RESULTS

Patients and vital signs

In total, 1,743 patients were included during the study period. In 1,433 (82.2%) of these patients, at least two complete sets of vital signs were measured (Table 2). Only these patients were included for analysis. The median age was 63 (IQR 51–72) years and 58.3% were male. The majority (63.1%) of patients were assigned triage urgency yellow.[7]

Table 2 – Baseline patient characteristics

		n
Age – years	63 (51-72)	1,433
Male	835 (58.3%)	1,433
Time between first and last measurement - min	158 (112-225)	1,433
Number of complete sets[a]		1,433
- 2	373 (26.0%)	
- 3	553 (38.6%)	
- 4	507 (35.4%)	
Triage urgency upon arrival at the ED		1,193
- Red	1 (0.1%)	
- Orange	233 (16.3%)	
- Yellow	904 (63.1%)	
- Green	55 (3.8%)	
Vital signs at ED arrival		
- Systolic blood pressure – mmHg	125 (111-140)	1,412
- Heart rate	75 (65-85)	1,412
- Respiratory rate – /min	19 (16-24)	1,275
- GCS	15 (15-15)	1,378
- Temperature - °C	37.5 (36.5-38.3)	1,341
- Peripheral oxygen saturation	96 (95-98)	1,404

Data are presented as median (IQR) or n (%)
Abbreviations: min – minute, GCS – Glasgow Coma Scale
a Complete set: systolic blood pressure, heart rate, respiratory rate, Glasgow Coma Scale, temperature, peripheral oxygen saturation

Alterations in clinical rule scores

In total, 637 (44.5%) patients experienced one or more alterations in the score of one of the clinical rules (Table 3). Least alterations were present in the qSOFA scores (11.2%),

whereas SIRS scores altered most often (26.4%). The total number of alterations was 1,593, of which 882 (55.4%) represented an improvement in patient status (abnormal to normal score) and 711 (44.6%) a deterioration (normal to abnormal score).

Table 3 – Alterations in clinical rule scores

	All rules	qSOFA	SIRS	MEWS	NEWS
Patients					
No alterations	796 (55.5%)	1,273 (88.9%)	1,055 (73.6%)	1,149 (80.2%)	1,059 (73.9%)
≥1 alteration[a]	637 (44.5%)	160 (11.2%)	378 (26.4%)	284 (19.8%)	374 (26.1%)
- 1 alteration		101 (7.0%)	292 (20.4%)	203 (14.2%)	240 (16.7%)
- 2 alteration		53 (3.7%)	75 (5.2%)	75 (5.2%)	120 (8.4%)
- 3 alterations		6 (0.4%)	11 (0.8%)	6 (0.4%)	14 (1.0%)
Alterations					
Total number of alterations	1593	225	475	371	522
- Switch: abnormal to normal	882 (55.4%)	120 (53.3%)	272 (57.3%)	211 (56.9%)	279 (53.4%)
- Switch: normal to abnormal	711 (44.6%)	105 (46.7%)	203 (42.7%)	160 (43.1%)	243 (46.6%)

Abbreviations: qSOFA, quick Sequential Organ Failure Assessment; SIRS, Systemic Inflammatory Response Syndrome; MEWS, Modified Early Warning Score; NEWS, National Early Warning Score

Patterns in clinical rule scores

Table 4 shows the different possible patterns of clinical rule scores during the patients' ED stay. In the majority of patients, the first scores were normal (75.6–91.5%). In this group, most scores also remained normal during ED stay (82.5–93.3%). In 6.7–17.5%, however, an abnormal score occurred later on, representing a (temporary) deterioration of the patient. Patients with an abnormal first clinical rule score had normal scores later on in 54.3–65.0%, representing a (temporary) improvement in patient status.

Table 4 – Patterns in clinical rule scores during emergency department stay

	qSOFA	SIRS	ME WS	NEWS
Total (n=1,433)				
First score negative	1,311 (91.5%)	1,083 (75.6%)	1,210 (84.4%)	1,098 (76.6%)
First score positive	122 (8.5%)	350 (24.4%)	223 (15.6%)	335 (23.4%)
First clinical rule score: negative				
Pattern	**qSOFA (n=1311)**	**SIRS (n=1083)**	**ME WS (n=1210)**	**NEWS (n=1098)**
	1,223 (93.3%)	921 (85.0%)	1,070 (88.4%)	906 (82.5%)
	424 (32.3%)	294 (27.1%)	363 (30.0%)	292 (26.6%)
	467 (35.6%)	367 (33.9%)	418 (34.5%)	371 (33.8%)
	332 (25.3%)	260 (24.0%)	289 (23.9%)	243 (22.1%)
	88 (6.7%)	162 (15.0%)	140 (11.6%)	192 (17.5%)
	12 (0.9%)	21 (1.9%)	14 (1.2%)	20 (1.8%)
	2 (0.2%)	9 (0.8%)	6 (0.5%)	8 (0.7%)
	1 (0.1%)	10 (0.9%)	5 (0.4%)	11 (1.0%)
	9 (0.7%)	11 (1.0%)	10 (0.8%)	23 (2.1%)
	9 (0.7%)	13 (1.2%)	13 (1.1%)	18 (1.6%)
	2 (0.2%)	6 (0.6%)	4 (0.3%)	8 (0.7%)
	5 (0.4%)	6 (0.6%)	12 (1.0%)	15 (1.4%)
	14 (1.1%)	24 (2.2%)	16 (1.3%)	16 (1.5%)
	5 (0.4%)	20 (1.8%)	15 (1.2%)	11 (1.0%)
	20 (1.5%)	10 (0.9%)	20 (1.7%)	28 (2.6%)
	9 (0.7%)	32 (3.0%)	25 (2.1%)	34 (3.1%)

Table 4 – continued

First clinical rule score: positive								
Pattern	**qSOFA (n=122)**		**SIRS (n=350)**		**ME WS (n=223)**		**NEWS (n=335)**	
●●●●	50 (41.0%)	13 (10.7%)	136 (38.9%)	42 (12.0%)	78 (35.0%)	17 (7.6%)	153 (45.7%)	42 (12.5%)
●●●		20 (16.4%)		52 (14.9%)		35 (15.7%)		64 (19.1%)
●●		17 (13.9%)		42 (12.0%)		26 (11.7%)		47 (14.0%)
●●●○	72 (59.0%)	9 (7.4%)	214 (61.1%)	33 (9.4%)	145 (65.0%)	24 (10.8%)	182 (54.3%)	19 (5.7%)
●●○○		5 (4.1%)		8 (2.3%)		9 (4.0%)		7 (2.1%)
●○○○		8 (6.6%)		30 (8.6%)		17 (7.6%)		17 (5.1%)
●●○●		0		8 (2.3%)		4 (1.8%)		8 (2.4%)
●○●●		2 (1.6%)		9 (2.6%)		3 (1.3%)		5 (1.5%)
●○●○		4 (3.3%)		5 (1.4%)		3 (1.3%)		6 (1.8%)
●○○●		2 (1.6%)		2 (0.6%)		3 (1.3%)		8 (2.4%)
●●○		9 (7.4%)		29 (8.3%)		19 (8.5%)		25 (7.5%)
●○○		13 (10.7%)		39 (11.1%)		23 (10.3%)		23 (6.9%)
●○●		5 (4.1%)		12 (3.4%)		7 (3.1%)		15 (4.5%)
●○		15 (12.3%)		39 (11.1%)		33 (14.8%)		49 (14.6%)

Data are presented as n (%)

Legend: grey bullet - negative clinical rule score, red bullet = positive clinical rule score

Abbreviations: qSOFA – quick Sequential Organ Failure Assessment, SIRS – Systemic Inflammatory Response Syndrome, MEWS – Modified Early Warning Score, NEWS – National Early Warning Score, ED – emergency department

Vital signs responsible for alterations in clinical rule scores

Table 5 shows which vital signs were responsible for the alterations in clinical rule scores. The respiratory rate was responsible for most alterations in all 4 clinical rules: 55.6% for qSOFA, 45.5% for SIRS, 50.9% for MEWS and 54.4% for NEWS. The least contributing vital sign for alterations in clinical rule scores was the level of consciousness (1.1–17.0%).

Table 5 – Vital signs responsible for alterations in clinical rule scores

			Responsible vital signs**					
Clinical rule	Alteration*	n	SBP	HR	RR	GCS	T	SpO2
qSOFA	Deterioration	105	59 (56.2%)		52 (49.5%)	15 (14.4%)		
	Improvement	120	58 (48.3%)		73 (60.8%)	23 (19.3%)		
	Total	225	117 (52.0%)		125 (55.6%)	38 (17.0%)		
SIRS	Deterioration	203		61 (30.0%)	98 (48.3%)		83 (40.9%)	
	Improvement	272		82 (30.1%)	118 (43.3%)		132 (48.5%)	
	Total	475		143 (30.1%)	216 (45.5%)		215 (45.3%)	
MEWS	Deterioration	160	39 (24.4%)	52 (32.5%)	87 (54.4%)	1 (0.6%)	52 (32.5%)	
	Improvement	211	40 (19.0%)	62 (29.4%)	102 (48.3%)	3 (1.4%)	107 (50.7%)	
	Total	371	79 (21.3%)	114 (30.7%)	189 (50.9%)	4 (1.1%)	159 (42.9%)	
NEWS	Deterioration	243	95 (39.1%)	67 (27.6%)	135 (55.6%)	4 (1.6%)	43 (17.7%)	117 (48.1%)
	Improvement	279	113 (40.5%)	84 (30.1%)	149 (53.4%)	4 (1.4%)	80 (28.7%)	143 (51.3%)
	Total	522	208 (39.8%)	151 (28.9%)	284 (54.4%)	8 (1.5%)	123 (23.6%)	260 (49.8%)

Data are presented as n (%)

* Deterioration – change from normal to abnormal score, Improvement – change from abnormal to normal score

** Sum of percentages can exceed 100% as more than 1 vital sign could contribute to a change in the clinical rule score

Abbreviations: qSOFA – quick Sequential Organ Failure Assessment, SIRS – Systemic Inflammatory Response Syndrome, MEWS – Modified Early Warning Score, NEWS – National Early Warning Score, SBP – systolic blood pressure, HR – heart rate, RR – respiratory rate, GCS – Glasgow Coma Scale, T – temperature, SpO2 – peripheral oxygen saturation

DISCUSSION

In this study, we investigated the frequency of alterations in qSOFA, SIRS, MEWS and NEWS scores in 1,433 patients with suspected infection during their ED stay. We showed that qSOFA alterations were present in 1 in 9 patients, SIRS in 1 in 4, MEWS in 1 in 5 and NEWS in 1 in 4. Approximately half of alterations were from a normal to an abnormal score and half vice versa. Interestingly, 6.7–17.5% of patients with an initially normal clinical rule score turned abnormal later on, while over 50% of patients with an abnormal first score turned normal later on. The respiratory rate was responsible for over half of the changes in clinical rule scores.

To our knowledge, our study is the first to investigate the effect of vital sign variation in the ED on the scores of qSOFA, SIRS, MEWS and NEWS. Even during a relatively short median ED stay of 158 min, the clinical rule score changed in 11–26% of patients. The exploration of the progression of these clinical rule scores over time is a unique feature. In contrast, most ED-based studies use a single set of vital signs, either the first or the worst values, which may provide an explanation for the known suboptimal performance of many diagnostic and prognostic clinical rules in the ED.[8-10] When using clinical rules to predict poor outcome (like sepsis), repeated measurements of vital signs can be of surplus value, since the optimal moment of assessing clinical rule scores is unknown.

It is reassuring that the over half of patients with an abnormal score at arrival turned normal during their ED stay. Possible explanations for the improvement in vital signs include adequate response to treatment and regression towards the mean. Previous studies have shown similar results: patients with sepsis tend to improve during the first 3h in the ED.[4] It is also known, however, that approximately one third of admitted medical patients with normal initial vital signs deteriorate within 24 h.[11] Depending on the clinical rule used, between one in 6–15 of our patients turned from normal to abnormal during their ED stay. Actual deterioration of these patients is the most likely explanation for this phenomenon. Since changes in vital signs can be subtle, it is not unlikely that gradual deterioration can be missed when vital signs are not measured on a regular basis. Although the clinical value of this finding has yet to be established, the potential value of repeated measurements has to be weighed against the time-consumption when performed manually or the background noise possibly created with automated or continuous measurements.

Worth mentioning as well is that a strong acute care chain is present in the Netherlands. Most ED patients are referred by a general practitioner (GP), and there is an important role for the highly trained emergency medical services (EMS) nurses.[12,13] These professionals often initiate therapy (e.g. oxygen or fluid therapy) even before a patient

arrives at the ED. As a result, vital signs may (temporarily) improve during a patient's prehospital journey. The first values measured in the ED may therefore be better than those measured at home by the GP, potentially underestimating a patient's severity of illness upon arrival in the ED. Therefore, it must be recognised that measurements taken in the ED are not 'the first measurements'. It is plausible that repeated measurements and adequate communication throughout the entire acute care chain can help optimise the care for these patients.

An interesting finding is that over half of all alterations in clinical rule scores could (partially or entirely) be attributed to variations in respiratory rate. The predictive value of the respiratory rate has long since been recognised, but the fact that it is usually measured manually reduces both the frequency and reliability of its measurements.[14-18] One could imagine that repeated manual measurements of respiratory rates in busy EDs are (too) labour intensive. We therefore feel that future research should investigate the reliability and value of non-invasive methods of either repeatedly or continuously measured respiratory rates.

Despite being the first to investigate the effect of vital sign variation in the ED on the scores of qSOFA, SIRS, MEWS and NEWS, our study has some limitations. First, the majority (63.1%) of our patients were triaged as MTS urgency yellow ('urgent'). As a result, generalisation of the results to other populations should be done carefully. We would like to stress, however, that this is likely the group of patients that could most benefit from repeated measurements. Patients who are triaged as urgency red ('immediately') or orange ('very urgent') are acknowledged as having acute life-threatening problems and are usually assessed (almost) immediately by a physician, whereas 'yellow' patients have to be assessed within 1 h. In this hour, unwanted delay can occur. A second limitation is that we did not take therapeutic interventions and patient outcomes into account. Conclusions on what changes vital signs (and clinical rule scores) and whether our reported alterations are associated with adverse outcomes, such as intensive care admission or mortality, can therefore not be drawn. A hypothetical study taking all this into account would be labour-intensive, as not only interventions performed in the ED would have to be registered, but also prehospital interventions.

We feel that future research should focus on the feasibility, implementation and predictive value of repeated or continuous measurement of vital signs, throughout the acute care chain. Specific focus should lie on the respiratory rate, as it has been repeatedly shown to be an important predictor of clinical deterioration, but measured infrequently and inadequately as well.

CONCLUSION

Almost half of patients with a suspected infection experience a change in the score of qSOFA, SIRS, MEWS and/or NEWS during ED stay. Approximately half of alterations were from a normal to an abnormal score and half vice versa. The respiratory rate was the most contributing vital sign to these alterations. Patients with a normal score at ED arrival had a 6.7–17.6% chance of displaying an abnormal score later during their ED stay, whereas 50% of patients with an initial abnormal score turned normal later on. Clinicians should be aware of the frequency of alterations in clinical rule scores and realise that the optimal moment of assessing clinical rule scores is unknown.

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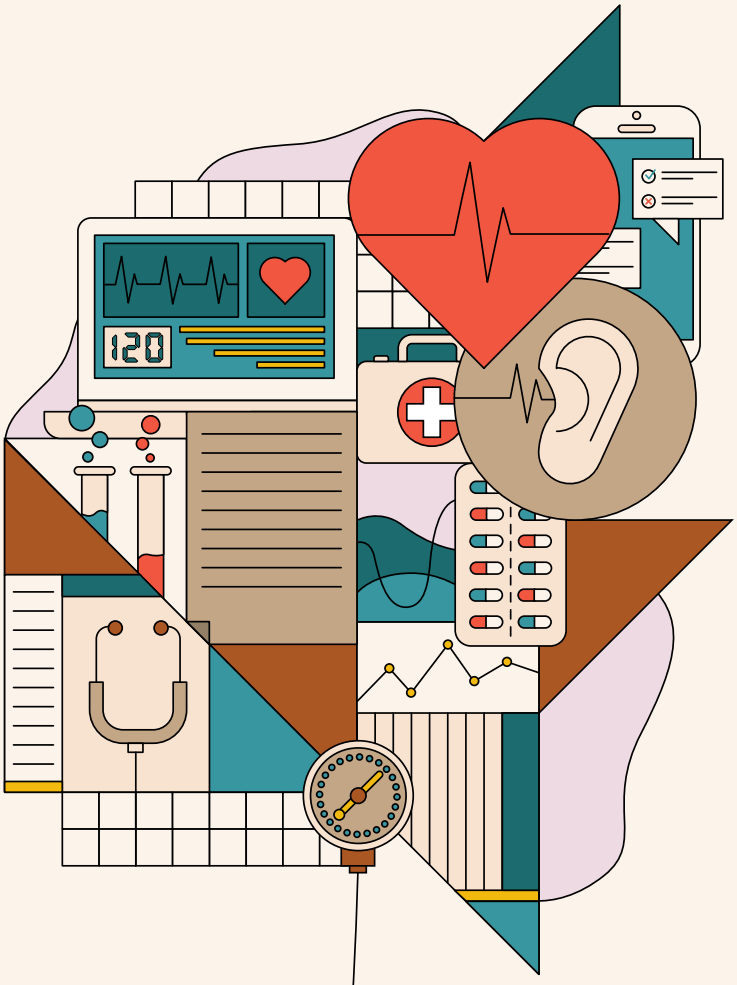
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CHAPTER 6

ACCURACY AND INTEROBSERVER–AGREEMENT OF RESPIRATORY RATE MEASUREMENTS BY HEALTHCARE PROFESSIONALS, AND ITS EFFECT ON CLINICAL RULE SCORES.

Gideon H.P. Latten

Michelle Spek

Jean W.M. Muris

Jochen W.L. Cals

Patricia M. Stassen

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ABSTRACT

Objective

In clinical prediction/diagnostic rules aimed at early detection of critically ill patients, the respiratory rate plays an important role. We investigated the accuracy and interobserver-agreement of respiratory rate measurements by healthcare professionals, and the potential effect of incorrect measurements on the scores of 4 common clinical rules: quick Sepsis-related Organ Failure Assessment (qSOFA), Systemic Inflammatory Response Syndrome (SIRS) criteria, Modified Early Warning Score (MEWS) and National Early Warning Score (NEWS).

Methods

Using an online questionnaire, we showed 5 videos with a healthy volunteer, breathing at a fixed (true) rate (13–28 breaths/minute). Respondents measured the respiratory rate, and categorised it as low, normal, or high. We analysed how accurate the measurements were using descriptive statistics, and calculated interobserver-agreement using the intraclass correlation coefficient (ICC), and agreement between measurements and categorical judgments using Cohen's Kappa. Finally, we analysed how often incorrect measurements led to under/overestimation in the selected clinical rules.

Results

In total, 448 healthcare professionals participated. Median measurements were slightly higher (1-3/min) than the true respiratory rate, and 78.2% of measurements were within 4/min of the true rate. ICC was moderate (0.64, 95% CI 0.39–0.94). When comparing the measured respiratory rates with the categorical judgments, 14.5% were inconsistent. Incorrect measurements influenced the 4 rules in 8.8% (SIRS) to 37.1% (NEWS). Both underestimation (4.5–7.1%) and overestimation (3.9–32.2%) occurred.

Conclusions

The accuracy and interobserver-agreement of respiratory rate measurements by healthcare professionals are suboptimal. This leads to both over- and underestimation of scores of four clinical rules. The clinically most important effect could be a delay in diagnosis and treatment of (critically) ill patients.

INTRODUCTION

An abnormal respiratory rate is an important predictor of deterioration of a patient.[1,2] Consequently, the respiratory rate has a prominent place in many clinical prediction/diagnostic rules, which aim to early identify critically ill patients. Adequate and timely identification of these patients is important, as a delay in treatment increases morbidity and mortality disproportionately.[3-5] Commonly used clinical rules for critical illness are the quick Sepsis-related Organ Failure Assessment (qSOFA), the Systemic Inflammatory Response Syndrome (SIRS) criteria, the Modified Early Warning Score (MEWS) and the National Early Warning Score (NEWS) (Table 1).[6-9]

Considering the predictive potential of the respiratory rate, one would expect healthcare professionals to assess it as often and accurate as possible. However, in daily practice, the respiratory rate turns out to be the least often recorded vital sign, both on wards as well as in emergency departments (EDs).[10-12] Contrary to body temperature, blood pressure, and heart rate, the respiratory rate is mostly measured manually, which could be one of the explanations of infrequent recording. In addition, counting the respiratory rate is believed to waste valuable time.[13] In order to improve documentation of the respiratory rate, some organizations use systems that force employees into recording it. This may however, lead to inaccurate estimations of the respiratory rate, causing a delay in the identification and treatment of patients with serious conditions, such as sepsis.[6,14]

Importantly, minor changes in the respiratory rate, just above or below normal, can have important effects on risk stratification for critically ill patients. Although the accuracy and interobserver-agreement of respiratory rate measurements by healthcare professionals has been reported to be fair to good, most of these studies used a wide and probably unnaturally low or high–range (5–60 breaths/minute), and the number of observers was small.[14,15] The impact of misclassification of respiratory rate measurements on important clinical rules for critically ill patients has not yet been studied.

In this study, we investigated the accuracy and interobserver-agreement of respiratory rate measurements by different healthcare professionals, using 5 videos with different respiratory rates of one healthy volunteer. We hypothesised that a substantial proportion of measurements would deviate more than 4/min from the true respiratory rate, and that there would be inconsistencies when comparing continuous measurements with categorical judgments. Furthermore, we expected that deviations from the true respiratory rate would influence the outcome of 4 frequently used clinical rules: qSOFA, SIRS, MEWS and NEWS.[6-9]

Table 1 – Four common clinical prediction/diagnostic rules for critical illness

qSOFA – quick Sequential Organ Failure Assessment

	Points
Respiratory rate ≥22/min	1
Altered mental state	1
SBP ≤100mmHg	1

Score: 0-3 points, positive/abnormal when score ≥ 2 points, respiratory rate gives 0-1 point

SIRS – Systemic Inflammatory Response Syndrome

	Points
Temperature >38°C or <36°C	1
Heart rate >90 bpm	1
Respiratory rate >20 /min or $PaCO_2$ <32mmHg/4.3kPa	1
White blood cell count >12,000/mm^3 or <4,000/mm^3 or >10% immature bands	1

Score: 0-4 points, positive/abnormal when score ≥ 2 points, respiratory rate gives 0-1 point

MEWS – Modified Early Warning Score

	Points						
	3	2	1	0	1	2	3
SBP (mmHg)	<70	71-80	81-100	101-199		≥200	
Heart rate (bpm)		<40	41-50	51-100	101-110	111-129	≥130
Respiratory rate (/min)		<9		9-14	15-20	21-29	≥30
Temperature (°C)		<35		35-38.4		≥38.5	
Level of consciousness				A	V	P	U

Score: 0-14 points, positive/abnormal when score ≥ 4 points, respiratory rate gives 0-3 points

NEWS – National Early Warning Score

	Points						
	3	2	1	0	1	2	3
Respiratory rate (/min)	≤8		9-11	12-20		21-24	≥25
Oxygen saturation (%)	≤91	92-93	94-95	≥96			
Supplemental oxygen		Yes		No			
Temperature (°C)	≤35.0		35.1-36.0	36.1-38.0	38.1-39.0	≥39.1	
SBP (mmHg)	≤90	91-100	101-110	111-219			≥220
Heart rate (bpm)	≤40		41-50	51-90	91-110	111-130	≥131
Level of consciousness				A			V-U

Score: 0-20 points, positive/abnormal when score ≥ 5 points, respiratory rate gives 0-3 points

Abbreviations: SBP – systolic blood pressure, bpm – beats per minute; AVPU score: A = Alert, V = reacting to voice, P = reacting to pain, U = unresponsive

METHODS

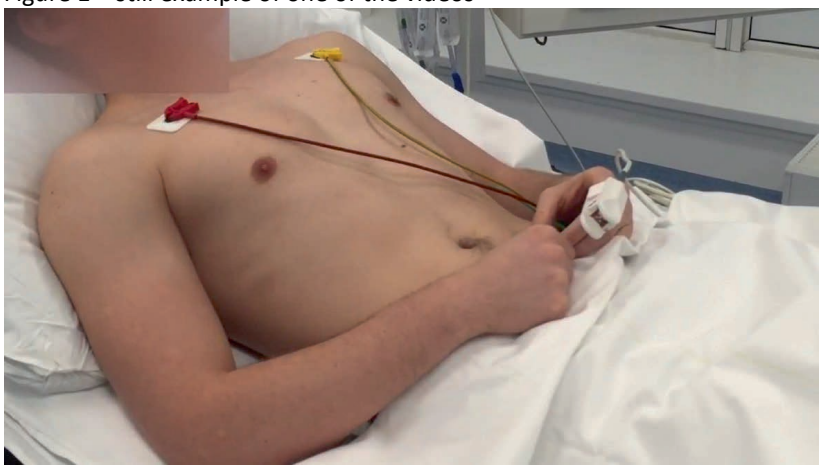
Design and setting

For this questionnaire-based study, we made videos of a healthy volunteer, breathing with different respiratory rates. We shared these videos and a corresponding questionnaire with healthcare professionals through e-mail and social media. The research protocol was judged by the ethics committee METC Z and approval was not deemed necessary. Participants were aware of the study aims and the intention of publishing the results in a peer-reviewed journal. They were asked to participate when interested.

Videos

We created five videos, showing a healthy, male volunteer in supine position in a quiet setting. In each video, the volunteer breathed with a constant respiratory rate between 13 and 28 breaths per minute (28, 13, 22, 19 and 25 breaths/minute for video 1 to 5, respectively). In order to breathe at a constant rate, our volunteer was guided by ECG derived respiratory signals on a monitor. We selected stable video recordings, to make sure there was no variation in the respiratory rate throughout the videos. We defined the true respiratory rate as the rate displayed on the monitor, which was confirmed by the investigators, by counting the breaths during the whole video, divided by the duration of the video. Each video lasted approximately 60 seconds. See Figure 1 for an example of one of the videos. Videos 1-5 can be viewed as supporting information in the published manuscript.[16]

Figure 1 – still example of one of the videos



Questionnaire

In March 2018, an invitation to participate in this questionnaire was distributed among different healthcare professionals throughout the Netherlands. We sent invitations by e-mail to the professional network of the authors, and we stimulated recipients to pass the invitation on to relevant colleagues. Furthermore, we posted the link to the (Dutch) survey on social media (Twitter, LinkedIn) in order to reach as many potential respondents as possible. The questionnaire could be filled out during a period of 3 weeks. We asked respondents about their profession, the years of experience in the current profession, and their preferred method of respiratory rate assessment. Thereafter, video 1 was shown. Respondents were asked to measure the respiratory rate, and after each video, they were asked to judge whether it was 'low', 'normal' or 'high'. We did not provide a definition of these three categories, as a categorical description of the respiratory rate is often used in daily practice.

Statistical analyses

All statistical analyses were performed using IBM SPSS statistical software version 25 (Chicago, Illinois, USA). We used descriptive statistics to summarise the respondents' profession, experience, and preferred method of respiratory rate assessment.

In order to assess how accurate the respondents' measurements were, we decided to use descriptive analysis and calculate medians with interquartile ranges (IQR). Subsequently, we calculated the proportion of measurements that were within 4 breaths/minute of the true respiratory rate. This cut-off value was chosen since we expected that a majority of the respondents would measure for 15 seconds and multiply by 4. A deviation of 1 breath would therefore result in a deviation of 4 from the true rate. To investigate if there were significant differences in measurements between groups of professionals, we compared groups for each video.

We further determined the interobserver-agreement of the measured respiratory rates, by calculating the intraclass correlation coefficients (ICC) and their 95% confidence intervals (CI), based on a single-measurement, absolute-agreement, 2-way random effects model. This was done for all videos together, as well as combined for video 1, 3 and 5 (respiratory rate >20 breaths/minute), and for videos 2 and 4 (respiratory rate <20 breaths/minute). ICC values less than 0.50 are considered indicative of poor interobserver-agreement, between 0.50 and 0.75 moderate agreement, between 0.75 and 0.90 good agreement, and values higher than 0.90 indicate excellent agreement.[17] In order to achieve a large, representative group of participants, we limited the number of videos to

5. This was in accordance with the sample size we calculated to investigate interobserver agreement. We additionally calculated the effect of showing 10 instead of 5 videos to reduce the width of the confidence intervals, but this did not result in narrower confidence intervals.

In addition, the respondents' measurements of the respiratory rate were compared with their categorical judgments ('low', 'normal', 'high'). We used the following cut-off values to define a low, normal and high respiratory rate: <12 breaths/minute for 'low', 12 through 20 for 'normal', and >20 for 'high'. These are widely used cut-off points for adults.[7] Cohen's Kappa statistics were used to measure the agreement between the respondents' measurements and their categorical answers. Kappa values of 0.6–0.8 represent moderate agreement, values of 0.8–0.9 strong agreement, and values >0.9 almost perfect agreement.[18]

In order to evaluate the potential clinical relevance of accurate respiratory rate measurements, we calculated how often an incorrect measurement of the respiratory rate would have resulted in an incorrect result on 4 clinical rules for critical illness: qSOFA, SIRS, MEWS and NEWS (Table 1).

RESULTS

Respondents and method of assessment

In total, 452 respondents filled out the questionnaire within 3 weeks after sending out the first invitation (median 3, IQR 2–7 days). After exclusion of 4 incomplete questionnaires, we included 448 respondents in the analyses. The study sample consisted of nurses, consultants, residents, medical students, general practitioners (GPs) and other healthcare professionals (Table 2). Of these participants, 432 (96.4%) assessed the respiratory rate on a regular basis.

Accuracy of respiratory rate measurements

Figure 2 shows the measured respiratory rates for each video. In general, the median reported respiratory rate was between 1–3 breaths/minute higher than the true rate. IQRs were between 2–4 breaths/minute, and the overall range of measurements was between 6 and 64/min.

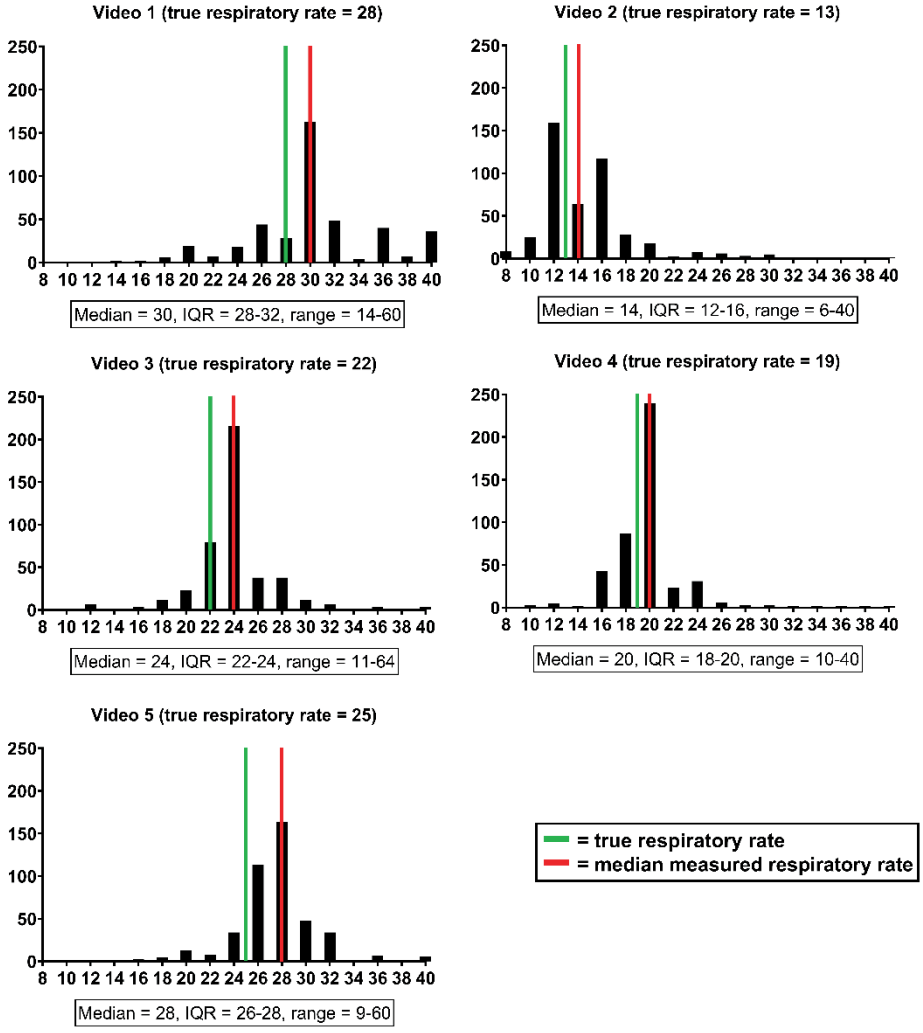
Table 2 shows the proportion of measurements within 4/min of the true respiratory rate. Overall, 78.2% of measurements were within this range (67.4%, 81.9%, 81.9%, 87.9%, and 71.7%% for video 1–5, respectively). We found no significant differences in this proportion between the different groups of professionals.

Table 2 – Respondents and proportion of measurements within 4/min from the true respiratory rate

Respondents								
	Total	Nurse	Consultant	Resident	Student	GP	Other	
	448 (100%)	163 (36.4%)	99 (22.1%)	94 (21.0%)	52 (11.6%)	37 (8.3%)	3 (0.7%)	
Experience current profession – years	*	8 (4-17)	6 (3-12)	2 (1-3)	4 (2-4)	5 (2-10)	6 (3-6)	
Preferred method of RR assessment								
- Measure <30 sec.	166 (37.1%)	57 (35.0%)	34 (34.3%)	37 (39.4%)	21 (40.4%)	16 (43.2%)	1 (33.3%)	
- Measure 30 sec.	161 (35.9%)	52 (31.9%)	34 (34.3%)	38 (40.4%)	22 (42.3%	13 (35.1%)	2 (66.7%)	
- Measure 1 min.	37 (8.3%)	15 (9.2%)	10 (10.1%)	4 (4.3%)	3 (5.8%)	5 (13.5%)	0	
- Monitor values	64 (14.3%)	35 (21.5%)	14 (14.1%)	10 (10.6%)	5 (9.6%)	0	0	
- Other methods	20 (4.5%)	4 (2.5%)	7 (7.1%)	5 (5.3%)	1 (1.9%)	3 (8.1%)	0	
Proportion of measurements within 4/min from the true respiratory rate								
Video (true rate)	Total	Nurse	Consultant	Resident	Student	GP	Other	**p**
– Video 1 (28)	302 (67.4%)	114 (69.9%)	65 (65.7%)	67 (71.3%)	37 (71.2%)	18 (48.6%)	1 (33.3%)	0.11
– Video 2 (13)	367 (81.9%)	133 (81.6%)	81 (81.8%)	81 (86.2%)	40 (76.9%)	30 (81.1%)	2 (66.7%)	0.77
– Video 3 (22)	367 (81.9%)	125 (76.7%)	80 (80.8%)	82 (87.2%)	46 (88.5%)	31 (83.8%)	3 (100%)	0.21
– Video 4 (19)	394 (87.9%)	139 (85.3%)	89 (89.9%)	87 (92.6%)	42 (80.8%)	35 (94.6%)	2 (66.7%)	0.12
– Video 5 (25)	321 (71.7%)	117 (71.8%)	70 (70.7%)	67 (71.3%)	40 (76.9%)	26 (70.3%)	1 (33.3%)	0.71

Values are N (%) or median (IQR), unless stated otherwise
* Median and IQR were not calculated for total group, since there was an important difference in experience between the profession groups
Abbreviations: GP – general practitioner, sec. – second(s), min. – minute(s)

Figure 2 – Measured respiratory rates for each video



* Extreme values (<8 or >40) are not depicted in these graphs

Interobserver-agreement

For all respiratory rate measurements of the 5 videos together, the ICC was 0.64 (95% CI 0.39–0.94), which indicates moderate agreement. For videos with a high respiratory rate (video 1, 3 and 5 (>20 and ≥22/min)), the ICC was 0.29 (95% CI 0.10–0.94), indicating poor

agreement. Videos with a low respiratory rate (video 2 and 4 (<20)) showed an ICC of 0.50 (95% CI 0.16–0.99), indicating moderate agreement.

Agreement between measurements and categorical judgments

Table 3 shows the agreement between the respondents' measurements and their categorical judgments. For all videos together, 324 (14.5%) inconsistencies were present. Most (n=194, 8.7%) of these occurred when a respondent measured a "normal" respiratory rate (12 through 20/min), and incorrectly judged this to be "high". In most (n=148, 76.3%) of these cases, the respiratory rate was measured as exactly 20/minute. In 68 cases (3.0%), a respondent measured a "high" respiratory rate (>20 breaths/minute), and incorrectly judged this to be "normal" (n=64, 2.9%) or "low" (n=4, 0.2%). Cohen's Kappa was 0.71 for all videos together, which represents moderate agreement. However, for all individual videos, Cohen's kappa was lower (0.27–0.59).

Table 3 – Agreement between measurements and categorical judgments*

			Categorical			
			Low	Normal	High	
All videos	Continuous	<12	29	21	1	Inconsistent answers: n=324 (14.5%)
		12-20	40	617	194	Consistent answers: n=1916 (85.5%)
		>20	4	64	1,270	Cohen's Kappa: 0.71
			Categorical			
			Low	Normal	High	
Video 1 (28/min)	Continuous	<12	0	0	0	Inconsistent answers: n=30 (6.7%)
		12-20	0	7	22	Consistent answers: n=418 (93.3%)
		>20	2	6	411	Cohen's Kappa: 0.29
			Categorical			
			Low	Normal	High	
Video 2 (13/min)	Continuous	<12	27	18	0	Inconsistent answers: n=84 (18.8%)
		12-20	38	327	11	Consistent answers: n=364 (81.3%)
		>20	2	15	10	Cohen's Kappa: 0.39
			Categorical			
			Low	Normal	High	
Video 3 (22/min)	Continuous	<12	0	2	0	Inconsistent answers: n=48 (10.7%)
		12-20	1	20	24	Consistent answers: n=400 (89.3%)
		>20	0	21	380	Cohen's Kappa: 0.42
			Categorical			
			Low	Normal	High	
Video 4 (19/min)	Continuous	<12	1	1	1	Inconsistent answers: n=144 (32.1%)
		12-20	1	250	126	Consistent answers: n=304 (67.9%)
		>20	0	15	53	Cohen's Kappa: 0.27
			Categorical			
			Low	Normal	High	
Video 5 (25/min)	Continuous	<12	1	0	0	Inconsistent answers: n=18 (4.0%)
		12-20	0	13	11	Consistent answers: n=430 (96.0%)
		>20	0	7	416	Cohen's Kappa: 0.59

* Respondents' measurements are compared with their categorical judgments. Inconsistencies (e.g. a respondent measured a "normal" respiratory rate (12 through 20/min), and incorrectly judged this to be "high") are presented in red. Consistent answers are presented in green

Potential effect on clinical rules

Table 4 shows the potential effect of incorrect respiratory rate measurements on qSOFA, SIRS, MEWS and NEWS. Of these rules, SIRS was least affected, with misclassification in 8.8%. qSOFA scores changed in 8.9%, NEWS in 18.2%, and MEWS scores changed in 37.1% of cases. Overall, 4.5–7.1% of patients would incorrectly receive a lower score, while 3.9–32.2% would receive a higher one, when compared to the score based on their true respiratory rate.

Table 4 – Effect of respiratory rate measurements on clinical rules*					
qSOFA					
Video	**1**	**2**	**3**	**4**	**5**
True respiratory rate (TRR)	**28/min**	**13/min**	**22/min**	**19/min**	**25/min**
Score based on TRR	**1**	**0**	**1**	**0**	**1**
0 points based on measurement	30 (6.7%)	422 (94.2%)	56 (12.5%)	386 (86.2%)	26 (5.8%)
1 point based on measurement	418 (93.3%)	26 (5.8%)	392 (87.5%)	62 (13.8%)	422 (94.2%)
Incorrect lower score: 112 (5.0%)					
Incorrect higher score: 88 (3.9%)					
SIRS					
Video	**1**	**2**	**3**	**4**	**5**
True respiratory rate (TRR)	**28/min**	**13/min**	**22/min**	**19/min**	**25/min**
Score based on TRR	**1**	**0**	**1**	**0**	**1**
0 points based on measurement	29 (6.5%)	421 (94.0%)	47 (10.5%	380 (84.8%	25 (5.6%)
1 point based on measurement	419 (93.5%)	27 (6.0%)	401 (89.5%)	68 (15.2%)	423 (94.4%)
Incorrect lower score: 101 (4.5%)					
Incorrect higher score: 95 (4.2%)					
MEWS					
Video	**1**	**2**	**3**	**4**	**5**
True respiratory rate (TRR)	**28/min**	**13/min**	**22/min**	**19/min**	**25/min**
Score based on TRR	**2**	**0**	**2**	**1**	**2**
0 points based on measurement	2 (0.4%)	248 (55.4%	8 (1.8%)	10 (2.2%)	4 (0.9%)
1 point based on measurement	27 (6.0%)	163 (36.4%)	39 (8.7%)	370 (82.6%)	21 (4.7%)
2 points based on measurement	98 (21.9%)	29 (6.5%)	371 (82.9%	63 (14.1%)	321 (71.7%)
3 points based on measurement	321 (71.7%)	8 (1.8%)	30 (6.7%)	5 (1.1%)	102 (22.8%)
Incorrect lower score: 111 (5.0%)					
Incorrect higher score: 721 (32.2%)					
NEWS					
Video	**1**	**2**	**3**	**4**	**5**
True respiratory rate (TRR)	**28/min**	**13/min**	**22/min**	**19/min**	**25/min**
Score based on TRR	**3**	**0**	**2**	**0**	**3**
0 points based on measurement	19 (6.5%)	376 (84.0%)	45 (10.0%)	377 (84.2%)	24 (5.4%)
1 point based on measurement	0 (0%)	35 (7.8%	2 (0.4%)	3 (0.7%)	1 (0.2%)
2 points based on measurement	25 (5.6%)	10 (2.2%	295 (65.8%)	54 (12.1%)	42 (9.4%)
3 points based on measurement	404 (90.2%)	27 (6.0%)	106 (23.7%)	14 (3.1%)	381 (85.0%)
Incorrect lower score: 158 (7.1%)					
Incorrect higher score: 249 (11.1%)					

Numbers are N (%)

* Incorrect lower or higher score means that the number of points that would be scored on the clinical rule was different when comparing a measurement with the true respiratory rate. In other words: the score of the clinical rule would be influenced by the respiratory rate measurement. Correct (or unaffected) scores are presented in green, incorrect scores are presented in red.

Abbreviations: TRR – true respiratory rate, qSOFA – quick Sequential Organ Failure Assessment, SIRS – Systemic Inflammatory Response Syndrome, MEWS – Modified Early Warning Score, NEWS – National Early Warning Score

DISCUSSION

This study is, to our knowledge, the first that used a large, heterogeneous group of professionals to measure and categorise different clinically relevant respiratory rates. Our study shows that these respiratory rate measurements by health care professionals are not accurate, and that the interobserver-agreement is suboptimal, which may have an important effect on the results of four common clinical rules.

We designed this study using simple tools, available to the majority of healthcare professionals today. We made five videos and shared them using e-mail and social media, after which 448 professionals completed and returned the questionnaire within three weeks. Median measured respiratory rates were slightly higher than the true respiratory rate, 78.2% of measurements were within 4 breaths per minute from the true rate, and the ICC was moderate. These results are in line with those of previous studies.[19,20] Remarkable is the fact that 14.5% of responses showed inconsistencies when comparing the respondents' measurements and their categorical judgments. In addition, incorrect respiratory rate measurements may in theory have led to both overestimation (12.9%) and underestimation (5.4%) of the score of four common clinical rules.

The median measured respiratory rates varied highly. While IQRs were between 2 and 4/min, ranges were wide (overall 6-64/min). Overall, 78.2% of measurements were within 4 breaths per minute from the true rate. We did not find any differences between professional groups regarding the proportion of measurements within 4/min from the true rate. These results suggest that respiratory rate assessment by different groups of healthcare professionals is suboptimal.

With a value of 0.64 (95% CI 0.39–0.94), the ICC was moderate. Previous studies have demonstrated values as low as 0.26 (95% CI 0.16–0.35), but also as high as 0.99 (95% CI 0.97–1.00).[14,15] A possible explanation for this low ICC is the difference in design between these studies. One study, with a low ICC (0.26), compared values recorded in patient charts to values measured manually by residents.[14] These values were not obtained at the exact same time, and while the participating residents were informed and prepared, the nurses who performed the measurements were not. Another study, with a high ICC (0.99), performed a simulation using 5 videos as well.[15] Respondents were mostly experienced nurses, and the respiratory rates in the videos varied largely: 5, 10, 15, 30 and 60 breaths/min. For professionals like these, it is relatively easy to differentiate between a respiratory rate of 15 and 60, or even 30 breaths/minute. However, measuring a respiratory rate just above or below commonly used cut-off points of >20 or ≥22 breaths/minute is more difficult. Therefore, the smaller range of respiratory rates in our videos, and our large, heterogeneous group of (future) healthcare professionals

may have resulted in our less favourable ICCs. As the respiratory rate has been proven to predict adverse outcomes and is incorporated in many clinical rules, this is an important finding.[1,2,21]

When comparing the respondents' measurements and their categorical judgments, 14.5% of the answers were inconsistent. Respondents measuring a normal (12-20/min) respiratory rate, while judging this as 'high', caused the most inconsistencies (8.7%). In over 75% of these cases, the measured respiratory rate was exactly 20/min, which could suggest that some respondents believe that a respiratory rate of 20/min is abnormal. We did not provide a definition of "low", "normal", or "high", but there is no current guideline which supports the use of a cut-off point <20/min for an abnormal respiratory rate. It would be worthwhile to investigate if education would improve these results, as these results suggest a lack of knowledge regarding common cut-off points.

One of the most interesting results of this study was found in the impact of incorrect respiratory rate measurements on daily practice. We entered the respondents' answers into four commonly used clinical rules, as a proxy of the "true consequence" of incorrect measurements. This resulted in incorrect scores for qSOFA in 8.9%, for SIRS in 8.8%, for MEWS in 37.1% and for NEWS in 18.2%. While median measurements were higher than the true respiratory rate in all videos, the incorrect measurements resulted in both incorrect lower and higher scores (Table 3). In daily practice, this could have led to delayed diagnosis and treatment of (critically) ill patients or overalerting and eventually alarm fatigue.

By performing this video-based questionnaire, we created the opportunity to have 448 healthcare professionals measure the respiratory rate of the same patient breathing at a constant rate. This design also has limitations. Respondents could only visually measure the respiratory rate. Some professionals normally use palpation of the chest to optimise their measurement. However, we made sure that the volunteer's breaths could be seen clearly in all videos, and we expect that the restriction to visual assessment had no major influence on the results. In order to provide high quality, stable recordings, we had to select specific sections of video, resulting in 4/5 videos being slightly less than 1 minute long. This could have resulted in suboptimal measurements by 8.3% of respondents, as they reported that they usually measure the respiratory rate for a full minute. Finally, we did not include a video with a low respiratory rate, so we cannot draw conclusions regarding the ability of healthcare professionals to recognise bradypnea.

Notwithstanding these limitations, this study shows that, even when professionals are asked to measure the respiratory rate at the best of their ability, results are still suboptimal. In crowded EDs, quick and reliable methods to accurately measure the

respiratory rate could be valuable, especially since many EDs and hospitals rely on these measurements to identify patients at risk, for instance, of sepsis. Therefore, further research should be undertaken to investigate the reliability of non-invasive methods to measure the respiratory rate, especially in EDs. This to avoid incorrect alarms, and even more important, delays in diagnosis and treatment, even when patients are potentially very ill.

In conclusion, using simple tools available to most healthcare professionals today, we showed that accuracy and interobserver-agreement of respiratory rate measurements by healthcare professionals are suboptimal. The clinical relevance of incorrect measurements is illustrated by alterations in the score of four common clinical rules. This happened in 8.8–37.1% of cases, with the clinically the most important effect being potential delay in diagnosis and treatment of (critically) ill patients.

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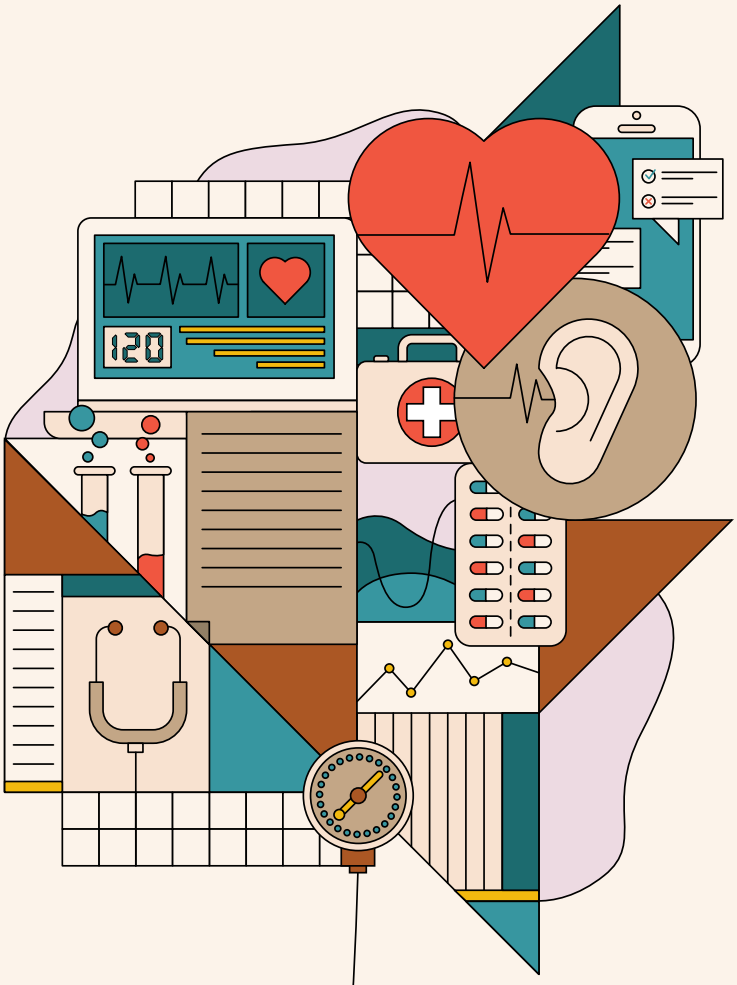
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CHAPTER 7

GENERAL DISCUSSION

GENERAL DISCUSSION

In the general discussion of this thesis, the results of three prospective single centre cohort studies, one prospective multicentre cohort study and one questionnaire study will be put into perspective. The main findings of this thesis will be discussed first, after which they will be placed in a broader context and compared with previous literature. Next, strengths and limitations of this thesis will be discussed, including methodological considerations. Finally, future perspectives are offered.

Main findings

This thesis aimed to provide more insight into the journey of patients with a severe infection through the acute care chain in the Netherlands, which includes the entire trajectory from the patient's home to the emergency department (ED). We specifically focused on possible targets for optimisation of care, as the effectiveness of treatment (e.g. antibiotics) is time dependent. The answers to the four main research questions are summarised below.

1. How do patients with a severe infection or sepsis 'travel' through the acute care chain, how long is their journey and who do they meet whilst in transit?

   In **chapter 2** we showed that the median symptom duration in 440 ED patients with a (suspected) infection was 3 days. Prior to the actual ED visit, almost half of the patients had already visited their GP once or more, and one in three patients had already used antibiotics during this period. On the day of the ED visit, more than 80% of the patients were referred by a GP and two-thirds were transported by ambulance.

2. How do GPs approach patients with fever during out-of-hours, with a specific focus on vital signs and gut feeling?

   In **chapter 3**, we investigated 108 patients with fever who visited two general practitioner cooperatives (GPCs) during out-of-hours. During assessment of their patients, GPs rarely (22.2%) measured 'all' vital signs. Of these, abnormal respiratory rate and altered mental status were associated with referral to the ED, which occurred in two out of five patients. Abnormal SIRS and qSOFA scores and the presence of a sense of alarm (gut feeling) were also associated with referral. The vast majority of patients who were not referred to the ED and thus treated at home were not admitted to hospital within a week of their GPC visit.

3. Do professionals within the acute care chain agree on and document the disease severity of patients with an infection?

   In **chapter 4**, we found documentation of sepsis and of a sense of urgency in about one in five medical records. In only one in twenty patients was sepsis documented by all professionals in the acute care chain, while in one of thirteen patients a sense of urgency was documented by all professionals. Despite a significant relationship between the documentation of 'sepsis' and of a sense of urgency, the agreement between these two was low.

4. How reliable are measurements of clinical rule scores, and how does the respiratory rate contribute to these scores?

   In **chapter 5**, we demonstrated that the scores of the clinical rules qSOFA, SIRS, MEWS and/or NEWS can vary over time. During ED stay, clinical rule scores changed in almost half of 1433 patients. Patients with a normal score on arrival in the ED had a 6.7-17.6% chance of showing an abnormal score later during their ED stay, while 50% of the patients with an initially abnormal score later became normal. Respiratory rate was the most frequent contributor to these changes.

   In **chapter 6**, we then found that both the accuracy of respiratory rate measurements as well as its interobserver-agreement were suboptimal. The clinical relevance of this phenomenon was illustrated by the finding that incorrect respiratory rate measurements alone altered clinical rule scores in 8.8-37.1% of patients, depending on the clinical rule (qSOFA, SIRS, MEWS, NEWS) that was used. This caused both underestimation and overestimation of clinical rule scores.

In the next part of this thesis, these findings will be discussed and compared with previous literature.

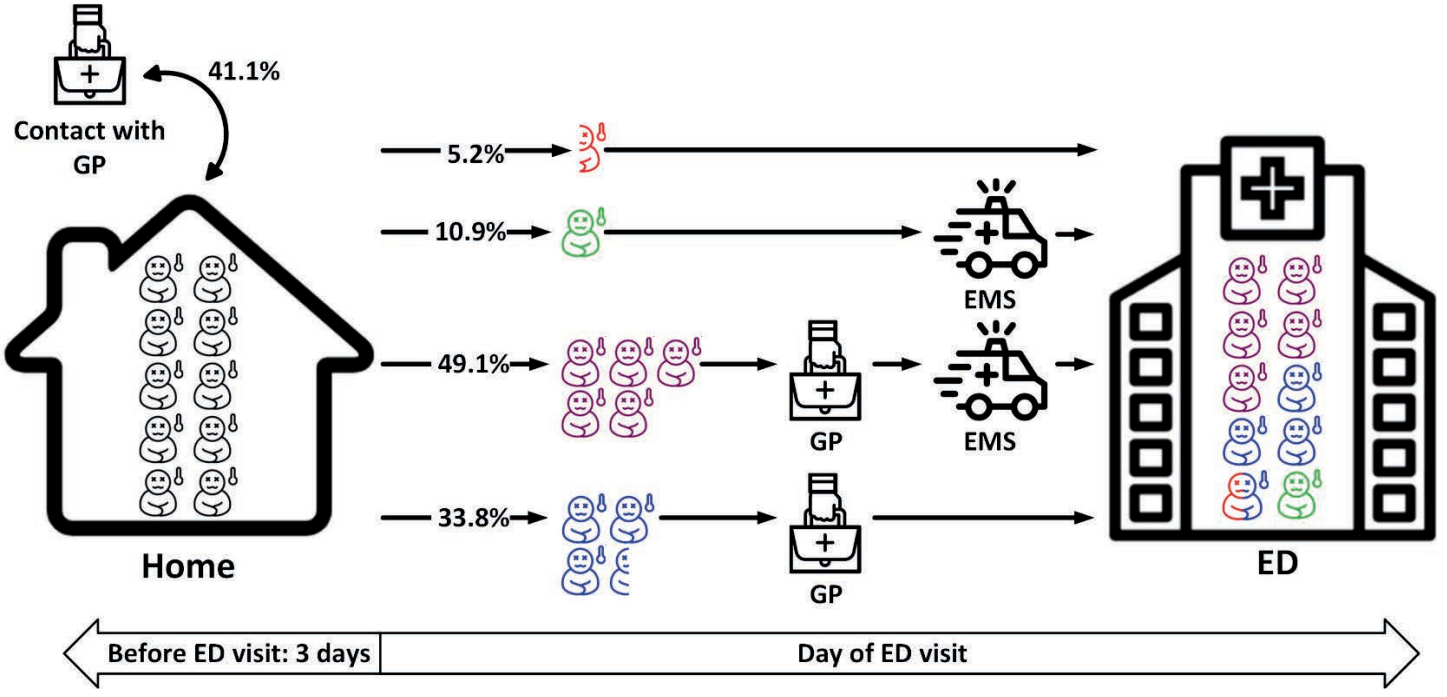
Severe infections – from home to hospital

The first part of this thesis focused on the trajectory of patients with an infection *before* assessment in the ED. Until now, few studies have focused on this phase, although there may be opportunities for optimising care. In several chapters, we look at the acute care chain from both the ED perspective as well as the primary care perspective.

Looking back – the ED perspective

Our findings in **chapter 2** fill a gap in the relatively unexplored field of prehospital research on patients with serious infections and sepsis.[1] The current literature focuses mainly on hospitalised patients, particularly those requiring intensive care.[2] As these studies are based on a selected population, their recommendations may therefore not be useful or realistic for primary care.[2-5] The model proposed in the introduction of this thesis already suggests that patients in the hospital or ICU are by default not comparable to those in the ED or primary care setting. Our findings in **chapter 2** contribute to the knowledge of the prehospital trajectory of ED patients with serious infections or sepsis (Figure 1). Moreover, they raise several new questions, for example whether we should take into account the duration of symptoms when assessing patients with an infection in the ED, whether we should treat patients who are already receiving antibiotic treatment the same as patients who are not receiving antibiotics, and whether our results illustrate the prehospital delay (related to the patient or the physician) or the natural course of the disease in patients with an infection. In our opinion, these issues should be addressed in future research, as they can all contribute to optimising care.

Figure 1 – The prehospital phase of emergency department patients with an infection



Abbreviations: GP – general practitioner, EMS – emergency medical services, ED – emergency department, IQR – interquartile range

We realise that by choosing the ED as the vantage point for this study, we were only able to draw conclusions for a select group of patients, namely those who ultimately had to be referred to the ED.[1] However, in primary care, GPs assess and treat many more patients than they refer to the ED. In the introduction to this thesis, we showed that GPs make >11 million consultations for infections per year, while at the same time 140,000 patients with an infection are admitted to hospital, of whom less than 4,000 to the ICU.[6,7]

In earlier retrospective research, Dutch authors already concluded that the assessment by GPs of patients with a possible serious infection is a complex process, in which vital signs, gut feeling and additional diagnostic tests can play a role.[8] Like these authors, we felt that further – prospective – research into the acute care journey of patients could help to answer the question of whether and where there are possibilities for optimising the care of patients with infections.

Looking forward – the primary care perspective

To further investigate the acute care trajectory of patients, we conducted the study presented in **chapter 3** of this thesis.[9] There, we looked ahead from a primary care perspective and focused on patients with fever, which is considered the hallmark symptom of infections. Of all adult patients who presented with documented fever, approximately 2 out of 5 were referred to the ED. Of these, almost 90% were subsequently admitted to hospital. Of the non-referred patients, 85% were not admitted to hospital during a 7-day follow-up period, again underlining the gatekeeping role of GPs in acute care.

Based on these findings, the current system seems – at first glance –to function well for most patients. GPs mostly 'got it right', as most of the referred patients were subsequently admitted to hospital, and almost no non-referred patients were admitted later on. However, one may question whether admission is a true indicator of 'doing well' by GPs. We did not investigate *why* patients were admitted; was it due to the severity of their illness, could the fact that they were referred by a GP have played a role in itself, or were there other – unknown – factors? The same question can be asked for referral; why were patients referred? As other studies have suggested, we think that GPs probably use a combination of history, vital signs and gut-feeling to decide whether patients need to be referred to the ED.[8,10-12]

Most sepsis guidelines pay considerable attention to vital signs.[2,13] Although in our study several vital signs were associated with referral to the ED, we found that complete sets of

vital signs were measured by GPs in only 1 in 5 patients. This suggests that they may be of less value to GPs than previously assumed.[8] Whether this provides an opportunity for optimisation of care will be discussed in the second part of this discussion, where we will elaborate on vital signs and place them in a broader perspective.

Although gut feeling has been investigated less often than vital signs, its value has been proven in various settings. Examples are severe illness in children, patients with dyspnoea and/or chest pain and patients with a possible malignancy.[14-16] For patients with fever, we found that gut feeling was also associated with referral and that the majority (76.5%) of referred patients evoked a feeling of alarm in the treating GP. This suggests that gut feeling plays a role in the diagnostic reasoning of GPs when they encounter patients with fever. Nevertheless, the findings that not all referred patients had an alarm signal and that 1 in 4 (27.8%) patients with a sense of alarm were not referred to the ED suggest that gut feeling is not the only determining factor for referral. As the Gut Feeling Questionnaire (GFQ) does not specify why there is a sense of alarm, there may be non-referral when a GP suspects severe, but not acute pathology, for instance an underlying malignancy or chronic disease. These situations can raise a sense of alarm, but do not warrant immediate ED referral. A second explanation for the non-referral of patients with alarm symptoms could be that some patients did not want to be referred to the ED, despite the fact that the GP treating them thought this was necessary. However, it is unlikely that this phenomenon is responsible for all non-referred patients in whom a feeling of alarm was triggered. Although we found associations between vital signs, gut feeling and ED referral, the decision to refer a patient appears to depend on several factors.

Since we aimed to identify possible targets of optimisation of care, we were triggered by the fact that 1 out of 7 patients who were initially not referred were admitted to the hospital later on (within a week). The question that comes to mind is why these patients were not referred in the first place. Although we did not investigate these patients specifically, the most likely explanation is natural disease progression and/or insufficient clinical response to oral antibiotics. These patients were probably not as ill during their first visit as they were later on, when they were referred to the ED. Other explanations include underestimation of disease severity by the GP during the initial assessment (e.g. due to not measuring all vital signs) and hospital admission due to other reasons (e.g. admission *because* a patient already visited a healthcare provider several times, specific patient's or caretakers' request, or insufficient care in home setting). Further investigation of these cases would be interesting.

It could be argued that optimal patient selection for referral is comparable to setting an optimal cut-off point for a diagnostic test. Increasing sensitivity (referring more patients) may result in fewer patients having delay in their treatment, but comes at the expense of

specificity (more 'unnecessary' referrals). These unnecessary referrals are not beneficial to either the patient or the healthcare providers, and they increase costs.[17,18] The optimal referral strategy (just in time) is therefore difficult to determine. Not only is the decision to refer a patient likely to be multifactorial and only partially dependent on disease severity, but it may also be subjective. Patient- or disease-related factors, as well as factors related to the organization of the healthcare system may play a role. An example of a disease-related factor is a patient who is not severely ill but is suspected of having an acute appendicitis. Referral is likely due to the need for hospital care (e.g. surgical appendectomy). A system-related factor occurs when a patient who is not severely ill is referred because the care that can be provided at home is insufficient.[19,20] A second example of a system-related factor could be that most EDs in the Netherlands are often crowded.[21] This problem can affect the GPs' decision whether or not to refer a patient and the willingness of healthcare providers in hospitals to accommodate a patient. If a patient is not considered 'seriously ill', one might decide to wait and see, so as not to burden the system unnecessarily. An undesirable side effect of such an approach could be that patients are only referred if there are unambiguous signs of serious illness. Particularly vulnerable in our system are patients with an infection, as there is no test to predict complications and/or adverse outcomes. It is likely that such a test will not exist in the near future, so we are forced to think about ways of optimising care within our own circle of influence. In other words, things we could change today, with current resources, to optimise patient care.

Interprofessional communication

An excellent example of a possible way to optimise patient care is communication between healthcare providers. When a GP has made the decision to refer a patient, it is essential that information is adequately communicated throughout the acute care chain. In a recent Dutch study, the time to antibiotics (TTA) in the ED was reduced by more than 20 minutes, only by training EMS personnel in recognising sepsis and communicating suspected sepsis to the ED during handover.[22] One can imagine that early recognition of sepsis throughout the entire acute care chain could shorten TTA and further optimise care. To investigate this issue, we conducted a study (**chapter 4**), which focused on the documentation of the suspicion of sepsis and/or a sense of urgency throughout the acute care chain, and the agreement between different healthcare providers on these two topics.[23]

In that study, we studied 800 patients records, created by GPs, EMS and ED physicians for 339 patients with possible sepsis (≥2 SIRS and/or qSOFA criteria). Both the word 'sepsis',

as well as a sense of urgency, indicating that the patient was deemed in need of immediate assessment by a physician in the ED, were documented in only one out of five records.

Previous research has shown similar documentation rates of sepsis in prehospital settings.[24-26] The most straightforward explanation for these low numbers is suboptimal recognition, but other factors may be important as well. In the general introduction of this thesis, we explained that the difficulty of diagnosing sepsis lies in the lack of an adequate diagnostic test. If sepsis is not recognised, it cannot be documented either. One can imagine that in less clear cases of sepsis, healthcare providers use different terminology to describe the same patient, for instance 'pneumonia' instead of 'pneumosepsis'. This would suggest that only the most severely ill patients are documented as 'septic'. Our findings, however, do not entirely support this hypothesis, as we found no difference between patients with and without an adverse outcome (ICU admission and/or mortality) regarding documentation of sepsis in prehospital (i.e. GP and EMS) medical records. In ED records, we were able to find a difference. There, sepsis was documented significantly more often in patients with an adverse outcome (47.9 vs. 13.7%, $p<0.001$). The most probable explanations include better recognition of sepsis by in-hospital healthcare providers, support for the 'diagnosis' of sepsis by laboratory and/or imaging results, progression of disease between the GP/EMS assessment and the ED assessment of the patient, and available observation time within the ED. It would be worthwhile to further investigate the potential barriers that prevent healthcare providers from documenting sepsis in patients' medical records.

Since the aim of documenting 'sepsis' early is to communicate that a patient may have a potential life-threatening condition, we also investigated how often the included medical records contained a sense of urgency. We found a significant association between the documentation of sepsis and that of a sense of urgency, but agreement between these two was low (kappa 0.19-0.39). This means that documenting the word 'sepsis' does not always generate a sense of urgency, but also that a sense of urgency is not only generated by the word 'sepsis'. This raises the question whether the term 'sepsis' adequately describes the disease severity as perceived by the healthcare provider. Possibly, other words than 'sepsis' are used to describe an severely ill patient with an infection, for instance 'shock', 'ill!', or 'hypotensive'. Conversely, professionals might feel compelled to use the word 'sepsis' when a patient meets a specific set of criteria (e.g. SIRS), even when they do not consider the patient to be severely ill. We should realise that the word sepsis likely does not have the same meaning for every healthcare provider in the acute care chain and that documenting it not necessarily creates a sense of urgency.

Zooming in on the trajectory of patients through the acute care chain, we found that not only was there poor agreement between the documentation of sepsis and of a sense of urgency, but also that healthcare providers often disagreed on the suspicion of both sepsis and sense of urgency (**chapter 4**, Figure 2). Sepsis was documented by GPs, EMS and ED physicians in 13.9, 12.3 and 18.6% of patients, respectively, but these were often not the same patients. For this lack of agreement, there are several explanations. First, a patient's condition can vary over time, which can make signs of sepsis or severe illness – and thus their documentation – more or less visible. In **chapter 5**, we showed that the phenomenon of changing vital signs is present in patients during their ED visit and that it affects clinical rule scores. It is likely that this also happens in the prehospital setting.[27] The majority of patients tends to respond to treatment initiated by the GP and/or EMS, which may cause their vital signs to normalise. As a result, healthcare providers' sense of urgency may decrease. This hypothesis is supported by the finding that in our study, GPs documented a sense of urgency in 31.0% of patients, EMS in 24.1% and physicians in the ED in 'only' 15.0%. Differences in healthcare providers' exposure to seriously ill patients may also contribute to this phenomenon, as frequent encounters with seriously ill patients (EMS/ED) may lower one's sense of urgency. Finally, it may be possible that the information from one healthcare provider is not adequately handed over to the next 'station' in the chain. Despite the presence of electronic patient records in almost all sectors of Dutch healthcare, sharing information between different systems is not always easy.

Regardless of the status of a patient, the healthcare system must be organised in such a way that the necessary information is always adequately passed on through the acute care chain. Healthcare providers in the acute care chain rely on the information available to them. This information is provided by the patient or his/her caregivers, or by the preceding healthcare provider in the chain. Particularly in the case of possible sepsis, adequate documentation of vital signs, suspicion of sepsis and a sense of urgency can contribute to early recognition, which demonstrably shortens the time until the administration of antibiotics.[22]

Severe infections – vital signs and clinical rules

The second part of this thesis focused on vital signs and vital sign-based clinical rules regarding sepsis. In the previous chapters, vital signs have been mentioned frequently. They are indispensable when determining – and substantiating – a suspicion of sepsis and can be used in any setting. In hospitals, vital signs are often (automatically) implemented in clinical rules, which can provide information about diagnosis and/or prognosis. The

clinical rule score can have important implications, such as triggering specific treatment protocols (e.g. for sepsis in case of positive qSOFA and SIRS scores), or prioritizing patients in crowded settings. One can imagine that there are certain requirements for these clinical rules to function properly, especially when they are used outside the settings in which they were developed.

Firstly, clinical rules must have strong face validity, or in other words measure what they are intended to measure. This may be the degree of illness or, for example, the likelihood of further deterioration. The desired outcome depends on the setting in which the clinical rule is used. Secondly, they must be simple and calculable in settings with limited resources, such as primary care. The use of vital signs offers the possibility to do this, but also has shortcomings. For example, certain vital signs must be measured manually, which can be time-consuming, and in specific populations (e.g. elderly patients) these vital signs may be influenced by the use of medication. Finally, clinical rules must yield the same score when different healthcare providers measure vital signs. In other words, interobserver agreement should be adequate. This underlines the importance of accurate vital sign measurements.

In the following paragraphs, we will discuss vital signs and clinical rules in relation to GPs referral strategy, the impact of vital sign variation on clinical rules throughout patients' ED stay, and the quality of respiratory rate measurements by healthcare providers.

Vital signs and clinical rules in primary care

Although it is clear that vital signs are essential in the 'diagnosis' of sepsis, no studies have – to our knowledge – prospectively investigated which vital signs are measured by GPs in patients with an infection and whether they are associated with referral. In a retrospective survey-based study, GPs indicated that they measure vital signs in the majority of patients with a possible serious infection, in order to decide whether or not a patient has to be referred.[8] In the same study, however, it was found that general appearance, gut feeling and medical history of the patient were considered even more important. As this study may have suffered from recall bias, we prospectively investigated the measurement of vital signs in primary care patients with fever (**chapter 3**).[9]

In our study, we found that GPs measured temperature most often (91.7%) and respiratory rate least often (31.5%). In general, only 1 out of 5 adult patients with fever had a complete set of vital signs measured, which is required for the calculation of SIRS/qSOFA scores. Associated with referral were an abnormal temperature, respiratory

rate and GCS, although they were not always actually measured by the GP. It is possible that patients reported a temperature reading, and a GCS does not truly need to be 'measured'. The respiratory rate, however, is different. First, it was measured in only 1 in 3 patients. Second, if a respiratory rate was not measured by the GP, we measured it afterwards and we reported 32 abnormal (elevated) findings back to the GP. Not once did this information change the decision to refer and half of these patients were *not* referred. This shows that the respiratory rate does not solely determine this decision. It is also possible that GPs do not recognise the prognostic value of an increased respiratory rate, despite extensive attention to this specific vital sign.[28-32] It is likely that GPs assess many patients with an elevated respiratory rate who recover without complications, thus diminishing the value of – slightly – increased respiratory rates. Perhaps, the strict cut-off point of >20 is not adequate for decision-making in a primary care setting.

The fact that both SIRS and qSOFA were also associated with referral is not surprising, since they are both largely made up of the abovementioned vital signs. Research has shown, however, that GPs are frequently not familiar with the 'sepsis-criteria' (e.g. SIRS and qSOFA) and assign most value to gut feeling when deciding whether a patient needs to be referred and when 'diagnosing' sepsis.[33] The fact that both positive SIRS and qSOFA scores are associated with referral suggests that clinical reasoning is in line with these clinical rules.

None of the items associated with referral (i.e. vital signs, clinical rules, gut feeling) were consistently present in all referred patients in our study. This is in line with previous retrospective studies, suggesting other factors are important as well.[8] If patients in our study were referred to the ED, the far majority of these patients were subsequently admitted to the hospital. Also interesting is 14% of patients who were not referred were admitted to hospital later on. Although it is reassuring that no ICU admission or mortality occurred in our sample of not referred patients, numbers were too small to draw definite conclusions.

As the current care system appears to function quite well, this raises the question whether promoting consistent measurement of all vital signs in primary care would result in further improvement of the quality of care for patients with possible infections. The answer to this question is not straightforward, as it is unclear how we should evaluate quality of care within the acute care chain. Several approaches can be used, but all have their drawbacks. For instance, we could measure the number of patients referred by GPs, but it is doubtful whether this accurately represents quality of care. More referrals do not necessarily mean that quality of care has improved, as it is probable that these also include more 'unnecessary' referrals. Even if more referrals would lead to less complications (e.g. less 'missed' cases of sepsis), this could come at the cost of more ED crowding, which in turn

causes other problems.[34] A second option is measuring the number of complications, but these are mostly multifactorial and it is unclear whether the frequency with which complications occur truly represents quality of care on a daily basis. Optimally, we would evaluate whether patients are referred at the right time, but this naturally raises the question how to judge/measure this. It is likely that in almost every patient, it is debatable whether a patient was referred too early, just in time, or too late. This applies to patients with infections and/or sepsis especially, as there is no gold standard test for serious illness and adverse outcome, nor for the need for referral.

In our opinion, the consistent measurement of vital signs has one major advantage. It creates a more complete picture of the patient, without having to make major changes to current practice As mentioned earlier, patients do not become ill the moment they enter the hospital, nor do they stop being ill the moment they are referred. By consistently measuring vital signs throughout the acute care chain, healthcare providers will be able to establish an accurate timeline of vital signs, allowing for better identification of patients at risk for deterioration.[35] . Of course, the administrative burden of these measurements must also be taken into account. In the next section, we will focus on the possible effects of repeated vital sign measurements in the ED.

Vital signs in the ED

When patients present to the ED, their first set of vital signs is often used to assess the severity of illness and subsequently the urgency with which they need to be treated. Often, this is done by using vital sign-based clinical rules, which have cut-off points that serve as warning triggers or activate specific treatment protocols. Due to variation in vital signs throughout a patient's ED stay, clinical rule scores can change over time. The clinical rules most used in guidelines are qSOFA, SIRS, MEWS and NEWS.[2,36-38] In **chapter 5**, we investigated how often the scores of these four frequently used clinical rules changed during the ED stay of 1433 patients with suspected infection.[27]

In our study, we showed that these clinical rule scores changed during ED stay in a substantial proportion of patients. Depending on the clinical rule, 7-17% of patients with an initially normal clinical rule score turned abnormal later on, while over 50% of patients with an abnormal first score turned normal later on (**chapter 5**, Table 4).

The exploration of the progression of these clinical rule scores over time is a unique feature of this study and our findings warranted a closer look at current studies on clinical rules and infections/sepsis. Consequently, we decided to investigate how the use of vital

signs in clinical rules is reported in studies on severe infections/sepsis. We performed a pragmatic PubMed search on 'sepsis' and either 'SIRS', 'qSOFA', 'MEWS' or 'NEWS' and selected studies (from the first 30 results) investigating one or more of these clinical rules in an ED setting. We analysed how investigators reported the vital signs they used by reading the main text and supplements, if applicable. From our findings, we drew two conclusions (Table 1). First, authors do not always report which vital signs were used. This makes interpreting the results of these studies difficult. Second, when authors do report their methods regarding the use of vital signs, several different approaches are reported. Investigators use the first set of measurements, the worst set of measurements (i.e. the most abnormal clinical rule score), or a combination of the worst vital signs measured throughout a patient's ED stay. In all of these cases, a single clinical rule score is eventually calculated. Previous research already showed that repeated vital sign measurements in the ED are better at predicting deterioration than single vital sign measurements and our study showed that clinical rule scores frequently alter throughout patients' ED stay.[35] In addition, by using a combination of the worst vital signs during ED stay, investigators essentially create a non-existing score, once again making interpretation of the results more difficult.

In our opinion, future ED studies should clearly state which vital signs are used when patients are included. In addition, healthcare providers should realise that measurements taken in the ED are not 'the first measurements'. It is plausible that repeated measurements and adequate communication throughout the entire acute care chain can help optimise the care for patients with an infection and/or possible sepsis. The frequent alterations of clinical rule scores in our study support these hypotheses.

Table 1 – Vital sign reporting in studies investigating clinical rules in an ED setting

Study	Location	PS/RS	n	Vital sign measurements
Askim A, et al. Poor performance of quick-SOFA (qSOFA) score in predicting severe sepsis and mortality - a prospective study of patients admitted with infection to the emergency department. Scand J Trauma Resusc Emerg Med 2017 Jun 9 25(1):56.	Norway	PS	1535	At ED arrival
Brink A, et al. Predicting mortality in patients with suspected sepsis at the Emergency Department. A retrospective cohort study comparing qSOFA, SIRS and National Early Warning Score. PLoS One 2019 Jan 25 14(1):e0211133.	Netherlands	RS	8,204	First vital signs, unclear if these were complete sets

Table 1 – continued

Cildir E, et al. Evaluation of the modified MEDS, MEWS score and Charlson comorbidity index in patients with community acquired sepsis in the emergency department. Intern Emerg Med 2013 Apr 8(3):255-260.	Turkey	PS	230	Unclear
Freund Y, et al. Prognostic Accuracy of Sepsis-3 Criteria for In-Hospital Mortality Among Patients With Suspected Infection Presenting to the Emergency Department. JAMA 2017 Jan 17 317(3):301-308.	France, Spain, Belgium, Switzerland	PS	879	Combination of highest RR and SBP and GCS during ED stay
Gando S, et al. The SIRS criteria have better performance for predicting infection than qSOFA scores in the emergency department. Sci Rep 2020 May 15 10(1):8095-020-64314-8.	Japan	RS	1,045	Unclear
Goulden R, et al. qSOFA, SIRS and NEWS for predicting inhospital mortality and ICU admission in emergency admissions treated as sepsis. Emerg Med J 2018 Jun 35(6):345-349.	UK	RS	1818	Unclear
Graham CA, et al. NEWS and qSIRS superior to qSOFA in the prediction of 30-day mortality in emergency department patients in Hong Kong. Ann Med 2020 Nov 52(7):403-412.	Hong Kong	PS	1,253	Unclear
Haydar S, et al. Comparison of QSOFA score and SIRS criteria as screening mechanisms for emergency department sepsis. Am J Emerg Med 2017 Nov 35(11):1730-1733.	USA	RS	200	Unclear
Henning DJ, et al. An Emergency Department Validation of the SEP-3 Sepsis and Septic Shock Definitions and Comparison With 1992 Consensus Definitions. Ann Emerg Med 2017 Oct 70(4):544-552.e5.	USA	PS	7,637	Unclear
Kaukonen KM, et al. Systemic inflammatory response syndrome criteria in defining severe sepsis. N Engl J Med 2015 Apr 23 372(17):1629-1638.	Australia/ New Zealand	RS	109,663	Unclear
Keep JW, et al. National early warning score at Emergency Department triage may allow earlier identification of patients with severe sepsis and septic shock: a retrospective observational study. Emerg Med J 2016 Jan 33(1):37-41.	UK	RS	500	Recorded at triage
Loritz M, et al. Prospective evaluation of the quickSOFA score as a screening for sepsis in the emergency department. Intern Emerg Med 2020 Jun 15(4):685-693.	Germany	PS	1,668	As quickly as possible after triage (<1h)

Table 1 - continued

Nieves Ortega R, et al. Clinical Scores and Formal Triage for Screening of Sepsis and Adverse Outcomes on Arrival in an Emergency Department All-Comer Cohort. J Emerg Med 2019 Oct 57(4):453-460.e2.	Switzerland	PS	2,523	Recorded at triage
Phungoen P, et al. Emergency Severity Index as a predictor of in-hospital mortality in suspected sepsis patients in the emergency department. Am J Emerg Med 2020 Sep 38(9):1854-1859.	Thailand	RS	8,177	First vital signs, unclear if sets were complete
Rothrock SG, et al. Derivation of a screen to identify severe sepsis and septic shock in the ED-BOMBARD vs. SIRS and qSOFA. Am J Emerg Med 2019 Jul 37(7):1260-1267.	USA	RS	143	Unclear
Seymour CW, et al. Assessment of Clinical Criteria for Sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016 Feb 23 315(8):762-774.	USA	RS/PS	148,907	Unclear
Tusgul S, et al. Low sensitivity of qSOFA, SIRS criteria and sepsis definition to identify infected patients at risk of complication in the prehospital setting and at the emergency department triage. Scand J Trauma Resusc Emerg Med 2017 Nov 3 25(1):108.	Switzerland	RS	886	Unclear
Usman OA, et al. Comparison of SIRS, qSOFA, and NEWS for the early identification of sepsis in the Emergency Department. Am J Emerg Med 2019 Aug 37(8):1490-1497.	USA	RS	115,734	Recorded at triage
Williams JM, et al. Systemic Inflammatory Response Syndrome, Quick Sequential Organ Function Assessment, and Organ Dysfunction: Insights From a Prospective Database of ED Patients With Infection. Chest 2017 Mar 151(3):586-596.	Australia	PS	8,871	Most abnormal values of each vital sign
van der Woude SW, et al. Classifying sepsis patients in the emergency department using SIRS, qSOFA or MEWS. Neth J Med 2018 May 76(4):158-166.	Netherlands	RS	198	Unclear

Abbreviations: ED – emergency department, PS – prospective, RS – retrospective, N – number, PMID – PubMed ID, qSOFA – quick Sequential Organ Failure Assessment, SIRS - Systemic inflammatory response syndrome, RETTS – Rapid Emergency Triage and Treatment System, NEWS – National Early Warning score, mMEDS – modified Mortality in Emergency Department Sepsis, RR – respiratory rate, SBP – systolic blood pressure, GCS – Glasgow Coma Scale, MEWS – Modified Early Warning Score, ESI – Emergency Severity Index

An interesting finding in our study is that more than half of all changes in clinical rule scores could be attributed (in whole or in part) to variations in respiratory rate. The

predictive value of respiratory rate has long been recognised, but the fact that it is usually measured manually reduces both the frequency and the reliability of its measurements. In the next section, we will focus on the reliability of respiratory rate measurements by healthcare providers and the effect of interobserver variation on clinical rule scores.

The (in)famous respiratory rate

The respiratory rate can be considered both renowned and notorious. It has been shown to predict deterioration and adverse outcome and is – probably for this reason – the only vital sign included in all the clinical rules mentioned (General introduction, table 3; see also **chapter 5**).[2,30,31,38-40] It is, however, also well-known to be the least recorded vital sign, probably due to it mostly having to be measured manually (see also **chapter 3**).[28,29,31,32,41-47] When a healthcare provider does measure the respiratory rate, an incorrect result can affect the score of clinical rules.[1,9,27,38,39] As these clinical rules are often used in patients with an infection, we investigated in **chapter 6** to what extent inaccurate respiratory rate measurements influence the scores of 4 frequently used clinical rules.

By showing 5 videos with different respiratory rates of one healthy volunteer to 448 healthcare providers, we found measurements to be inaccurate and interobserver-agreement to be suboptimal. The inaccuracy was shown by the finding that – in near-optimal circumstances – almost 25% of the measurements was over 4 breaths per minute lower or higher than the true respiratory rate. Suboptimal agreement was shown by a moderate ICC of 0.64 (95% CI 0.39-0.94).

One could challenge the relevance of somewhat inaccurate respiratory rate measurements by stating that in more than 75% of the patients, the measured value was only up to 4 breaths per minute away from the true respiratory rate. We demonstrated the potential effects of these suboptimal – or incorrect – measurements in our study by using the measured respiratory rates in 4 frequently used clinical rules: qSOFA, SIRS, MEWS and NEWS. When comparing the scores of the clinical rules with the measured and the true respiratory rates, we found differences in scores in a relevant proportion of cases. For qSOFA and SIRS, this occurred in 1 out of 11 cases, for MEWS in 1 out of 3 cases and for NEWS in 1 out of 5 cases. In crowded EDs, the potential effects of this phenomenon are probably significant. Effects in daily practice include excessive alerts with subsequent alarm fatigue, as well as delay in diagnosis and treatment of (critically) ill patients. As a result, we should aim to invest in reliable bedside methods (e.g. using devices) to optimise the measurement of respiratory rates, both in quantity as well as in quality.

Strengths, limitations and future perspectives

In this thesis, we studied the Dutch acute care chain for patients with (severe) infections. The main strengths are the prospective design of our studies, as well as the use of different perspectives: we looked back in the acute care chain from the ED, and forward from the primary care perspective. We specifically chose to 'ignore' existing (hospital) walls, in order to thoroughly explore patients' trajectory through the acute care chain. Another strength in executing research in acute medicine is our use of research students in a GPC setting for optimal data collection (**chapter 3**) and the organisation of a large study using only simple tools, available to most healthcare professionals (**chapter 6**). This is a relatively unexplored field of research and we have identified several potential targets for optimisation of the already well-organised Dutch acute care system. Although most of these possibilities need to be further investigated further to determine whether they will actually lead to better care, it is plausible that optimisation of care is possible, even in the current system and with the resources that are currently available.

In addition to the limitations already discussed, there are some general limitations of this thesis. The most important one is that due to the unique organisation of Dutch (acute) care, our results may not be applicable to other countries. A second limitation lies in the prospective, real-world approach of our studies. We have found that predicting the number of eligible patients in the acute care chain is difficult. This can affect the number of inclusions, especially when patients are prospectively included during a short, labour-intensive inclusion period. As a result, the number of inclusions was sometimes somewhat disappointing, despite a maximum effort to include patients, which may have affected the power of our analyses. Finally, inclusion bias cannot be excluded.

Despite its limitations, this thesis provides a basis for future studies on optimising the care for patients with (severe) infections in the acute care chain. These studies should focus on the following topics: patient journey, interprofessional communication, and reliable vital sign measurements.

First, the journey – or trajectory – of patients with severe infections should be further investigated, with specific attention to the patient's perspective. Although such a study is labour-intensive, it might make it possible to determine whether, and in which patients, prehospital delays have occurred, and whether these delays would have been avoidable. As no reliable diagnostic test for sepsis/adverse outcomes exists, nor will it become available in the near future, we should focus on the diagnostic and prognostic value of vital signs, point-of-care testing (POCT) and gut feeling in the primary care setting. The results may contribute to the development of diagnostic algorithms that help GPs not only in deciding whether to refer, but also *when* to refer and with what urgency.

Second, qualitative research into the experiences of healthcare providers could contribute to the question of why 'sepsis' and a sense of urgency are so rarely documented in handovers. If professionals are reluctant to document their suspicion of sepsis, we need to investigate what is causing this. Is it uncertainty about the diagnosis, lack of knowledge, or do healthcare providers disagree about the severity of the illness?

Third, we must optimise the measurement and documentation of vital signs. Particular attention should be paid to respiratory rate, as it has been shown to be a significant predictor of adverse outcomes. A reliable non-invasive bedside method (e.g. wearables or biosensors) for measuring respiratory rate throughout the acute care chain could be an innovation, as repeated measurements have been shown to predict the outcome better than a single measurement.

Conclusion

In conclusion, we have shown that patients with severe infections are present throughout the entire acute care chain, which runs from the patient's home to the ED. Dutch GPs have a pivotal role in acute care and are often already involved in the treatment of patients with infections before these patients visit the ED. The decision to refer can be difficult, not least due to the lack of a proper diagnostic test for sepsis or adverse outcomes. Nevertheless, most referral decisions appear to be justified, as almost all referred patients are admitted to hospital and the vast majority of non-referred patients are not admitted to hospital later on.

In their assessment of patients with fever, GPs use a combination of history, vital signs and gut feeling to decide whether a patient should be referred. Vital signs are not measured consistently in all patients, with respiratory rate being measured least. Furthermore, the quality of respiratory rate measurements in general appears to be suboptimal, which poses a risk when these measurements are used in clinical rules.

Throughout the acute care chain, documentation of sepsis and a of sense of urgency is suboptimal. Not only is the frequency with which both are documented low, but the agreement between documentation of sepsis and of a sense of urgency is poor and healthcare providers often disagree with each other on the suspicion of both sepsis and sense of urgency.

To improve the care for patients with an infection in the already well-functioning Dutch acute care chain, the topics discussed in this thesis should be further investigated. In addition, healthcare providers could already make a start on further optimising care for

patients without major additional investments. First of all, it would be wise to measure vital signs consistently and accurately throughout the acute care chain. This would allow trends in vital signs to be identified, which are known to predict adverse outcome better than single measurements. Secondly, investments should be made in optimising communication between healthcare providers, not only with regard to vital sign values, but also with regard to the suspicion of sepsis and the sense of urgency among healthcare providers. Accurate information about a patient's condition – and his or her trend – can enable better prioritisation of patients in the ED, which is the funnel of the acute care chain. As EDs become increasingly crowded, these recommendations can be seen not only as optimising care, but also as a necessity. As always, collaboration is key.

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IMPACT PARAGRAPH

In this thesis, we aimed to provide more insight into the journey of patients with a severe infection through the Dutch acute care chain, or, in other words, from home to hospital. In these studies, we focused on optimising care. Below is a summary of the scientific and social impact of this thesis. After that, we will reflect on our experiences with conducting research in acute care.

Scientific impact

The scientific impact of this thesis lies mainly in the identification of possible ways to optimise the care for patients with an infection in the already well-functioning Dutch acute care system. Topics include insight into the prehospital trajectory of patients with an infection in the Emergency Department (ED), reliability of vital sign measurements, and interprofessional communication.

Prehospital trajectory of ED patients with an infection

Prior to this thesis, most research on severe infections and sepsis focused on the hospital environment. However, patients do not become ill the moment they enter the hospital. We therefore investigated the trajectory prior to ED visit and found that most ED patients with an infection already had contact with a general practitioner (GP) and emergency medical services (EMS, ambulance service). In addition, their symptoms had been present for a median of 3 days. These findings suggest that this phase may offer a window of opportunity that allows for a good start of treatment, and that future research should focus on this phase as well. An example could be qualitative research to evaluate individual patient trajectories, both from a physician perspective (e.g. consensus meetings), and from a patient perspective.

Reliability of vital sign measurements

Throughout several chapters, we described the frequency and quality of vital sign measurements, which are essential in the suspicion/diagnosis of sepsis. The finding that vital signs are not consistently measured suggests that there is room for improvement in daily practice, although we did not investigate the effect of measuring vital signs.

Special attention should be paid to the respiratory rate; a vital sign which has been known to reflect severe illness, but is measured least frequently. Both of these characteristics

were confirmed once again in our studies, and in addition, we showed that manual measurements of the respiratory rate are often inaccurate. This can affect clinical rule scores, especially when these rules use strict cut-off values. In our opinion, it would be wise to investigate the added value of reliable non-invasive methods to measure the respiratory rate throughout the entire acute care chain.

Finally, many studies use routinely gathered vital sign measurements in their datasets. This strategy has drawbacks, specifically when it is unknown whether a patient already received therapy prior to the measurements, and if so, what therapy. These drawbacks should be taken into account when interpreting the results from these studies. The finding that vital signs are not measured consistently, and some (e.g. respiratory rate) not accurately, affects the reliability of studies that use vital sign measurements. Especially in case of – manually measured – respiratory rate values, one should realise that some of these values will be inaccurate. Future studies performed in the acute care chain should at a minimum document when vital signs were measured, in order to make interpretation of findings possible.

Interprofessional communication

Due to the lack of a diagnostic test for serious illness, sepsis, or the need for referral, and the caveats regarding vital sign measurements, it is indispensable that healthcare providers have relevant and accurate information at their disposal. Our findings suggest that there is room for improvement in the documentation of sepsis and of a sense of urgency. Future – preferably qualitative – studies should focus on why sepsis and a sense of urgency are so poorly documented in medical records, and how this can be improved. It should then be measured whether better documentation indeed leads to better care, taking into account the administrative workload.

Social impact

Relevance for healthcare providers

Several of the research findings described in this thesis are important for healthcare providers working in acute care every day. By providing additional insight in the population of patients with an infection in the Dutch acute care system, we hope to contribute to the knowledge of this population of patients and identify potential targets for optimisation of care. An important finding is that, prior to their ED visit, patients have

already been having symptoms for several days. Healthcare providers should realise this and acknowledge that vital signs measured at arrival in the ED are not the first, nor are they the last measurements. This is especially relevant as vital signs vary over time. In our case this happened during patients' ED stay, but it is likely that this also happens in the prehospital setting. Healthcare providers should realise that – even if measurements are 100% accurate – variation in vital signs can influence healthcare providers' perception of severity of illness. These vital signs are also not the only factor that decides whether a patient should be referred or not. As such, it is important for referring healthcare providers to hand over all relevant considerations, but also for receiving healthcare providers to actively ask relevant questions. Collaboration between healthcare providers, using each other's specific knowledge and skills, is likely the best way to further optimise care for patients.

Relevance for patients, caregivers and society

This thesis provides insight in the trajectory of patients with a severe infection through the acute care chain. Luckily, most infections are self-limiting or resolve with oral antibiotics, but sometimes referral to the ED is necessary. In this thesis, we provided insight in the Dutch approach to patients with serious infections and defined possible targets for optimisation of care. The major challenge that healthcare providers are faced with is identifying who is at risk of deterioration and who is likely to recover without complications. In the absence of a definite diagnostic test for sepsis/serious infection, healthcare providers need to base their decision on information shared by the patient and/or his or her caregivers and a physical examination of the patient. Society should realise that – even though we live in 2022 – healthcare providers often need to make estimations, especially in case of infections, and cannot always truly diagnose a disease. Variation in vital sign values and inaccuracy of vital sign measurements complicate this estimation, making it impossible for healthcare providers to provide patients with a 100% accurate prediction for the future. We do feel, however, that systematic measurement of vital signs and the development of diagnostic aids could improve accuracy, and subsequently the efficacy of the acute care system.

A logical question after reading this thesis would be what the impact of the COVID-19 pandemic on the findings in this thesis has been. Based on experience from the field, we know that patients with a COVID-19 infection often stayed at home as long as possible, possibly changing the duration of symptoms prior to ED visit. In addition, we have found that the COVID-19 pandemic has expanded the development and implementation of remote monitoring enormously, making it possible to gather more vital signs than

previously possible. It is likely that this progress will continue in the future, for instance through the recording of data by patients themselves by wearing intelligent monitoring devices. Whatever the effects of these developments, the primary aim should always be to provide high quality care.

Personal insights, likely to be relevant for acute care researchers

In addition to its scientific and social impact, this thesis has provided myself insight in how to carry out clinical research in acute care settings. In my opinion, it is valuable for readers to share my experiences, as this might make future colleagues' work easier.

First, inclusion of patients in acute care settings can be difficult. Every day in the ED is different and reliable planning of inclusions is nearly impossible. At quiet times, there are little patients eligible for inclusion, while at busy times, professionals can be so occupied that research projects are – understandably – not given priority. A great solution for us was the use of dedicated research students. Advantages of this approach included relieving bedside professionals of the burden of research administration, a continuous flow of inclusions (independent of the situation in the ED) and likely more time for informed consent procedures. Feedback from students showed that they particularly enjoyed the opportunity to peek inside the world of acute care, which – to them – can feel like 'uncharted territory'. I would therefore wholeheartedly recommend this approach for future projects.

Second, it is important to note that patients can be hesitant to participate in acute care research projects, even for non-interventional studies. When patients were asked why they did not want to participate, explanations included 'not feeling like it', 'not having time to answer all questions', or the feeling that it was inappropriate of researchers to ask for study participation in 'such an acute situation'. While this can be disappointing for researchers, a personal experience with acute care reminded me to put effort in the informed consent approach. Taking time and acknowledging the fact that patients are likely occupied with quite different things than research makes a huge difference. The organisation of future research projects should take this into account.

The importance of adequate communication in acute care research does not only apply to patients, but to healthcare professionals as well. As illustrated in this thesis, the acute care chain consists of several stations, which are in turn manned by several professionals, who often work in shifts. The absolute number of GPCs and EDs in the Netherlands keeps decreasing, creating larger organisations with complex infrastructures. As a result, the

number of potential colleagues involved in one's research project can be massive. In addition to having a pivotal role in acute care, I have come to believe that emergency physicians are also indispensable for acute care research. By working as a staff member in the ED every day and fully understanding the acute care chain, we are able to make small adjustments in research-related processes. In addition, we often personally know colleagues inside and outside the hospital, whose participation in research projects is crucial.

As a physician, I believe that it is up to us as professionals to guide ill patients through the acute care chain. I would like to apply that same statement to research as well, once again underling the importance of a dedicated team of staff members working in the ED.

Implementation in daily practice

The results of this thesis will be shared with others in several ways. First, all chapters have already been published in peer-reviewed medical journals, most of which are openly accessible online. Secondly, this thesis will be published online, in order to make it readable for everyone interested. Finally, we will present the results of this thesis at scientific meetings, congresses or webinars. By sharing this information with others, new collaborations can be created.

SUMMARY

Infections are among the most common reasons for people to visit a healthcare provider. As described in **chapter 1**, the majority of infections are self-limiting or resolve with oral antibiotics. Sometimes, however, additional care in hospital is needed. Decisions on referral and treatment depend on several factors, among which the risk of sepsis.

Sepsis is a syndrome defined as "life-threatening organ dysfunction caused by a dysregulated host response to infection". It is the most prominent complication of an infection and its treatment and prognosis is time-sensitive. To minimize the risk of further deterioration, patients with sepsis should receive intravenous antibiotics as soon as possible.

Unfortunately, there is no definite diagnostic test that proves or rules out sepsis. Healthcare providers therefore primarily rely on their own skills to establish suspicion of sepsis. Secondly, they can use clinical rules, developed over the past decades as aids in clinical decision-making. Sepsis-specific examples include the quick Sequential Organ Failure Assessment (qSOFA) score and the Systemic Inflammatory Response Syndrome (SIRS) criteria. Other, more general rules which indicate severity of disease are the Modified Early Warning Score (MEWS) and the National Early Warning Score (NEWS). Although practically useable in nearly all settings, evidence on their diagnostic value in primary care settings is lacking.

The Dutch acute care chain is unique in its design, with a pivotal – gatekeeper – role for GPs. The primary goal of this system is to provide appropriate care for acute medical problems by the person best suited for the task at hand, as close to home as possible. Although the Dutch system is recognised as one of the best care systems worldwide, we deemed it necessary to investigate the trajectory of patients with a severe infection through the Dutch acute care chain. Herein, we paid specific attention to possible targets for optimisation of care.

In **chapter 2**, we showed the results of a prospective cohort study on 440 emergency department (ED) patients with an infection ("the ED perspective). We found that for most of these patients, the acute care chain started with a contact with the GP (≈80%) and transport by emergency medical services (EMS, ≈60%)). Median symptom duration was 3 days prior to the ED visit. Almost half of the patients had already visited their GP once or more and nearly one in three patients had already used antibiotics. These findings provided a basis for future research on the prehospital phase of ED patients with an infection and sepsis.

Subsequently, we described the results of a second prospective cohort study from the primary care perspective in **chapter 3**. Herein, we included 108 patients with fever who visited one of two general practitioner cooperatives (GPCs) during out-of-hours. After the GP's assessment, two out of five patients were referred to the ED, after which ≈90% were admitted to hospital. Of the not referred patients, one in seven patients was admitted to hospital later on (within a week of the GPC visit).

During the assessment of patients, GPs rarely (≈20%) measured all vital signs needed to calculate SIRS and qSOFA scores. The respiratory rate was – by far – measured least often (≈30%). Although signs of sepsis could potentially be missed by not measuring all vital signs, we found that referred patients had higher respiratory rates and temperatures, and more often an abnormal level of consciousness than not referred patients. Positive SIRS and qSOFA scores, as well as a sense of alarm (gut feeling) were associated with referral.

We concluded that although ED referral was associated with some vital signs, clinical rules and gut feeling, the decision to refer a patient is not dependent on one of these factors alone. Future research may focus on the diagnostic and prognostic value of vital signs, the use of point-of-care tests (POCT), such as lactate and/or CRP, and gut feeling in primary care to help develop diagnostic algorithms for GPs that aid in the decision to refer, especially since more and more possibilities for treatment at home are emerging. For these algorithms to be developed and to work adequately, systematic measurement and recording of vital signs is indispensable, either manually or by using electronic devices.

When different healthcare providers are involved in a patient's care, sharing relevant information is key. Therefore, in **chapter 4**, we prospectively examined the documentation of the diagnosis/suspicion of sepsis and a sense of urgency in patients with possible sepsis throughout the acute care chain. We found that sepsis or a sense of urgency were documented in approximately one in five medical records. In only one in twenty patients was sepsis documented by all professionals in the acute care chain, while a sense of urgency was documented by all professionals in one in thirteen patients.

Despite a significant association between the documentation of sepsis and that of a sense of urgency, the agreement between these two was low (kappa 0.19-0.39). This shows that the word sepsis likely does not have the same meaning for every healthcare provider in the acute care chain and that documenting it not necessarily creates a sense of urgency.

Perhaps even more interesting is that not only the agreement between the documentation of sepsis and of a sense of urgency was poor, but also that healthcare

providers often disagreed with each other on the suspicion of both sepsis and of a sense of urgency. Despite similar percentages of documentation of sepsis and a sense of urgency in the letters created by GPs, EMS and ED physicians, these were often not the same patients.

We concluded that regardless of a patient's status, the care system must be organised in such a way that the necessary information is always passed on adequately. Especially in the case of possible sepsis, reliable documentation of vital signs, suspicion of sepsis and a sense of urgency can contribute to early recognition, which in turn demonstrably shortens the time to the initiation of appropriate therapy.

In **chapter 5**, we explored how the variation in vital signs during the ED stay of patients with suspected infection affects the score of qSOFA, SIRS, MEWS and NEWS, and which vital signs caused most changes in these clinical rule scores. We found that during ED stay, qSOFA scores altered in 1 in 9 patients, SIRS in 1 in 4 patients, MEWS in 1 in 5 patients and NEWS in 1 in 4 patients. Approximately half of alterations were from a normal to an abnormal score and half vice versa. Depending on the clinical rule, 7-17% of patients with an initially normal clinical rule score turned abnormal later on, while over 50% of patients with an abnormal first score turned normal later on. Over half of all changes in clinical rule scores could be attributed (in whole or in part) to variations in respiratory rate. Our findings showed that vital sign variation affects clinical rule scores in a relevant proportion of patients. Healthcare providers should be aware of this phenomenon, as the timing of vital sign measurement may affect the score of clinical rules, both during ED stay as well as in the prehospital setting.

Chapter 6 focused on the respiratory rate. By showing 5 videos with different respiratory rates of one healthy volunteer to 448 healthcare providers, we found measurements to be inaccurate and interobserver-agreement to be suboptimal. The inaccuracy was shown by the finding that almost 25% of the measurements was over 4 breaths per minute lower or higher than the true respiratory rate. Suboptimal agreement was shown by a moderate ICC of 0.64 (95% CI 0.39-0.94). We illustrated the clinical relevance of these findings by using the measured respiratory rates in the qSOFA, SIRS, MEWS and NEWS scores. When comparing the scores of these clinical rules with the measured and the true respiratory rates, we found differences in scores in a relevant proportion of cases. For qSOFA and SIRS, this occurred in 1 out of 11 cases, for MEWS in 1 out of 3 cases and for NEWS in 1 out of 5 cases. The potential effects of this phenomenon are probably important and include

both excessive alerts with subsequent alarm fatigue, as well as delay in diagnosis and treatment of (critically) ill patients.

In **chapter 7**, we present the general discussion of this thesis. The main findings are summarised, placed in a broader context and compared with previous literature, after which future perspectives are offered.

In summary, we have shown that patients with severe infections are present all across the acute care chain and that Dutch GPs fulfil a pivotal role. In their decision whether or not to refer, GPs use a combination of history, vital signs and gut feeling. Vital signs are not measured consistently in all patients, with respiratory rate being measured least often and less optimal than required. Although this does not appear to lead to serious problems at first sight, it could pose a risk when these measurements are used in clinical rules. Since vital signs vary over time, clinical rules vary with them. When erroneous measurements are used in these clinical rules, their performance is suboptimal, both in primary care as well as in the ED. The frequency of documentation of the suspicion of sepsis and of a sense of urgency throughout the acute care chain is suboptimal and deserves the attention of healthcare providers.

Aside from serving as a basis for future research, this thesis provides two important recommendations. First, we should measure vital signs consistently and accurately in order to establish their true value, and second, we should communicate clearly regarding these vital signs, the suspicion of sepsis and whether or not we have concerns about a patient (sense of urgency). As always, collaboration is key.

SAMENVATTING

Infecties vallen onder de meest voorkomende redenen voor mensen om zorg te vragen bij een medisch professional. In **hoofdstuk 1** beschreven wij dat het merendeel van de infecties vanzelf, al dan niet ondersteund door orale antibiotica, overgaat. Soms is echter extra zorg in een ziekenhuis nodig. Beslissingen ten aanzien van verwijzing en behandeling zijn afhankelijk van verschillende factoren, waaronder het risico op sepsis.

Sepsis is een syndroom met als definitie “een levensbedreigende orgaandysfunctie, veroorzaakt door een disregulatie in de gastheer respons ten gevolge van een infectie.” Het is de meest prominente complicatie van een infectie en diens behandeling en prognose zijn tijdsgevoelig. Om het risico op verdere achteruitgang te minimaliseren dienen patiënten met sepsis zo snel mogelijk intraveneus antibiotica toegediend te krijgen.

Er is helaas geen goede diagnostische test die sepsis aantoont of uitsluit. Medische professionals zijn daarom aangewezen op hun eigen kennis en vaardigheden bij het vaststellen van een (verdenking op) sepsis. Klinische beslisregels kunnen gebruikt worden ter ondersteuning, waarbij de quick Sequential Organ Failure Assessment (qSOFA) score en de Systemic Inflammatory Response Syndrome (SIRS) criteria sepsis-specifieke voorbeelden zijn. Andere, meer algemene beslisregels, zoals de Modified Early Warning Score (MEWS) en de National Early Warning Score (NEWS) zijn ontwikkeld om een acute achteruitgang in iemands conditie vast te stellen. Hoewel ze praktisch bruikbaar zijn in vrijwel alle settingen ontbreekt bewijs voor de diagnostische waarde in de eerste lijn.

De Nederlandse acute zorgketen is uniek, met een essentiële – poortwachters – rol voor huisartsen. Met deze werkwijze probeert men patiënten met een acute zorgvraag de beste zorg te leveren, door de persoon die het meest geschikt is voor de gevraagde taak, zo dichtbij huis als mogelijk. Wij onderzochten het traject van patiënten met een ernstige infectie door deze zorgketen heen en besteedden specifiek aandacht aan waar dit – wereldwijd geroemde – zorgsysteem nog verder verbeterd kan worden.

In **hoofdstuk 2** presenteerden wij de resultaten van een prospectieve cohortstudie met 440 patiënten op de spoedeisende hulp (SEH) met een infectie (“het SEH-perspectief”). Onze resultaten lieten zien dat het merendeel van deze patiënten in de acute zorgketen contact heeft met een huisarts (≈80%) en met een ambulance naar het ziekenhuis komt (≈60%). De mediane duur van symptomen was 3 dagen voorafgaand aan het SEH bezoek. Bijna de helft van de patiënten had al eerder zijn/haar huisarts bezocht gedurende de huidige ziekteperiode en bijna 1 op de 3 patiënten had reeds antibiotica gebruikt. Deze studie diende als basis voor meer onderzoek naar de prehospitale fase van patiënten op de SEH met een infectie en/of sepsis.

Vervolgens beschreven we de resultaten van een tweede prospectieve cohortstudie vanuit het perspectief van de eerste lijn in **hoofdstuk 3**. In deze studie includeerden we 108 patiënten met koorts die buiten kantooruren behandeld werden door een huisarts van een van twee deelnemende huisartsenposten (HAPs). Na de beoordeling door de huisarts werden 2 van iedere 5 patiënten verwezen naar de SEH, waarna ≈90% werd opgenomen in het ziekenhuis. Van de niet verwezen patiënten werd 1 op de 7 alsnog opgenomen in het ziekenhuis binnen een week na het HAP bezoek.

Tijdens de beoordeling van hun patiënten maten huisartsen zelden (≈20%) alle vitale waarden die nodig zijn om SIRS en qSOFA scores te kunnen berekenen. De ademfrequentie was – veruit- het minst vaak gemeten (≈30%). Hoewel sepsis theoretisch gemist zou kunnen worden door het niet meten van alle vitale waarden, bleken verwezen patiënten vaker een hogere ademfrequenties en temperatuur te hebben, als ook vaker een abnormaal bewustzijn, dan niet verwezen patiënten. Positieve SIRS en qSOFA scores, als ook een niet pluisgevoel waren geassocieerd met verwijzing naar de SEH.

Ondanks de gevonden associaties tussen verwijzing naar de SEH en vitale waarden, klinische beslisregels en het pluis-/niet pluisgevoel, concludeerden wij dat het besluit om een patiënt te verwijzen niet bepaald wordt door één van deze items op zichzelf. In toekomstige studies is het verstandig aandacht te besteden aan de diagnostische en prognostische waarde van vitale parameters, point-of-care testen (POCT) en het pluis-/niet pluisgevoel. Wellicht is het nadien mogelijk om diagnostische algoritmen te ontwikkelen die kunnen helpen bij het besluit al dan niet te verwijzen, en op welk moment. Dit besluit wordt waarschijnlijk alleen maar belangrijker, zeker als we meer gebruik gaan maken van de mogelijkheden om patiënten thuis te behandelen. Om de genoemde algoritmen goed te laten functioneren is het systematisch meten en registreren van vitale waarden onontbeerlijk, al dan niet middels het gebruik van elektronische apparatuur.

Als er verschillende professionals betrokken zijn bij de medische zorg voor een patiënt is het belangrijk relevante informatie met elkaar te delen. In **hoofdstuk 4** onderzochten wij daarom prospectief hoe de documentatie van ‘sepsis’ en van het urgentiegevoel bij patiënten met mogelijke sepsis is binnen de acute zorgketen. We vonden dat sepsis of een gevoel van urgentie gedocumenteerd werd in 1 op de 5 patiëntbrieven. In slechts 1 op de 20 patiënten documenteerden alle betrokken professionals sepsis, terwijl een gevoel van urgentie door iedereen werd gedocumenteerd in 1 op de 13 patiënten.

Ondanks een significante associatie tussen de documentatie van sepsis en die van een urgentiegevoel was de overeenstemming tussen beide laag (kappa 0.19-0.39). Dit laat zien dat het woord sepsis waarschijnlijk niet hetzelfde betekent voor alle professionals binnen

de acute zorgketen. Daarnaast zorgt het documenteren van het woord 'sepsis' waarschijnlijk niet altijd voor een gevoel van urgentie.

Een interessante bevinding in deze studie was dat niet alleen de overeenstemming tussen de documentatie van sepsis en die van een gevoel van urgentie laag was, maar ook dat zorgprofessionals het vaak niet met elkaar eens zijn over de verdenking op sepsis en het gevoel van urgentie. Ondanks het feit dat de percentages van documentatie van beide overeenkwamen tussen huisartsen, ambulance medewerkers en artsen op de SEH, waren dit vaak niet dezelfde patiënten.

Wij concludeerden dat het zorgsysteem, ongeacht de klinische toestand van een patiënt, zo georganiseerd moet worden dat relevante informatie altijd goed overgedragen kan worden aan de volgende hulpverlener in de keten. Zeker in het geval van sepsis zijn betrouwbare documentatie van vitale waarden, de verdenking op sepsis en het gevoel van urgentie essentieel om vroege herkenning te verbeteren. Als sepsis eerder herkend wordt, kan de benodigde therapie ook eerder ingezet worden.

In **hoofdstuk 5** onderzochten we hoe de variatie van vitale waarden tijdens een SEH-bezoek van patiënten met een infectie de scores van qSOFA, SIRS, MEWS en NEWS beïnvloedt en welke vitale waarden deze veranderingen veroorzaakten. We vonden dat tijdens een SEH bezoek, de score van qSOFA veranderde in 1 op de 9 patiënten, bij SIRS in 1 op de 4, bij MEWS in 1 op de 5 en bij NEWS in 1 op de 4. Ongeveer de helft van de veranderingen waren van een negatieve (normale) naar een positieve (abnormale) score en de helft vice versa. Tussen de 7 en 17% van de patiënten met een initieel normale score had later een abnormale score, terwijl meer dan de helft van de patiënten met een initieel abnormale score later een normale score liet zien. Meer dan de helft van de veranderingen in de scores van de klinische beslisregels kon toegeschreven worden aan de ademfrequentie. Onze bevindingen laten zien dat variatie in vitale waarden in een aanzienlijk deel van de patiënten invloed heeft op de scores van klinische beslisregels. Zorgprofessionals moeten zich realiseren dat het moment waarop vitale waarden gemeten worden van invloed kan zijn op de scores van klinische beslisregels, zowel tijdens SEH bezoek als in de prehospitale setting.

In **hoofdstuk 6** lichtten we de ademfrequentie uit door 5 video's met verschillende ademfrequenties van een gezonde vrijwilliger te laten zien aan 448 zorgprofessionals. We vonden onnauwkeurigheid in de metingen, zichtbaar in de bevinding dat bijna 25% van de gerapporteerde metingen zich meer dan 4/min. boven of onder de werkelijke ademfrequentie bevond. Een matige intraclass correlation coëfficiënt van 0,64 illustreerde daarnaast een suboptimale overeenstemming tussen respondenten. De klinische relevantie van deze bevindingen werd zichtbaar door de gemeten ademfrequenties te

gebruiken in de qSOFA, SIRS, MEWS en NEWS scores. Door de scores van de deze beslisregels met de gemeten en de werkelijke ademfrequenties te vergelijken vonden we in een relevant deel van de gevallen een verschil in score. Dit gebeurde in op de 11 keer bij qSOFA en SIRS, 1 op de 3 keer bij de MEWS en 1 op de 5 keer bij de NEWS. De potentiële gevolgen van dit fenomeen zijn waarschijnlijk belangrijk. Dit kan zowel te vaak alarmeren zijn, maar ook vertraging in de diagnostiek en behandeling van (kritiek) zieke patiënten.

Het laatste hoofdstuk in dit proefschrift is **hoofdstuk 7**, waarin de algemene discussie te vinden is. De belangrijkste bevindingen van dit proefschrift worden hier in een bredere context geplaatst en vergeleken met bestaande literatuur. Ook worden er aanbevelingen gedaan voor de toekomst.

Samengevat hebben we laten zien dat patiënten met ernstige infecties aanwezig zijn in de Nederlandse acute zorgketen en dat Nederlandse huisartsen een belangrijke rol vervullen. Bij het besluit om een patiënt al dan niet te verwijzen gebruiken huisartsen een combinatie van voorgeschiedenis, vitale waarden en pluis-/niet pluisgevoel. Vitale waarden worden niet consistent gemeten bij alle patiënten, waarbij de ademfrequentie het minst vaak en suboptimaal gemeten wordt. Hoewel dit niet tot problemen lijkt te leiden zou dit een risico kunnen veroorzaken wanneer deze metingen gebruikt worden in klinische beslisregels. Aangezien vitale waarden fluctueren over de tijd variëren de scores van klinische beslisregels ook. Als foutieve metingen gebruikt worden in deze beslisregels zullen ze suboptimaal presteren, zowel in de eerste als in de tweede lijn. Daarnaast is de documentatie van de verdenking op sepsis en het gevoel van urgentie suboptimaal in de gehele acute zorgketen. Dit verdient de aandacht van alle betrokken zorgprofessionals.

Dit proefschrift dient niet alleen als een basis voor toekomstig onderzoek, maar bevat ook twee belangrijke aanbevelingen. Allereerst moeten we vitale waarden consequent en accuraat meten om hun klinische waarde te kunnen bepalen. Daarnaast zullen we als zorgverleners duidelijk moeten communiceren met elkaar, niet alleen met betrekking tot de vitale waarden, maar ook de eventuele verdenking op sepsis en of we ons al dan niet zorgen maken om een patiënt (gevoel van urgentie). Zoals altijd blijft samenwerken de sleutel tot de oplossing.

DANKWOORD

Het is klaar! Het zit erop! Eindelijk is mijn proefschrift klaar. Dit boekje, het product van enkele jaren onderzoek. Zonder de begeleiding, de hulp en de ondersteuning van een aantal mensen was dit boekje er nooit geweest. Aan iedereen die zich nu aangesproken voelt: bedankt!

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Alle patiënten die deel hebben genomen aan een van de onderzoeken. Zonder deelname van patiënten geen onderzoek. Ook in acute situaties toch bereid om deel te nemen, waarvoor veel dank!

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de juiste plek. Niet alles gaat altijd vanzelf, maar weet één ding; ik kijk naar je op. Je kunt veel meer dan je denkt. Janou, wat ben ik enorm trots op je. Elke keer verleg je je grenzen, fantastisch! Mam, bedankt voor alles. Ik vind het zo knap dat je weer terug de zorg in bent gegaan. Als ik mijn kinderen half zo goed opvoed als jij gedaan hebt ben ik tevreden.

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CURRICULUM VITAE

Gideon Latten was born on the 14th of April 1986 in Sittard, the Netherlands. He grew up in Sittard and completed secondary school at Trevianum in Sittard. He subsequently started medical school in Maastricht and graduated in 2010. In 2012, he started his specialisation in emergency medicine under the supervision of Guy Mostard and Mark Klein Ovink. In 2015, he graduated and started his work as an emergency medicine consultant in Zuyderland Medical Centre, where he has continued to work until now. In 2016, his PhD trajectory started in collaboration with dr. Patricia Stassen and Prof. dr. Jochen Cals. Together with his supervisors, he started to explore the Dutch acute care chain and searched for ways to optimise care. His publications on this subject are presented in the current thesis.

In his free time Gideon enjoys cycling, swimming and working on old cars. He lives happily in Maasbracht, together with his wife Loes and kids Evi, Siem and Jip.