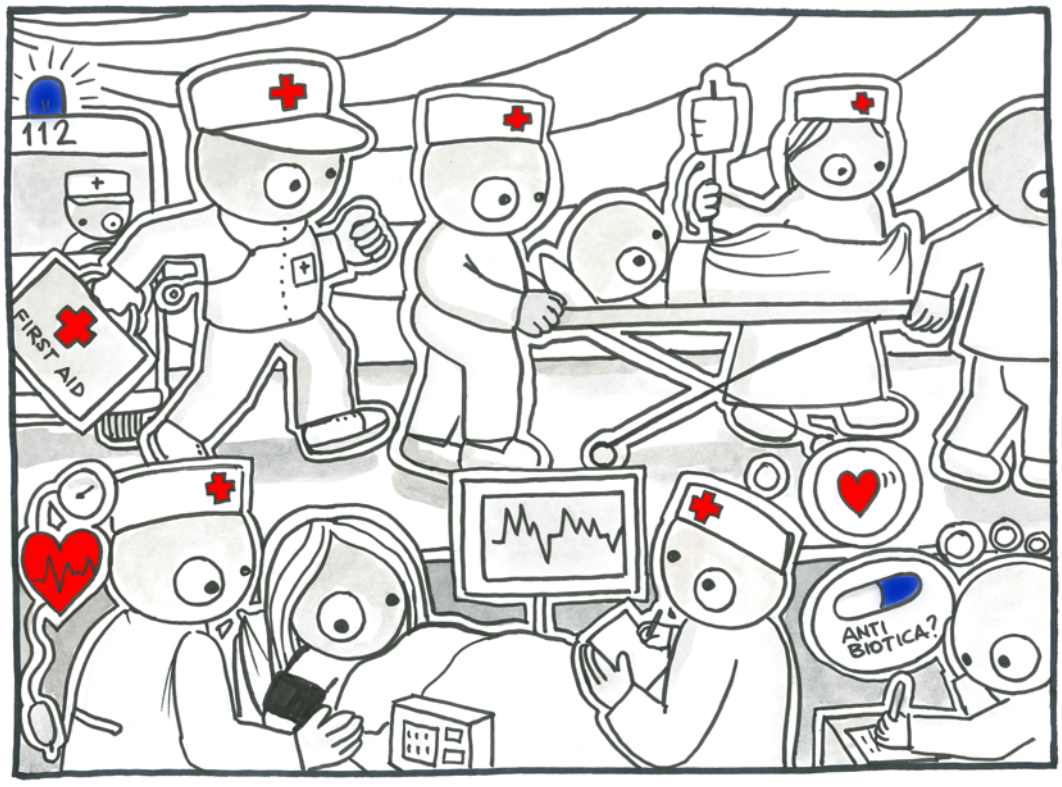
Predicting the Severity of Illness and Outcomes in the Emergency Department



Jelmer Alsma

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Predicting the Severity of Illness and Outcomes in the Emergency Department

Het voorspellen van de ernst van ziekte en van uitkomsten op de Spoedeisende hulp

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Jelmer Alsma
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Erasmus University Rotterdam

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"Life is what happens to you, while you're busy making other plans."

John Lennon

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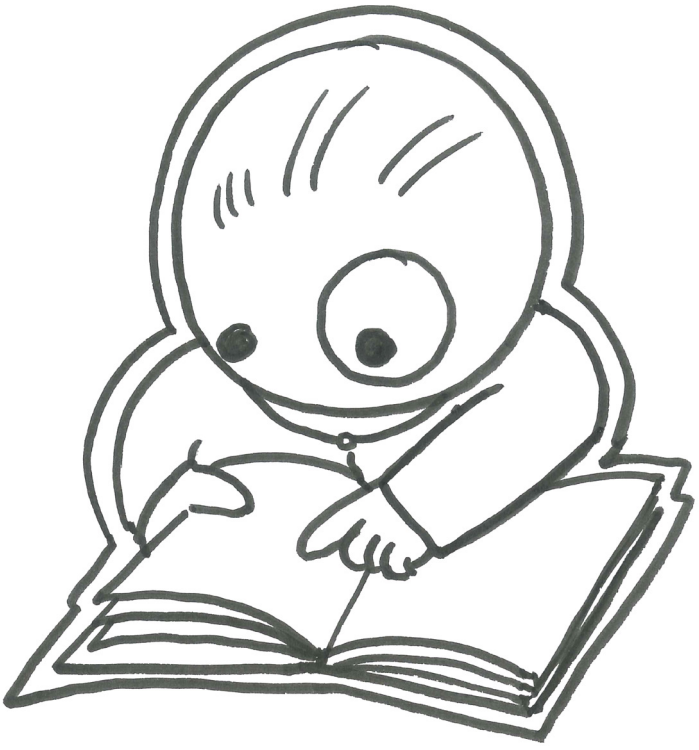
Introduction



Chapter 1

General Introduction

History of acute medicine

In the midst of the previous century, the emergency department (ED) started to evolve from 'accident rooms' to emergency units with most specialties present, and who work in multidisciplinary teams.[1] During these years, the majority of patients were sent home after treatment.[1] The role of ambulances changed in the following decades from merely being modes of patient transportation to mobile hospitals with skilled staff, which resulted in patients reaching the hospital alive, who would have previously died. This required a change in staffing of the ED accordingly. Initially, physicians in the ED were not adequately trained and were often more junior and largely unsupervised. When the conditions were too complex, surgeons and other specialists, such as internists, were consulted and care was then handed over.[1] Increase in both complexity and severity of illness of patients presenting to the ED resulted in the introduction of emergency physicians approximately 70 years ago in the United States and the United Kingdom, and only 10 years ago in the Netherlands.[2] Dutch emergency physicians have a three-year training program consisting of training in the ED, intensive care medicine, anaesthesiology, cardiology and paediatrics. The first task of these emergency physicians was to assess whether a patient is critically ill; subsequently they initiated treatment and decided if – and which – medical specialist should be consulted.

It was not until the end of the previous century that realization came that there was a need for skilled senior medical presence in the ED, and in recently introduced acute medical units (AMU).[3,4] This was the result of increasing numbers of patients with growing complexity due to more chronic illnesses and advanced age. In 2003, the Specialist Training Authority of the Medical Royal Colleges in the United Kingdom recognized acute medicine as a subspecialty of internal medicine. The Netherlands followed in 2012, and acute medicine was likewise recognized as a subspecialty of internal medicine, requiring a training of six years. In the Netherlands, internists specialized in acute medicine, i.e. acute physicians, are increasingly manning EDs to improve care for medical patients where they encounter overcrowding, patients with more complex diseases, multiple chronic illnesses and complications of novel therapies. These acute physicians try to predict which patient is most ill and who can be safely discharged, and which therapy will be most beneficial for which patient. For this process they use medical history, physical examination, results of additional testing as well as guidelines and prediction models. A recent survey in 76 of 90 Dutch hospitals with an ED showed that approximately 67% of the Dutch hospitals have acute physicians (i.e. internists), and 84% have emergency physicians. The working arrangements between internists and emergency physicians vary between hospitals. In 85% of the hospitals internists are present on the work floor as consultant, coordinator or as manager.[5]

Triage, Prediction Models and Early Warning Systems

To ensure that the most gravely ill patient requiring urgent care is treated first, physicians rely on triage. Triage is employed not only in the ED but also in prehospital mass-casualty

disasters; its aim is to identify which patient needs immediate care and which patient can wait. The word triage originates from the French word *trier*, which means to select or to separate and its modern form was invented by the French surgeon Dominique Jean Larrey (1766-1842) of the Napoleonic Grand Armee.[6] Simple prehospital triage uses only vital signs whilst in-hospital triage systems use a combination of vital signs and presenting symptoms, which most often result in a 5-step triage level. Examples are the Manchester Triage System (MTS) and Emergency Severity Index (ESI).[6] A frequent problem with these models is under- and over triage, in which the severity of the condition of the patient is either under- or overestimated. Undertriage results in delayed care with potential detrimental effects on outcomes and costs; overtriage allocates care to patients who do not critically need it, potentially delaying care for patients who do need it most.[7] Patients who are at the extremes of age (i.e. children and the elderly), especially those with chronic illness, are most at risk for incorrect triage. The elderly are mostly undertriaged and the risk increases with age.[8,9] Reasons for over- and undertriage are complex and multifactorial. For example, elderly patients often have atypical presentation of illness as well as multiple comorbidities – resulting in polypharmacy; making it more challenging to identify the acute problem.[10]

Therefore, as a complement to triage, physicians in the ED developed clinical prediction models to support decision making. A prediction model quantifies the individual contribution to predicting the diagnosis, prognosis, or therapeutic effect from a combination of factors such as history, physical examination, and laboratory results.[11] In their optimal form, these models improve clinical judgment, save costs, and change medical behaviour with minimal risk for the patient.[11] Steyerberg and Vergouwe proposed a seven-step framework for developing prediction models. The steps are summarized in *Table 1*.

The first step is to consider the problem, define the research question and inspect the data. The second step is to code (and recode) predictors. In the third step the model should be specified and predictors for the model should be chosen. In the fourth step the regression coefficients need to be estimated. In the fifth step the quality and performance of a model need to be determined. In the sixth step the model should be validated. Ideally, the validity of a prediction model is assessed using independent data. There are four key measures to evaluate the performance of a prediction model, namely

Table 1: 7 steps for developing a prediction model

Step	Action
1	Problem definition and data inspection
2	(Re)coding of predictors
3	Model specification
4	Model estimation
5	Model performance
6	Model validation
7	Model presentation

the model intercept, calibration slope, discrimination and clinical usefulness. As a final step the model should be presented in a form appropriate for the potential users.[12] Prediction models are probably underused in clinical practice. This may be the result of inappropriate model development, lack of validation, and no impact analysis.

There are many prediction models used in the ED by various specialties to predict diagnosis, prognosis, or treatment effect. An example of a diagnostic prediction model used by acute physicians is the Wells' criteria for deep vein thrombosis.[13] This score uses findings from history and physical examination, combined with a laboratory test (i.e. d-dimer) to rule out deep vein thrombosis, or to recommend further testing. Other examples include the YEARS criteria and Wells' criteria for pulmonary embolism.[13,14] An example of a prognostic decision tool is the Acute Presenting Older Patient (APOP) screener, which predicts functional decline after 90 days in elderly patients presenting in the ED based on eight items. This results in a recommendation specific for the vulnerable elderly patients, and advises the physician on additional measures to improve outcome.[15] In patients with suspected sepsis the quick Sepsis Related Organ Failure Assessment (qSOFA) is used to predict sepsis-related mortality. Patients who meet 2 of the 3 items of the qSOFA *(Table 2)*, have a 30-day mortality of approximately 10 percent.[16] There are also several prediction models that prognosticate effect of therapy. In patients with pneumonia, the severity and the subsequent risk of dying can be determined using the CURB-65 score or the Pneumonia Severity Index (PSI). These prognostic models provide guidance to the physician with respect to patient disposition and choice of antibiotic therapy. In patients with febrile neutropenia the MASCC score and the CISNE score can be used; these instruments identify patients at low risk of dying who can be treated at home with oral instead of intravenous antibiotics.[17]

Table 2: Items of the quick Sepsis Related Organ Failure Assessment (qSOFA) score

Systolic blood pressure < 100 mmHg
Respiratory rate > 22 per minute
Glasgow Coma Scale < 15

Another example of a prediction rule is the Early Warning Score (EWS). These scores (there are several variants) were introduced to detect patients at risk for catastrophic deterioration based on progressive worsening of physiological parameters, and indicate the need for an early medical intervention to prevent further harm.[18] Details of the National Early Warning Score (NEWS) are provided as an example in *Table 3*. Throughout the years the scores have been revised and adapted for specific patient groups (e.g. pregnant women, children).[19,20] Although these scores were derived at hospital wards, they were also introduced in the ED and may aid physicians to prognosticate the outcome of patients upon arrival in the ED, as well as a method for evaluation of subsequent assessments or interventions.

Prediction models incorporating parameters that are more specific and therefore often more difficult to obtain (e.g. laboratory results) perform better than models that use

standard, readily available parameters (e.g. age, sex, vital signs). However, the improved prediction also requires more waiting time prior to decision making.[21]

Table 3: Items of the NEWS score

				Score			
Parameter	3	2	1	0	1	2	3
Respiration Rate per minute	≤8		9-11	12-20		21-24	≥25
Oxygen saturations in %	≤91	92-93	94-95	≥96			
Any supplemental oxygen		Yes		No			
Temperature in °C	≤25		35.1- 36.0	36.1-38.0	38.1-39.0	≥39.1	
Systolic Blood Pressure (mmHg)	≤90	91-100	101-110	111-219			≥220
Heart Rate per minute	≤ 40		41-50	51-90	91-110	111-130	≥131
Level of consciousness (AVPU)				A			V, P or U

AVPU: Alert Verbal Pain Unresponsive

Assessment and treatment of patients with potentially critical illness

When assessing patients in the ED who are potentially critically ill, healthcare professionals rely on the ABCDE approach (i.e. Airway, Breathing, Circulation, Disability, Exposure). This structured method to evaluate a patient was introduced in 1978 in the Advanced Trauma Life Support course[22] and likely improves outcome by detecting and treating the most life-threatening clinical problems first. In the Netherlands, training in this systematic approach is obligatory for all residents who work in the ED. Diseases that acute physicians encounter that benefit from early identification and treatment are, amongst others, shock and sepsis.[23]

Shock

In the assessment of the 'C' (i.e. 'circulation') healthcare professionals assess the patient for signs of shock. Shock is a state of hypoxia at cellular and tissue level due to imbalance of oxygen delivery and oxygen consumption, and is the result of circulatory failure. There are four types of shock: hypovolemic, distributive, cardiogenic, and obstructive shock *(Table 4)*. Many patients with circulatory failure have a combination of more than one form of shock. The types of shock encountered in the ED depends the services provided by the ED (e.g. level 1 trauma centre, percutaneous coronary intervention (PCI) centre, tertiary referral centre), as well as the population served by the ED (e.g. rural or urban, socioeconomic characteristics). The prevalence and aetiology of non-traumatic undifferentiated shock in the ED is not well described, but has an in-hospital mortality of more than 10 percent.[24,25] In its initial stage shock can be reversible, but unrecognized and untreated it can progress to irreversible organ dysfunction and subsequent organ failure. Therefore, it is paramount that shock is recognized early and treated adequately.

Hypovolemia can be caused by 'volume depletion' and 'dehydration'. Volume depletion is the loss of sodium from the extracellular space (i.e. intravascular and interstitial fluids), which can result in hemodynamic instability. 'Dehydration' is the loss of water, which results in a rise of plasma sodium and osmolality. Assessment of a patient for the initial signs of hypovolemia is difficult and few findings from physical examination are of proven value.[26] Most studies have shown that physical examination has low sensitivity and specificity in the assessment of cardiac output and timely detection of shock.[27,28] Therefore there is a need for novel indices (e.g. clinical parameters, biomarkers) that aid physicians in detecting shock in an earlier stage.

Table 4: Types of shock and characteristics

Type of Shock	Cause	Preload	Cardiac Output	Afterload
Hypovolemic	Haemorrhage Dehydration	↓	↓	↑
Cardiogenic	Acute myocardial infarction Valvular disease Arrhythmia	↑	↓	↑
Distributive	Sepsis Anaphylaxis CNS injury	↓/ -	↑	↓
Obstructive	Cardiac tamponade Pulmonary embolism Tension pneumothorax	↑	↓	- /↑

CNS: central nerve system

Sepsis

Infections are frequently encountered at the ED. Infections range from mild, self-limiting to the life-threatening condition sepsis. In developed countries, sepsis occurs in approximately 2% of all admitted patients. In patients admitted to the intensive care unit (ICU), sepsis occurs in between 6 and 30% of all patients, depending on the type of ICU.[29] In the Netherlands, there were more than 3,500 deaths due to sepsis in 2012.[30]

Sepsis is derived from the Greek term 'σήψις' meaning decay and putrefaction of meat, and was introduced in the fourth century BC by the Greek physician Hippocrates.[31-33] In 1914, the term sepsis was changed when Schottmueller defined septicaemia as "a state of microbial invasion from a portal of entry into the blood stream which causes signs of illness". Terms such as "bacteraemia", "septicaemia", "sepsis", and "septic shock" were used to describe patients who were severely ill due to an infection, without any predefined criteria.[34] Nowadays sepsis is considered a complex process in which an infection induces a variable, prolonged host response to clear infection and recover damaged tissue. The proinflammatory mechanisms in this process can induce organ damage on the one hand, whilst the anti-inflammatory mechanisms can cause secondary infections on the

other hand; imbalance in either direction leads to harm.[33,35]

Sepsis definitions and sepsis management

In order to assist both physicians treating and researchers studying sepsis, uniform sepsis definitions were introduced in 1992. Sepsis was defined as a systemic inflammatory response to an infection.[34] Systemic inflammation, defined as a systemic inflammatory response syndrome (SIRS) consisted of four criteria (i.e. body temperature < 36 °C or > 38 °C, heart rate > 90 beats per minute, respiratory rate > 20 breaths per minute, white blood cell count < 4 or > 12 x 10^9/L). The combination of two or more SIRS criteria and an infection defined sepsis. SIRS however is not specific for infection, but can also be the result of non-infectious causes, such as pancreatitis, burns and trauma *(Figure 1a)*. With the introduction of these uniform sepsis definition, severe sepsis (i.e. sepsis with acute organ dysfunction), and septic shock (i.e. severe sepsis with refractory shock) were also introduced, and these were proposed as comprising a disease continuum *(Figure 1b)*. The further the disease progressed in this continuum, the higher the chance of mortality.[34] In 2001 these definitions were slightly revised, incorporating additional signs and symptoms for the diagnosis of sepsis.[36]

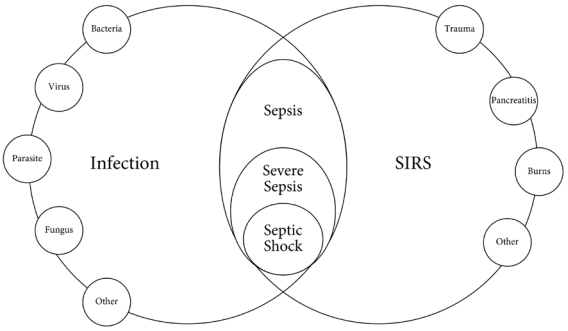


Figure 1 a: Presentation of Sepsis, Severe Sepsis and Septic Shock

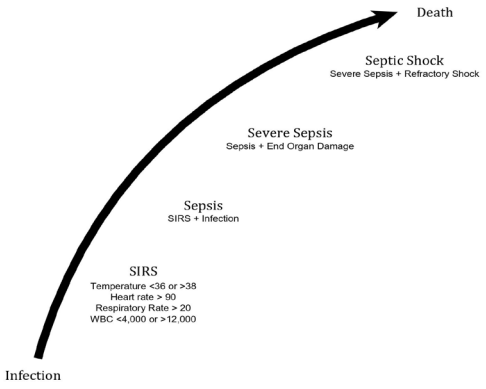


Figure 1b: Sepsis continuum

In 2002 the surviving sepsis campaign (SSC) was launched to reduce sepsis-related mortality by 25% in the next five years. In 2004, the first internationally accepted guidelines to improve outcomes in severe sepsis and septic shock were published.[37] These guidelines were developed by a group of experts on sepsis and were supported by 11 medical societies. The SSC introduced a 6-hour resuscitation bundle specifically for the ED and a 24-hour management bundle, specifically for the intensive care. The components of the first resuscitation bundle are given in *Table 5*.[37,38]

These guidelines endorsed the early goal directed therapy (EGDT) of Rivers *et al*., who showed that hemodynamic optimization before admission to the intensive care unit

(i.e. at the ED) improved outcome in patients with severe sepsis and septic shock.[39] This subsequently led to development of standards for early management of severe sepsis and septic shock in the ED. The SSC also stressed the importance of early initiation of antibiotics in sepsis, which was reinforced by Kumar *et al*. in 2006 who showed that

Table 5: Initial items in the Surviving Sepsis Campaign
1. Measure (and when elevated, remeasure) serum lactate
2. Blood cultures prior to antibiotics
3. Broad spectrum antibiotics within 3 hours after presentation, within 1 hour in hospital
4. Fluid resuscitation, followed by vasopressors guided by the mean arterial pressure if a patient is unresponsive to fluid therapy.
5. Maintain adequate central venous pressure and adequate central venous oxygen saturation in persistent arterial hypotension using vasopressors, inotropes or blood transfusion

every hour of delay in the initiation of antibiotics in patients with septic shock resulted in a 7.6% increase in mortality.[40] Compliance to the surviving sepsis bundles have been shown to lower mortality rates.[38,41]

As a result of studies with either new findings or that failed to reproduce results of previous studies the content of, and suggested timeframe in which these bundles needed to be completed, changed over the following years.[41] In 2012, the resuscitation bundle was modified into two bundles, a 3-hour and a 6-hour bundle, and the management bundle was discarded. The 'severe sepsis 3-hour resuscitation bundle' contained therapeutic goals that had to be completed within 3 hours after presentation of septic shock, whereas the 'the 6-hour septic shock bundle' contained the goals that needed to be completed within 6 hours.[42] In 2014 and 2015 three large trials (ProCESS, ARISE, and ProMISe) were published in which 'usual care' was shown to be as good as EGDT in patients with severe sepsis and septic shock,[41,43] and in 2015 the SSC bundles were revised based on these findings.[44]

In 2016, the definition of sepsis changed as a result of improved knowledge on pathobiology, management, and epidemiology of sepsis. Sepsis is now defined as "life-threatening organ dysfunction caused by a dysregulated host response to infection', and septic shock as 'a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone". The term severe sepsis was abandoned.[16] The qSOFA (Table 2) was introduced as a bedside prompt to screen for organ dysfunction, and should be followed by the Sepsis associated Organ Failure Assessment (SOFA, Table 6) if the qSOFA is positive (> 1 item). In 2018, the SSC updated its bundle to its current form, combining the 3-hours and 6-hours into a single '1-hour bundle' with the explicit goal to initiate resuscitation immediately.[23,45]

Despite the advantages of standard sepsis definitions and the SSC, criticisms remains. SIRS was too sensitive and not specific enough, resulting in overtreatment. This could lead to antibiotic resistance, as well as side effects of antibiotics.[46,47] The benefit of EGDT

Table 6: SOFA score

	SOFA score					
Variable	0	+1	+2	+3	+4	
Respiratory	≥400	<400	<300	<200 and mechanically ventilated	<100 and mechanically ventilated	PaO2/FiO2 (mmHg)
	>302	<302	<221	<142	<67	SpO2/FiO2 (mmHg)
Cardiovascular	MAP ≥70	MAP <70	dopamine ≤5	dopamine >5 epinephrine ≤0.1 norepinephrine ≤ 0.1	dopamine >15 epinephrine >0.1 norepinephrine >0.1	MAP in mmHg Doses in mcg/kg/min
Liver	<20	20-32	33-101	102-204	>204	Bilirubin in µmol/L
Renal	<110	110-170	171-299	300-440	>440	Creatinine in µmol/L
				Urine output <500	Urine output <200	Ml/day
Coagulation	≥150	<150	<100	<50	<20	Platelets $\times 10^3/\mu l$
Neurologic	15	13-14	10-12	6-9	<6	Glasgow Coma Scale

A new increase in SOFA score of 2 or more in the presence of infection makes the diagnosis of sepsis. Increasing SOFA scores are associated with increases in mortality.

was already questioned by the outcome of studies that showed usual care is as good as EGDT. The value of early initiation of antibiotic therapy in all patients with sepsis is also being questioned, as a recent trial on prehospital antibiotics failed to demonstrate reduced mortality.[48] Even though qSOFA is more specific than SIRS, it lacks sensitivity and therefore is not effective as a screening tool for sepsis. Furthermore, it is not universally supported by all medical societies.[49]

Despite the changes in the severe sepsis and septic shock management guidelines and the criticism that surrounds it, the cornerstone of surviving sepsis remains early identification of sepsis and septic shock, and subsequent early initiation of antibiotics and aggressive hemodynamic stabilization. However, there is ongoing need to identify those patients who truly benefit from early antibiotic treatment, and distinguish them from those who can await further diagnostics to inform more targeted antibiotic therapy. This is all the more relevant in an era of growing antibiotic resistance, which physicians also need to take into account.

Aims and outline of this thesis

This thesis covers studies that investigate clinical research questions relevant to acute and emergency physicians. This thesis consists of three main parts. The **first part** includes Chapters 2 to 7 where we focus on the value of history, clinical examination and additional testing in the identification of severity of illness in patients in the ED. In **Chapter 2** we

take a closer look at capillary refill time (CRT) using a novel research method called Flash Mob Research, to determine interobserver agreement between various methods used to measure CRT, as well as to relate CRT measurements with hemodynamic parameters. In **Chapter 3** we demonstrate how axillary humidity, peripheral temperature gradient, perfusion index (PI) and pleth variability index (PVI) can serve as potential indices of fluid deficit. In **Chapter 4** we investigate, both retrospectively and prospectively, the role of drug non-adherence as a cause of hypertensive urgency in the ED. In **Chapter 5** we describe characteristics of patients who visit the ED with medically unexplained physical symptoms and compare these characteristics to patients with explained physical symptoms. In **Chapter 6** we describe two cases of postural orthostatic tachycardia syndrome (POTS). In POTS, a change from a supine to an upright position causes an abnormally large increase in heart rate and orthostatic hypotension. We provide a review of the current literature on the subject. In **Chapter 7** we study the quality of sleep of hospitalized patients, and show how decisions made in the ED influence the course of hospitalization.

In the **second part** of this thesis, covering Chapters 8 to 10, we focus on prediction models and early warning scores. In **Chapter 8** we provide an extensive overview of the literature concerning models to predict mortality in the ED. In **Chapter 9** we describe how we develop and validate a clinical prediction tool for hospital admission, applicable to the elderly in the ED. In **Chapter** 10 we evaluate the performance of qSOFA, SIRS criteria and NEWS in predicting mortality among patients with suspected infection presenting to the ED.

The **third part** of this thesis zooms in on factors that influence of antibiotic susceptibility (Chapters 11 to 13). In **Chapter 11** we determine the impact of international travel on the risk of post-travel faecal carriage of multidrug-resistant *Enterobacteriaceae*. In **Chapter 12** we study pathogens causing urinary tract infections and their antibiotic susceptibility. In **Chapter 13** we re-evaluate whether administration of empiric antibiotics is associated with reduced mortality among adult patients with blood stream infections consulting at the ED. We particularly focus on why previous studies were unable to confirm this supposedly well-established biological rationale.

In **Chapter 14** we discuss the main finding of the studies we performed, provide conclusions per part and we provide suggestions for future research. In **Chapter 15** we summarize the results of these studies.

The Value of History, Clinical Examination and Additional Testing in the Early Identification of Illness

Chapter 2

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Chest. 2017; 151(5):1106-13

The Power of Flash Mob Research - Conducting a Nationwide Observational Clinical Study on Capillary Refill Time in a Single Day

Abstract

Background

Capillary refill time (CRT) is a clinical test used to evaluate the circulatory status of patients, and there are various methods to assess CRT. Conventional clinical research often demands large numbers of patients, making it costly, labour-intensive and time consuming. We studied the interobserver agreement on CRT in a nationwide study using a novel methodology of research called flash mob research (FMR).

Methods

Physicians in the Netherlands were recruited by word-of-mouth, conventional media and social media to participate in a nationwide, single-day, "nine-to-five", multi-centre, cross-sectional, observational study to evaluate CRT. Patients ≥ 18 years presenting to ED or who were hospitalized were eligible for inclusion. CRT was measured independently (by two investigators) at the patient's sternum and distal phalanx after application of pressure for 5 (5s) and 15 s (15s).

Results

On October 29th 2014, a total of 458 investigators in 38 Dutch hospitals enrolled 1,734 patients. The mean CRT measured at the distal phalanx was 2.3 s (5s, SD 1.1) and 2.4 s (15s, SD 1.3). The mean CRT measured at the sternum was 2.6 s (5s, SD 1.1) and 2.7 s (15s, SD 1.1). Interobserver agreement was higher for the distal phalanx (κ-value 0.40) than for the sternum (κ-value 0.30).

Conclusions

Interobserver agreement on CRT is, at best, moderate. CRT measured at the distal phalanx yielded higher interobserver agreement compared with sternal CRT measurements. FMR proved a valuable instrument to investigate a relative simple clinical question in an inexpensive, quick and reliable manner.

Background

Evidence assessing the usefulness and reliability of commonly used bedside diagnostic tests is not always available or easily obtained. Capillary refill time (CRT) is frequently used to judge a patient's circulatory status: a prolonged CRT is thought to be associated with an inadequate perfusion.[50,51] Despite few outcome data to support the use of CRT in adults outside of the ICU, the use of CRT is widespread.[52-54] CRT is a standard part of rapid primary assessment of critically ill patients in various advanced life support guidelines.[51,55]

Originally, CRT was defined without strict time limits (as "normal", "definite slowing", and "very sluggish")[56] which left room for subjective interpretation, making reproducibility difficult. In the 1980s, an operational definition of 2 seconds as upper limit of normal CRT was recommended, which was replaced in 1988 with less used upper limits of normal adjusted for age and sex.[50,57] Despite these recommendations, the measurement and interpretation of CRT remain inconsistent.[58,59] CRT is measured at different sites and with different pressure times. In adult ICU settings, application of pressure at the fingertip for 15 s is considered the standard; in children, CRT is mostly measured at the sternum.[54,59-61] Interpretation is hindered by ambient and patient factors that are not always easy to control (e.g. ambient temperature, light, patient peripheral temperature).[26,51,62-64] Even in controlled circumstances, the interobserver reliability of CRT measurements has been questioned.[51,60,65-67] In addition, the different methods to measure CRT have been never compared in adults.

CRT is used in daily clinical practice worldwide, but it remains questionable which method should be used to measure CRT (sternum or phalanx) and whether the results are reproducible. The present study was therefore designed to compare the most frequently used methods to measure CRT in adult patients with variable hemodynamic status; the study setting resembled daily practice to determine which measurement has the highest interobserver agreement and to determine if the sternum and distal phalanx measurements can be used interchangeably.

Conventional clinical research used for answering clinically oriented research questions often demands large numbers of patients, making it costly, labour-intensive, and time-consuming. We saw a possible solution in flash mob research (FMR). This technique is a novel method of organizing research and allows the investigation of clinically relevant questions on a large scale in an abbreviated time course.[68] FMR is based on the concept of flash mobs: "a sudden and planned gathering of many people at a particular place that has been arranged earlier on an internet website."[69] Using the numerical strength of multiple hospitals, as well as the professional and social networks of their medical staff, it is possible to obtain sufficient data with FMR in a short time course[68] while upholding the same quality standards.

The primary objective of the present study was to determine the interobserver agreement of CRT measurements as measured at the sternum and at the distal phalanx

using pressure times of 5 and 15 s and to relate the measurements with hemodynamic characteristics. Our secondary aim was to establish the feasibility of using FMR as a fast, inexpensive, and robust method to investigate clinical questions by using the power of social networks and new and conventional media to gather as many relevant data as possible in a short period of time.

Patients and Methods

Study Design

This trial was a nationwide, single-day, "nine-to-five," multicentre, cross-sectional observational study.

Setting up an FMR

As in flash mobs, preparations for FMR were made in a small group. The research question and study design were conceived in the Erasmus University Medical Center (Erasmus MC) in Rotterdam, the Netherlands. The Erasmus MC acted as coordination centre for the duration of the study. A steering committee with members from all of the Netherlands further elaborated the research question and study protocol. The protocol was approved by the medical ethics committee of the Erasmus MC. Members of the steering committee invited physicians from their professional networks from all eight Dutch university hospitals, and subsequently physicians from affiliated regional hospitals, to participate; the result was nationwide participation. In each participating hospital, a local investigator, designated the "ambassador," coordinated the study; ambassadors were either medical specialists or residents. Ambassadors obtained local ethical board approval of the protocol, recruited and instructed investigators, and were responsible for handling data. Similar to flash mobs, communication with participating investigators, public, and peers was mainly conducted by using e-mail, social media, and our Website.

Setting, Patients, and Variables

On October 29th, 2014, between 9:00 AM and 5:00 PM, data were simultaneously collected in all participating hospitals. Patients aged ≥ 18 years who were able to provide informed consent and who presented to the ED or were hospitalized within this period were eligible for enrolment. After providing consent, patients were examined independently by two investigators working within a 5-min interval. Investigators were physicians (medical specialists or residents), nurses, and medical students in their clinical rotations. Investigators were instructed on (and worked according to) standard operating procedures, which described the order of the tests. Investigators measured CRT at two sites twice: the sternum (CRTs) and the distal phalanx of the finger (CRTp). The first measurement occurred after application of pressure for 5 s ($CRTs_5$ and $CRTp_5$, respectively), and the second after application of pressure for 15 s ($CRTs_{15}$ and $CRTp_{15}$).

CRTp was measured by applying sufficient pressure at the distal phalanx of the finger with the hand held at heart level to cause blanching of the skin, and CRT was defined as the time necessary for the skin to regain its colour.[50] CRTs were measured by applying sufficient pressure to achieve blanching of the skin of the sternum, and again CRT was defined as the time necessary for the skin to regain its colour. Investigators were advised to determine CRT by counting, and no timing devices were advised, mimicking daily practice. CRT was measured in seconds, and the results were rounded off to the nearest half-second. This resolution allowed categorization of the outcome by using upper values of normal as suggested in other studies[50,54,57] this method was previously used by Anderson *et al.*[65]

Investigators subjectively assessed the peripheral temperature by placing the back of the hand on the patients' hand (cold vs not cold). Investigators provided their subjective conclusion of the patient's hemodynamic status (adequate vs inadequate) using all available clinical information. Investigators also provided their subjective conclusion of the observed CRT (normal vs prolonged), without predefining normality. The subjective conclusion was chosen to resemble daily practice, as clinicians often present measured CRT with a dichotomous outcome. Pulse rate, blood pressure, respiratory rate, temperature, and oxygen saturation were measured by using local standard procedures. All data were entered into local databases, which were subsequently combined at the Erasmus MC. All patients with CRT measured by two investigators were included in the final analysis. Mean arterial pressure (MAP) was calculated and dichotomized (< 65 mmHg vs ≥ 65 mmHg). MAP < 65 mmHg was considered inadequate.[42] Pulse rate was categorized into one of the following three groups: < 60 beats/min, 60 to 100 beats/min, and > 100 beats/min. CRT was categorized by using definitions found in the literature. $CRTs_5$ and $CRTp_5$ were categorized using the upper limits of normal (2.0 s) as defined by Champion *et al.*[57] and the age and sex adjusted upper values of normal (male subjects, aged < 62 years: $CRTs_5$ and $CRTp_5$ 2.0 s; female subjects, aged < 62 years: $CRTs_5$ and $CRTp_5$ 3.0 s; male and female subjects aged ≥ 62 years: $CRTs_5$ and $CRTp_5$ 4.0 s) as defined by Schriger and Baraff.[50] For $CRTs_{15}$ and $CRTp_{15}$, an upper limit of normal of 4.0 s was used.[54]

Study Size

The study size could not be predicted due to the FMR design. In principle, a successful FMR should include a large sample size for reliable conclusions.

Statistical Methods

Data were summarized in terms of mean, median, 95% CIs, and SD when appropriate. Categorical data were analysed by using $\chi 2$ tests. The means of two groups were compared by using the Student t-test (normal distribution) or the Mann-Whitney U test (non-normal distribution); the means of three groups were compared by using the Kruskal-Wallis test. Differences between continuous data with non-normal distribution were analysed by using Wilcoxon signed-rank sum tests. Interobserver agreement was

analysed for discrete values of CRT by using the intraclass correlation coefficient. In addition, interobserver agreement was analysed for categorical values of CRT by using k statistics. The variation of CRT with age and sex was analysed with the use of linear regression. Missing data were considered missing at random and were therefore ignored. A difference of 0.5 s between CRTs and CRTp was considered clinically relevant.[59,65] A P value < .05 was considered statistically significant. Statistical analyses were performed by using SPSS version 21.0 (IBM SPSS Statistics, IBM Corporation).

Results

Participating Hospitals

A total of 38 hospitals, located all over the Netherlands, participated in the study (representing 45% of the total number of 85 Dutch hospital organizations); this total included all eight university hospitals, 29 teaching hospitals (56% of non-academic teaching hospitals), and one nonteaching hospital. Mean inclusion was 46 patients per hospital (median, 39; range, 3-130). Of the participating hospitals, almost 40% provided data within 24 h and 76% within 1 week. All data were available within 19 days.

Participating Investigators

A total of 458 investigators participated in the study (33 medical specialists, 246 residents, 122 medical students, and 57 nurses).The mean number of enrolments was seven patients per investigator (range, 1-65). Most enrolments were done by residents (n = 1,916; mean, 8), followed by medical students (n = 1,096; mean, 9), medical specialists (n = 288; mean, 9), and nurses (n = 168; mean, 3).

Patient Characteristics

A total of 1,734 patients (3,468 examinations) were included in the study, with a slight preponderance of male subjects (51.6%; n = 894). Patients overall had a mean age of 65 years. The majority (78.1%) were inpatients. Patient characteristics are presented in *Table 1*.

Capillary Refill Time

The mean peripheral CRT was 2.3 s ($CRTp_5$, SD 1.1) and 2.4 s ($CRTp_{15}$, SD 1.3) and mean sternal CRT was 2.6 s ($CRTs_5$, SD 1.1) and 2.7 s ($CRTs_{15}$, SD 1.1). $CRTp_5$ was shorter in women (2.2 s, SD 1.0) than in men (2.4 s, SD 1.2; P = .006) and increased with age (0.16 s per 10 years; P < .001) (*Figure 1*). On average, $CRTp_5$ was 0.3 s shorter than $CRTs_5$ (P < .001), and $CRTp_{15}$ was 0.3 s shorter than $CRTs_{15}$ (P < .001). CRT correlated positively with MAP, subjective peripheral temperature, and subjective assessment of the hemodynamic status. There was no correlation with pulse rate (*Table 2*).

Table 1: Patient Characteristics

Characteristic	Male (n = 894 [51.6%])	Female (n = 840 [48.4%])	Total (N=1,734)
Age,[a] y (n = 1,734)	65 ± 16	65 ± 18	65 ± 17
Systolic blood pressure,[a] mmHg (n = 1,728)	131 ± 21	133 ± 23	132 ± 22
Diastolic blood pressure,[b] mmHg (n = 1,728)	75 ± 12	72 ± 13	173 ± 13
Mean arterial pressure[a] (n = 1,728)	93 ± 14	92 ± 14	93 ± 14
Pulse,[c] frequency/min (n = 1,731)	79 ± 16	81 ± 16	80 ± 16
Oxygen saturation in percentage[a] (n = 1,628)	96 ± 3	96 ± 3	96 ± 3
Respiratory rate,[a] breaths/min (n = 1,598)	17 ± 4	16 ± 4	17 ± 4
Temperature,[b] °C (n = 1,723)	36.8 ± 0.7	36.9 ± 0.7	36.9 ± 0.7

Data are expressed as mean SD. a: Not significant. b: P < .001. c: P = .008.

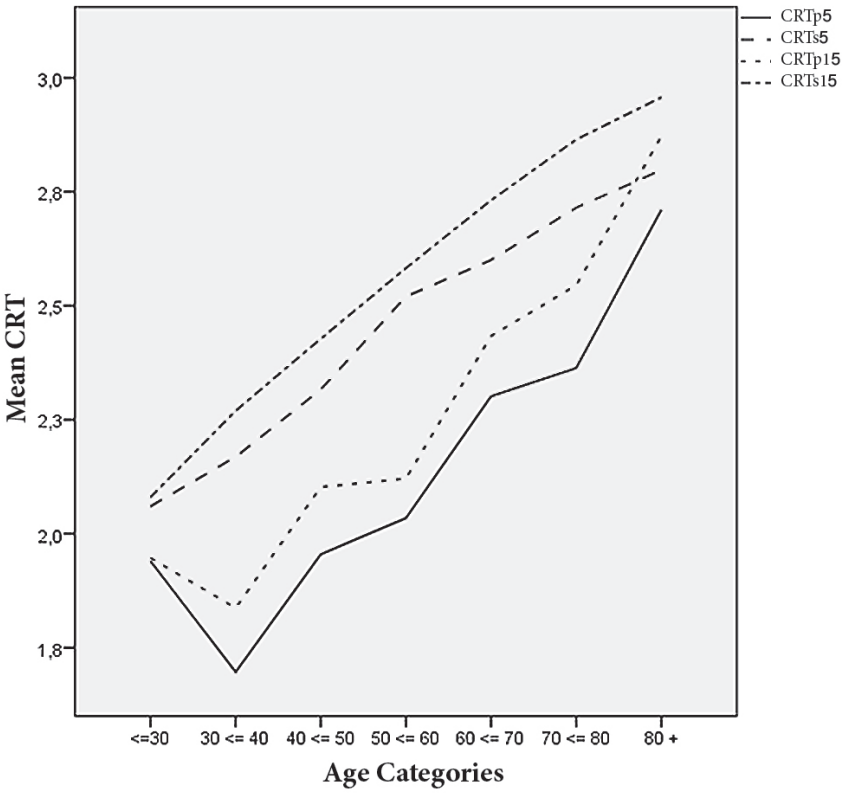

Figure 1: Mean CRT in seconds for different age categories in years.

CRT: capillary refill time; P5: peripheral measurement after application of pressure for 5 s; P15: peripheral measurement after application of pressure for seconds; S5: sternal measurement after application of pressure for 5 s; S15 : sternal measurement after application of pressure for 15 s.

Table 2: Mean Capillary Refill Times

Parameter	**CRTp5** (95% CI)	**CRTp15** (95% CI)	**CRTs5** (95% CI)	**CRTs15** (95% CI)
Total	2.3 (2.2-2.3)	2.4 (2.4-2.5)	2.6 (2.5-2.6)	2.7 (2.7-2.8)
Subjective peripheral temperature				
Cold	3.2 (3.0-3.4)	3.3 (3.1-3.6)	2.9 (2.5-2.6)	3.0 (2.9-3.2)
Warm	2.1 (2.1-2.2)	2.3 (2.2-2.3)	2.5 (2.8-3.1)	2.6 (2.6-2.7)
P[a]	< .001	< .001	< .001	< .001
Subjective hemodynamic status				
Inadequate	3.2 (2.8-3.5)	3.6 (3.1- 4.2)	3.2 (2.9-3.5)	3.5 (3.2-3.8)
Adequate	2.2 (2.2-2.3)	2.4 (2.3-2.4)	2.6 2(.5-2.6)	2.7 (2.6-2.7)
P[a]	< .001	< .001	< .001	< .001
Mean arterial pressure, mmHg				
< 65	3.0 (2.6-3.5)	3.3 (2.7-3.9)	3.4 (2.7-4.1)	3.6 (3.0-4.2)
≥ 65	2.3 (2.2-2.3)	2.4 (2.3-2.5)	2.6 (2.5-2.6)	2.7 (2.6-2.7)
P[a]	.001	< .001	.01	.002
Pulse rate per minute				
< 60	2.3 (2.1-2.5)	2.6 (2.3-2.9)	2.6 (2.5-2.9)	2.8 (2.5-3.0)
60-100	2.3 (2.2-2.3)	2.4 (2.3-2.5)	2.6 (2.5-2.6)	2.7 (2.6-2.8)
> 100	2.2 (2.0-2.4)	2.4 (2.2-2.6)	2.6 (2.4-2.7)	2.7 (2.5-2.9)
P[b]	.407	.397	.800	.862
Subjective conclusion of the CRT				
Prolonged	3.5 (3.3-3.7)	3.9 (3.6-4.1)	3.6 (3.4-3.7)	3.8 (3.6-4.0)
Normal	2.1 (2.1-2.1)	2.2 (2.2-2.3)	2.5 (2.4-2.5)	2.6 (2.5-2.6)
P[a]	< .001	< .001	< .001	< .001
Temperature, °C				
< 36	2.6 (2.4-2.9)	2.8 (2.6-3.1)	2.6 (2.4-2.8)	2.8 (2.5-3.0)
36-38	2.3 (2.2-2.3)	2.4 (2.3-2.5)	2.6 (2.5-2.6)	2.7 (2.6-2.8)
> 38	2.2 (1.9-2.5)	2.5 (2.1-2.8)	2.5 (2.3-2.8)	2.7 (2.4-3.0)
P[b]	.003	.002	.907	.870

95% CI 95% CI of the mean (lower bound and upper bound); CRT capillary refill time; CRTp5 peripheral capillary refill time, application of pressure 5 s; CRTp15 peripheral capillary refill time, application of pressure 15 s; CRTs5 sternal capillary refill time, application of pressure 5 s; CRTs15 sternal capillary refill time, application of pressure 15 s. a: Determined by using the Mann-Whitney U test. b: Difference between groups as determined by using the Kruskal-Wallis test.

The mean difference between measurements of the first and second investigator was 0.1 s (CRTp$_5$, 0.1 s [95% CI, 0.0-0.1]; CRTp$_{15}$, 0.1 [95% CI, 0.0-0.1]; CRTs$_5$, 0.1 [95% CI, 0.0-0.1]; and CRTs$_{15}$, 0.1 [95% CI, 0.0-0.1]). The median difference was 0 s in all groups. Interobserver agreement, assessed by calculating the intraclass correlation coefficient between the CRTp measurements of both investigators, was 0.52 for CRTp$_5$ (95% CI, 0.49-0.56) and 0.54 for CRTp$_{15}$ (95% CI, 0.50-0.57) (P < .001), and interobserver agreement on

Table 3: Agreement Between Two Investigators Assessed by Using the Intraclass Correlation Coefficient

Variable	Intraclass Correlation Coefficient	95% CI	Interpretation
$CRTp_5$	0.52	0.49-0.56	Moderate correlation
$CRTp_{15}$	0.54	0.50-0.57	Moderate correlation
$CRTs_5$	0.43	0.39-0.47	Low correlation
$CRTs_{15}$	0.46	0.42-0.49	Low correlation

All results, P < .001. See Table 2 legend for expansion of abbreviations.

Table 4: Agreement Between Two Investigators Assessed by Using κ Statistics

Variable	κ Statistic 95% CI	Interpretation
$CRTp_5$, upper range of normal 2 s	0.40 (0.36-0.45)	Fair agreement
$CRTs_5$, upper range of normal 2 s	0.30 (0.26-0.35)	Fair agreement
$CRTp_5$, upper range of normal based on age and sex	0.20 (0.12-0.29)	Slight agreement
$CRTs_5$, upper range of normal based on age and sex	0.13 (0.04-0.22)	Slight agreement
$CRTp_{15}$, upper range of normal of 4 s	0.32 (0.24-0.41)	Fair agreement
$CRTs_{15}$, upper range of normal of 4 s	0.23 (0.15-0.31)	Fair agreement
Subjective conclusion on CRT	0.44 (0.37-0.51)	Moderate agreement

All results, P < .001. See Table 2 legend for expansion of abbreviations.

measurements of CRTs was 0.43 for $CRTs_5$ (95% CI, 0.39-0.47) and 0.46 for $CRTs_{15}$ (95% CI, 0.42-0.49) (P < .001) (*Table 3*).

The agreement between the two investigators on whether the subjective CRT was normal or prolonged was assessed by using κ statistics. Application of pressure for 5 s yielded a κ value of 0.40 for CRTp (95% CI, 0.36-0.45) and 0.30 for CRTs (95% CI, 0.26-0.35) (both fair agreement)[70] when using 2 s as the upper value of normal, and a κ value of 0.20 for CRTp (95% CI, 0.12-0.29) and 0.13 for CRTs (95% CI, 0.04-0.22) (both slight agreement)[70] when using upper limits of normal based on age and sex.

The agreement between the two investigators on whether the subjective CRT was normal or prolonged was assessed by using κ statistics. Application of pressure for 5 s yielded a κ value of 0.40 for CRTp (95% CI, 0.36-0.45) and 0.30 for CRTs (95% CI, 0.26-0.35) (both fair agreement)[70] when using 2 s as the upper value of normal, and a κ value of 0.20 for CRTp (95% CI, 0.12-0.29) and 0.13 for CRTs (95% CI, 0.04-0.22) (both slight agreement)[70] when using upper limits of normal based on age and sex. Using 4 s as the upper value of normal after application of 15 s of pressure yielded a κ value of 0.32 for CRTp measurements (95% CI, 0.24-0.41) and 0.23 for CRTs measurements (95% CI, 0.15-0.31) (both fair agreement). Agreement between two investigators on the subjective conclusion of whether the CRT was normal or prolonged yielded a κ value of 0.44 (95% CI, 0.37-0.51) (moderate agreement) (*Table 4*).[70]

Discussion

To our knowledge, our nationwide, single-day, nine-to-five, multicentre, cross-sectional observational study is the first to analyse the interobserver agreement of four frequently used methods to measure CRT. These measurements were performed in a setting specifically designed to resemble daily practice at the ED and the ward, with two observers using identical methods under similar conditions. CRT measurements had slight to moderate agreement at best using a dichotomous outcome (normal vs prolonged) and moderate correlation using a continuous outcome (seconds).

To be of use in clinical practice, the interpretation of the results of CRT measurements should be easily reproducible. To date, there are only three studies in adults that report on interobserver agreement of CRT measurement at the distal phalanx after 5 s of pressure.[65-67] These studies show moderate agreement at best. In only one study was CRT measured without a timing device.[65] The other studies either showed a video with CRT[66] or used healthy volunteers in controlled circumstances, and CRT was determined with a chronometer or a video,[67] which does not reflect the worldwide use and interpretation of CRT in daily practice.[58]

To our knowledge, our study is the first to assess the optimal site and duration of pressure for CRT measurement in adults. As expected, our study found a correlation between the CRT measured at the distal phalanx and sternum. CRT measured at the distal phalanx was shorter than that measured at the sternum, as was found in children,[59] and we concluded that the phalanx and the sternum cannot be used interchangeably. The interobserver agreement on CRT was higher for the distal phalanx than for the sternum. A prolonged application of pressure (15 s), as used solely in the ICU, only resulted in a slightly higher interobserver correlation.[54,61] Application of pressure for 5 s at the distal phalanx is easier to use, and most studies on CRT in the ED and the ward use 5 s application of pressure. Therefore, based on these findings, we recommend uniform use of CRT and propose that CRT should only be measured at the distal phalanx with 5 s of pressure.

However, why measure CRT? CRT was introduced by Beecher in World War II to identify shock in battlefield survivors[56] it is still used today to assess peripheral circulation and in early detection of shock.[51,55] Although our study showed a correlation between CRT and a MAP < 65 mmHg, we found no correlation between CRT and an abnormal pulse rate, which is an early indicator of shock. In the detection of shock in its early stages, the additional value of CRT seems limited, which is supported by previous research.[26,63] However, some studies show the predictive value of CRT on long- and short-term mortality. In a retrospective study in oncology patients, a prolonged CRT (≥ 2 s) was predictive for both coronary care unit admission and 30-day mortality.[52] A prospective study in ED patients found that a prolonged CRT as a continuous variable was associated with an increased risk of mortality at 1 and 7 days.[53]

The present study also illustrated the power of FMR study design and its potential as a methodologic tool for clinical research. Compared with conventional studies, FMR has multiple similarities. In preparation of the study, FMR requires the same steps in

designing and setting up (e.g. protocol development, ethical board approval, instruction of collaborators). However, FMR exhibited many additional advantages. It facilitated inclusion of large numbers of patients from multiple centres (and the resulting data) within a short period of time. This inspiring and new research method, combined with an appealing research question, led to high participation of hospitals. The FMR approach also encouraged all the members of the medical team to participate in research. Most investigators in our study and almost one-half of the ambassadors were residents, who are often mainly focused on patient care and otherwise not regular participants of research. FMR engaged them in the process of research and exposed them to its various aspects. All these advantages come with limited time investment and low costs.

Our study has limitations. Given the cross-sectional nature of this study, no follow-up data were collected. Therefore, no associations with outcomes of disease, including mortality, were examined. Data collection was performed by using standardized procedures after provision of standardized instructions; however, given the large number of centres and investigators, it is inevitable that small differences exist in the collection of data. Many of the collected variables are subjective and therefore open to interpretation, and they can be influenced by the clinical experience of the investigator. The application of pressure could differ between investigators, which could also affect CRT. In children, light pressure resulted in shorter CRT,[51] but in adults this effect has not been studied. We propagated counting, instead of using timing devices, to a resolution of one-half second, which could have led to lower agreement. Because the mean difference between all measurements was 0.1 s, the influence on our results was negligible while enabling us to compare various upper limits of normal. We believe that our study represents how CRT is used as a bedside test in daily practice worldwide, with all its shortcomings that hinder its users. In addition, with 45% of the Dutch hospital organizations involved, our results are generalizable.

Conclusions

Based on the results of our study, especially the low interobserver agreement on a test that is difficult to standardize, combined with the currently available evidence, we concluded that the value of CRT in clinical practice is limited, and its routine use should be reconsidered. When CRT is used, it should be measured at the distal phalanx after applying pressure for 5 s. The practice of using the sternum for CRT measurement should be discarded. In addition, the FMR method proved to be an inexpensive, quick, and reliable method to investigate "simple" clinical questions. FMR was used to recruit 1,734 participants in 1 day, and the majority of the data were ready for analysis within 24 h. We therefore believe this study exemplifies the power of FMR.

Collaborators FAMOUS Study

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All hospitals are situated in the Netherlands

Chapter 4

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Drug Nonadherence is a Common But Often Overlooked Cause of Hypertensive Urgency and Emergency at the Emergency Department

Abstract

Objectives

Over 70% of patients who visit the emergency department with a hypertensive emergency or a hypertensive urgency have previously been diagnosed with hypertension. Drug nonadherence is assumed to play an important role in development of hypertensive urgency and hypertensive emergency, but exact numbers are lacking. We aimed to retrospectively compare characteristics of patients with hypertensive urgency and hypertensive emergency and to prospectively quantify the attribution of drug nonadherence.

Methods

We retrospectively analysed clinical data including information on nonadherence obtained by treating physicians of patients with systolic blood pressure (SBP) at least 180 mmHg and diastolic blood pressure (DBP) at least 110 mmHg visiting the emergency department between 2012 and 2015. We prospectively studied drug adherence among patients admitted to the emergency department with severely elevated BP by measuring plasma drug levels using liquid chromatography tandem mass spectrometry from September 2016 to March 2017.

Results

Of the 1,163 patients retrospectively analysed, 257 (22.0%) met the criteria for hypertensive urgency and 356 (30.6%) for hypertensive emergency. Mean SBP (SD) was 203 (19) mmHg and mean DBP 121 (12) mmHg.

Mean age was 60.1 (14.6) years; 55.1% were men. In 6.3% of patients with hypertensive urgency or hypertensive emergency, nonadherence was recorded as an attributing factor. Of the 59 patients prospectively analysed, 18 (30.5%) were nonadherent for at least one of the prescribed antihypertensive drugs.

Conclusion

Hypertensive urgency and hypertensive emergency are common health problems resulting in frequent emergency department admissions. Workup of patients with a hypertensive urgency or hypertensive emergency should include an assessment of drug adherence to optimize treatment strategy.

Introduction

A markedly elevated blood pressure (BP) is a common finding at the emergency department (ED): at least 5% of patients in the ED have one or more severely elevated measurements, usually defined as systolic blood pressure (SBP) at least 180 mmHg or diastolic blood pressure (DBP) at least 120 or 110 mmHg, although terminology and cut-offs differ between studies.[91,92] In most of these patients, the high BP is transient and is a reaction to pain, anxiety or stress. This is sometimes referred to as a pseudo hypertensive crisis, and warrants no further action.[93] Around 0.5% of ED visits are primarily for severe hypertension. In such cases, the most important aim is to differentiate between a 'hypertensive emergency', when acute target organ damage is present or impending, and a 'hypertensive urgency' when this is not the case.[94-96] Hypertensive urgency and hypertensive emergency were previously summarized as 'hypertensive crisis' but as this terminology seems outdated, we will use the terms hypertensive urgency and hypertensive emergency.[97,98] Hypertensive emergency requires immediate action to lower the BP using intravenous antihypertensive drugs in an intensive or high care unit, whereas hypertensive urgency allows BP regulation using oral therapy in an outpatient setting.[92,96] When patients visit the ED primarily for severe hypertension, depending on complaints and findings of a physical examination, extensive tests (e.g. laboratory testing, ophthalmoscopy) may be needed to distinguish between hypertensive urgency and hypertensive emergency and to determine whether hospital admission is necessary.[95,99]

Hypertensive urgency and hypertensive emergency can occur in patients with previously unidentified hypertension as a first presentation of their hypertensive condition. However, over 70% of patients presenting at the ED have been previously diagnosed with hypertension and have been prescribed antihypertensive drugs.[92,99-101] Drug nonadherence, defined as not taking drugs as previously agreed on with the treating physician, is assumed to play an important role in the development of a hypertensive emergency and hypertensive urgency, but exact numbers are lacking. Poor drug adherence of antihypertensive and other cardiovascular drugs is associated with a higher risk of developing cardiovascular disease.[102,103]

When a patient presents at the ED with severe hypertension, it is crucial to distinguish nonadherence to therapy from treatment failure. In nonadherent patients, physicians should discuss reasons for nonadherence and methods to improve adherence, whereas in adherent patients, drug therapy should be optimized.

In this study, we combined a retrospective and a prospective study to answer two related and important research questions considering severely elevated BP at the emergency department. The first objective was to compare characteristics of patients with hypertensive urgency and those with hypertensive emergency, including assessment of drug adherence by the treating physician. The second objective was to prospectively determine the incidence of nonadherence to prescribed antihypertensive drugs in patients with severely elevated BP at the ED by measuring plasma drug levels.

Methods

Study design

In this manuscript we describe two studies. We performed a retrospective cross-sectional study among patients who visited the ED from 1 January 2012 to 31 December 2015 with at least one BP measurement. Due to the large number of patients with elevated BP caused by stress, anxiety or pain, we restricted the number of cases for analysis by choosing to only include patients who met both the SBP and DBP cut-off values. We performed a prospective study in which we analysed plasma drug levels of prescribed antihypertensive drugs in patients who visited the ED from 1 September 2016 with severely elevated BP suspected of hypertensive urgency or hypertensive emergency. Here we used the formal cut-offs for hypertensive emergency described in the current American and European guidelines (SBP at least 180 mmHg or DBP at least 120 mmHg).[98]

Study population

The studies were performed at Erasmus University Medical Center in Rotterdam, the Netherlands (Erasmus MC), which is a large urban tertiary care hospital. The ED is an open access department located in the city centre, and has visits from approximately 30,000 patients annually.

Retrospective study

We used a database containing all patient records from ED visits in the period from 1 January 2012 to 31 December 2015 to select patients who had a SBP at least 180 mmHg and a DBP at least 110 mmHg at triage. Patients 18 years of age and older were included. For patients with multiple visits to the ED during the inclusion period, only the first visit was included.

Prospective study

Inclusion commenced from 1 September 2016 until the number of patients required was reached as determined in sample size calculations. We included all patients aged 18 years or older presenting to the ED or the fast-track program with a SBP at least 180 mmHg or a DBP at least 120 mmHg at triage, who were prescribed one or more antihypertensive drugs that we were able to measure in plasma at least 24 h after intake using a validated liquid chromatography - tandem mass spectrometry (LC-MS/MS), and from whom routine blood samples were obtained.[104] We excluded patients who were unable to give informed consent or when severe hypertension was likely to have been caused by severe pain or stress.

Variables and measurement

We defined hypertensive emergency as a severely elevated BP according to the inclusion

criteria with the presence of acute end-organ damage (i.e. ischemic stroke, haemorrhagic stroke, myocardial infarction, unstable angina, acute aortic dissection, acute pulmonary enema, hypertensive encephalopathy and bilateral hypertensive retinopathy grade 3 or 4).[93,97] Hypertensive urgency was defined as severely elevated BP without acute or impending end- organ damage.[92,93,97] Patients were labelled as 'non-hypertensive emergency and non-hypertensive urgency severe hypertension' when the BP was a result of extreme pain, anxiety or stress. This was based upon reasons for referral or presentation (other than hypertension) to the emergency department, on physicians' remarks in patient files and spontaneous recovery of BP after pain or stress relief.

We manually extracted data from electronic patient records including demographic data (i.e. age, sex), complaints (specifically headache, distorted vision, chest pain, palpitations, paraesthesia, paresis, gastrointestinal complaints, pain at any location), medical history, information on use of drugs and on drugs of abuse. Whenever available, we collected test results including laboratory measurements, ECGs focusing on left ventricular hypertrophy (LVH) using Sokolow-Lyons criteria[105] and radiological examinations (i.e. chest radiography for cardiothoracic ratio (CTR) assessment: > 0.5 was considered enlarged). The working diagnosis and patient disposition after discharge from the ED were recorded.

Measuring drug levels and definition of nonadherence

All patients received standard care in the emergency department. In this workup, routine blood samples were taken to diagnose or exclude end-organ damage (e.g. measurement of serum creatinine level, presence of schistocytes).[97] For the prospective study, we used the remainder of these blood samples to measure levels of prescribed antihypertensive drugs in plasma using a validated LC-MS/MS multimethod.[104] Using this method, we were able to detect losartan, valsartan, enalapril, perindopril, spironolactone, amlodipine and nifedipine and four active metabolites perindoprilate, enalaprilate, losartan carboxylic acid and canrenone. With this method, drug levels are detectable for 24 h or more after intake, allowing an objective assessment on adherence without knowledge of last moment of drug intake. Partial nonadherence was defined as self-reported nonadherence or nondetectable (concentration less than lower limit of detection) drug levels of one of the prescribed drugs or its active metabolite, and complete nonadherence as self-reported nonadherence to all drugs or nondetectable drug levels of all tested drugs. Drug levels exactly at the lower level of detection, in other words extremely low drug levels, were scored based on time of last ingestion, drug levels of other antihypertensive drugs taken at the same time and discussion of (non)adherence during stay in the hospital.

Statistical methods

Patient characteristics were presented as mean and standard deviation (SD), or as an absolute number (proportion). For the retrospective study, continuous variables were compared with one-way analysis of variance (ANOVA). Categorical variables were compared using the Pearson chi-squared test. For all variables for which more than

10% was missing, 'missingness' is shown separately. A P value < 0.05 was considered significant. All analyses were conducted with IBM SPPS Statistics for Windows version 21 (IBM Corp., Armonk, New York, USA). For the prospective study, we performed a pre-emptive power calculation based on assumptions, as this was the first study to assess nonadherence at the ED in patients with a suspicion of a hypertensive emergency. Assuming 50% nonadherence, 50 patients needed to be included to have 80% power (one-sample t test).

Ethical approval

For the retrospective study, the Medical Ethics Committee of Erasmus MC concluded that the study did not fall under the scope of the Medical Research Involving Human Subjects Act (WMO), because of its retrospective nature and the anonymization of patient details, therefore no informed consent needed to be obtained. For the prospective study, the Medical Ethics Committee concluded that the study did not fall under the scope of the Medical Research Involving Human Subjects Act, as previously obtained blood samples were used. Informed consent was only deemed necessary for the collection and analyses of clinical data. Patients were informed about the study and informed consent was obtained from all eligible patients, and a withdrawal of consent form was given because of the short consideration time. To prevent a potential bias assuming nonadherent patients are less likely to give consent, we anonymously analysed samples of patients who did not give or withdrew consent after registering the expected drugs. For patients who gave consent, data were collected from the electronic patient records.

Results

Retrospective study

A total of 123,552 patients visited the ED in the 4-year inclusion period, of whom 64,979 had a recorded BP measurement. Of these ED visits, 1237 (1.9%) had SBP at least 180 mmHg and DBP at least 110 mmHg. As 75 patients visited the ED at least two times, we analysed a total of 1,163 patients (*Figure 1*).

Incidence of patients visiting the ED with BP at least 180/110 mmHg, increased from 136 patients (0.6% of all ED visits) in 2012 to 414 patients (1.9%) in 2015. Patients were predominantly men with a mean age of 60 years (SD 15 years). Mean SBP was 203 mmHg (SD 19 mmHg) and mean DBP was 121 mmHg (SD 12 mmHg) (*Table 1*).

Of all patients presenting with severely elevated BP, the combined incidence of hypertensive urgency and hypertensive emergency was 52.7%, of which hypertensive emergency was diagnosed more frequently than hypertensive urgency (30.6 vs 22.1%; P < 0.001). Patients with hypertensive emergency were older than patients with hypertensive urgency (64 vs 58 years; P < 0.001) and had a higher BPs (SBP: 209 vs 203 mmHg; P < 0.001 and DBP: 124 vs 121 mmHg; P < 0.001).

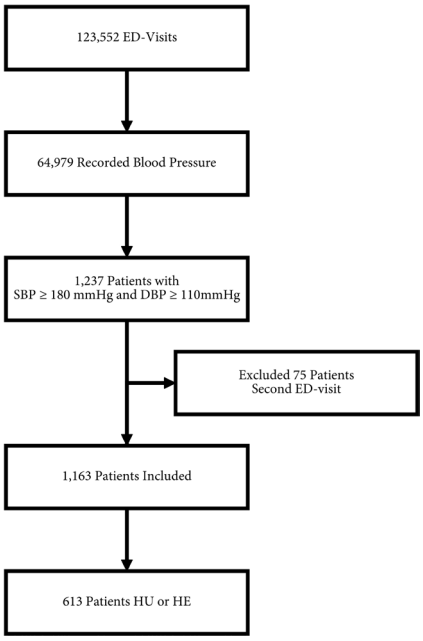

Figure 1: Flow chart retrospective study.

ED: emergency department; SBP: systolic blood pressure DBP: diastolic blood pressure; HE: hypertensive emergency; HU: hypertensive urgency .

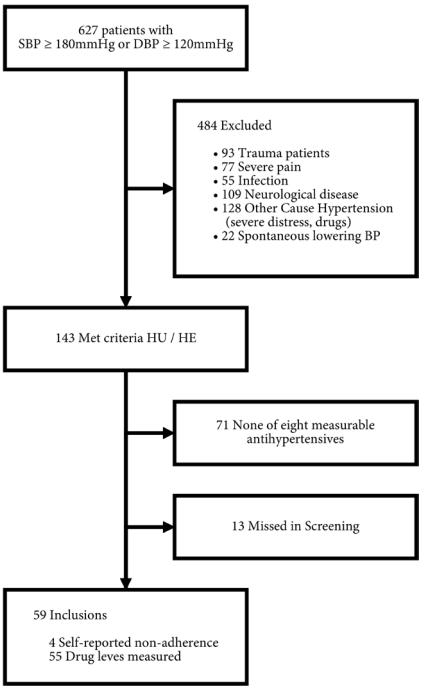

Figure 2: Flow chart prospective study.

SBP: systolic blood pressure DBP: diastolic blood pressure; HE: hypertensive emergency; HU: hypertensive urgency .

The most frequent diagnoses in patients with hypertensive emergency were stroke (10.7% ischemic, 8.5% haemorrhagic), acute pulmonary enema (4.1%) and myocardial infarction (4.0%) (*Table 1*). As women suspected of (pre)eclampsia were according to local guidelines referred to the obstetric clinic, no preeclampsia was recorded.

Seventy-nine patients (6.8%) were referred primarily for hypertension to exclude hypertensive emergency. Of these, 57 patients (72.2%) met the criteria of hypertensive urgency and seven (8.9%) of hypertensive emergency. The most frequently reported symptoms were headache, symptoms of the gastrointestinal tract, chest pain and dyspnoea (*Table 2*). Sixty-four patients with either hypertensive emergency or hypertensive urgency were asymptomatic. Of this group, 55 patients had hypertensive emergency (85.9%) and nine (14.1%) had hypertensive urgency. In most cases (90.3%), laboratory tests were performed. An ECG was made for 65.3% of patients, which showed left ventricular hypertrophy in 19.1% of patients (*Table 3*). Of all patients, 572 (49.2%) patients were not prescribed any antihypertensive drugs, 272 (23.3%) patients were prescribed one antihypertensive drug and 319 (27.4%) patients were prescribed two or more. Of the patients using antihypertensive drugs, 26.1% used beta blockers, 18.4% angiotensin-converting enzyme (ACE)-inhibitors, 16% diuretics, 14.5% calcium

Table 1: Patient characteristics retrospective study

	Total n=1,163	No HE/HU (e.g. severe pain) n=550	Hypertensive urgency n=257	Hypertensive emergency n=356
Mean (SD) age (years)	60.1 (14.6)	58.8 (14.9)	58.2 (13.4)	63.5 (14.7)
Male	641 (55.1)	301 (54.7)	125 (48.6)	215 (60.4)
Mean (SD) SBP (mmHg)	203 (19)	199 (16)	203 (17)	209 (20)
Mean (SD) DBP (mmHg)	121 (12)	119 (10)	121 (12)	124 (14)
Mean (SD) BMI (kg/m^2)	27 (5.6)	26.7(5.4)	28.0 (5.8)	27.3 (5.7)
History Hypertension	695 (59.8)	292 (53.0)	173 (67.3)	230 (64.4)
History Hypertensive crisis				
Yes	57 (4.9)	14 (2.5)	21 (8.2)	22 (6.2)
No	411 (35.3)	212 (38.5)	89 (34.6)	110 (30.9)
Missing	695 (59.8)	324 (58.9)	147 (57.2)	224 (62.9)
Diabetes	208 (17.9)	103 (18.7)	31 (12.1)	74 (21.2)
Alcohol use				
Yes	284 (24.4)	125 (23.3)	73 (28.4)	86 (24.3)
No	317 (27.3)	121 (22.0)	88 (34.2)	108 (30.3)
Missing	561 (58.3)	303 (55.3)	96 (37.4)	162 (45.5)
Smokers				
Yes	270 (23.2)	97 (17.7)	70 (27.2)	103 (28.9)
No	454 (39.1)	186 (33.9)	124 (48.2)	144 (40.4)
Missing	438 (37.7)	266 (48.5)	63 (24.5)	109 (30.6)
Previously reported non-adherence	111 (9.5)	35 (6.4)	38 (14.8)	38 (10.7)
Yes	355 (30.5)	167 (30.4)	92 (35.8)	96 (27.0)
No	697 (59.9)	348 (63.3)	127 (49.4)	222 (62.4)
Missing				
Chronic kidney disease	92 (7.9)	41 (7.4)	18 (7.0)	33 (9.3)
Previous stroke or TIA	136 (11.7)	41 (7.4)	26 (10.2)	69 (19.5)
Previous coronary artery disease	110 (9.5)	39 (7.1)	29 (11.2)	42 (11.8)
Antihypertensive drugs prescribed	591 (50.8)	256 (50.6)	147 (57.2)	191 (53.6)
Number antihypertensive drugs				
Mean (SD) overall	1 (1.1)	1 (1.4)	1.1 (1.2)	1.2 (1.6)
Mean (SD) users only	2 (1.0)	1.7 (0.95)	2 (1.0)	2 (1)
Taking ≥ 2 antihypertensive drugs	319 (27.4)	126 (22.9)	87 (33.9)	106 (29.7)
Taking ≥ 3 antihypertensive drugs	150 (12.8)	59 (10.7)	40 (15.6)	51 (14.3)
Angiotensin II receptor blocker	129 (11.1)	55 (10.0)	29 (11.3)	45 (12.6)
ACE-inhibitor	217 (18.4)	91 (16.5)	51 (19.9)	75 (21.2)
Calcium channel blocker	169 (14.5)	79 (14.3)	44 (17.2)	46 (13.0)
Diuretic	186 (16.0)	76 (13.8)	46 (17.9)	64 (17.9)
Beta blocker	304 (26.1)	117 (21.2)	80 (31.1)	107 (30.0)
Fixed-dose combination	57 (4.9)	26 (4.7)	15 (5.9)	16 (4.5)

Target organ damage				
Haemorrhagic Stroke	99 (8.5)		-	99 (8.5)
Ischemic Stroke	124 (10.7)		-	124 (10.7)
Pulmonary edema	48 (4.1)		-	48 (4.1)
Myocardial infarction	46 (4.0)		-	46 (4.0)
Aortic dissection	9 (0.8)		-	9 (0.8)
Acute kidney failure	4		-	4
Retinopathy grade III/IV	0		-	0
Thrombotic microangiopathy	1		-	1
Suspicion non-adherence				
Yes	54 (4.6)	15 (2.7)	24 (9.3)	15 (4.2)
Missing	1108 (95.3)	535 (97.3)	233 (90.7)	341 (95.8)
Hospital admission	764 (65.6)	166 (51.7)	92 (35.6)	335 (93.8)
Mean (SD) days	6 (12)	4.9 (7.4)	2.1 (4)	8.3 (14)
ICU admission	103 (8.9)	23 (7.7)	0	61 (17.2)
Change in drug regime after discharge (ED/hospital)	388 (28.7)	80 (14.5)	115 (60.5)	191 (54.2)
Drugs first 24 hours				
Labetalol intravenously	145 (12.5)	18 (3.3)	8 (3.1)	119 (33.7)
Nitroglycerin intravenously	89 (7.7)	12 (2.2)	16 (6.3)	61 (17.1)
Nifedipine retard	121 (10.4)	27 (4.9)	69 (27.0)	25 (7.1)
Captopril	32 (2.8)	0	25 (9.8)	7 (2.0)
Died after admission	92 (8)			
In-hospital mortality	108 (9.2)	47 (5.3)	0	57 (16.2)

Values are numbers (percentages) unless stated otherwise. HE: hypertensive emergency; HU: hypertensive urgency; ACE: angiotensin-converting enzyme; SD: standard deviation; TIA: transient ischemic attack.

channel blockers and 11.1% angiotensin-II receptor blockers. Only 4.9% of prescribed antihypertensive drugs were a fixed-dose combination.

Labetalol was used most often when treatment with an intravenous antihypertensive drug was needed and was given to 23.1% of all patients, and to 59.2% of patients with hypertensive emergency. The most commonly administered oral antihypertensive drug was nifedipine retard (10.4%). Oral therapy was mostly given in case of a hypertensive urgency, although a limited number of patients with a hypertensive emergency (9%) also received oral therapy. Suspicion of nonadherence was documented more often in patients with hypertensive urgency than those with hypertensive emergency (9.4 vs 4.2%; $P < 0.001$).

Prospective study

During the inclusion period, 59 patients met our inclusion criteria (*Figure 2*). Four patients spontaneously reported nonadherence. Of the remaining 55 patients, plasma drug levels were analysed. On the basis of drug levels, 14 out of 55 patients (25.5%) were deemed nonadherent for at least one drug. Of these 14, seven patients were completely nonadherent for all measured drugs. Combined with the four patients who spontaneously reported nonadherence for all prescribed drugs, this means 30.5% of patients was nonadherent

Table 2: Symptoms retrospective study

Symptoms	Total (n=1,163)	No HE/HU (n = 550)	Hypertensive urgency (n = 257)	Hypertensive emergency (n = 356)
Headache				
Yes	266 (22.9)	94 (17.1)	96 (37.5)	76 (21.3)
No	161 (13.8)	70 (12.7)	37 (14.4)	54 (15.2)
Missing	736 (63.3)	386 (70.2)	124 (48.2)	226 (63.5)
Blurred vision				
Yes	69 (5.9)	18 (3.3)	29 (11.3)	22 (6.2)
No	181 (15.6)	62 (11.3)	75 (29.2)	44 (12.4)
Missing	913 (78.5)	470 (85.5)	153 (59.5)	290 (81.5)
Dizziness				
Yes	113 (9.7)	27 (4.9)	56 (21.8)	30 (8.4)
No	56 (4.8	19 (3.5)	24 (9.3)	13 (3.7)
Missing	994 (85.5)	504 (91.6)	177 (68.9)	313 (87.9)
Neurological deficit				
Yes	128 (11.0)	19 (3.5)	12 (4.7)	97 (27.2)
No	602 (51.8)	301 (54.7)	150 (58.4)	151 (42.4)
Missing	433 (37.2)	230 (41.8)	95 (37.0)	108 (30.3)
Altered consciousness				
Yes	191 (16.4)	85 (15.5)	15 (5.8)	91 (25.6)
No	624 (53.7)	285 (51.8)	158 (61.5)	181 (50.8)
Missing	348 (29.9)	180 (32.7)	84 (32.7)	84 (23.6)
Chest pain				
Yes	216 (18.6)	51 (9.3)	97 (37.7)	68 (19.1)
No	311 (26.7)	131 (23.8)	97 (37.7)	83 (23.3)
Missing	636 (54.7)	368 (66.9)	63 (24.5)	205 (57.6)
Palpitations				
Yes	71 (6.1)	14 (2.5)	45 (17.5)	12 (3.4)
No	244 (21.0)	92 (16.7)	84 (32.7)	68 (19.1)
Missing	848 (72.9)	444 (80.7)	128 (49.8)	276 (77.5)
Dyspnoea				
Yes	200 (17.2)	73 (13.3)	51 (19.8)	76 (21.3)
No	272 (23.4)	112 (20.4)	107 (41.6)	53 (14.9)
Missing	691 (59.4)	365 (66.4)	99 (38.5)	227 (63.8)

Values are numbers (percentages). HU: hypertensive urgency; HE: hypertensive emergency.

of which more than half (61%) fully nonadherent and 39% partially nonadherent. Of the 41 patients who gave informed consent for collection of clinical data, 11 (26.8%) were partially or totally nonadherent (*Table 4*), so there was no significant correlation between giving or withdrawing informed consent and adherence. Nonadherence was found in both hypertensive urgency (64%) and hypertensive emergency (36%). The difference in nonadherence between hypertensive urgency and hypertensive emergency was not statistically significant.

Nonadherence was the highest for spironolactone and amlodipine (*Figure 3*). No significant differences in clinical characteristics between the adherent and nonadherent

Table 3: Additional investigations and results retrospective study

Additional investigations and findings	Total (n =1,163)	No HE/HU (n = 550)	Hypertensive urgency (n = 257)	Hypertensive emergency (n = 356)
Laboratory investigation	1,053 (90.3)	454 (82.5%)	246 (95.7%)	353 (99.2%)
Cardiac markers	90 (7.6)	16 (2.9%)	13 (5.1%)	61 (17.2%)
Urinalysis performed	260 (22.4)	100 (18.2)	105 (40.9)	55 (15.4)
Proteinuria present	97 (8.3)	42 (7.6)	24 (9.3)	31 (8.7)
Chest radiography	424 (36.5)	185 (33.6)	99 (38.5)	140 (39.3)
Increased CTR	82	17	31	34
Ophthalmoscopy	116 (10)	11 (2.0)	77 (29.9)	28 (8.2)
Retinopathy	10			10
ECG	760 (65.3)	234 (42.5)	225 (87.5)	301 (84.6)
ECG abnormalities				
Left ventricular hypertrophy	221	254 (9.9)	60 (23.3)	107 (30.1)
Signs of ischemia	104	29 (5.3)	21 (8.2)	54 (15.2)
Echocardiography	90 (7.7)	14 (2.5)	23 (9.0)	53 (14.9)
Left ventricular hypertrophy	40	5	12	23
Head CT scan	304 (26.1)	44 (17.1)	26 (17.2)	234 (65.7)

Values are numbers (percentages). CTR: cardiothoracic ratio; CT-scan: computed tomography scan.

group could be identified, aside from the higher number of previously prescribed antihypertensive drugs in the non- adherent group (3.7 vs 2.7 antihypertensive drugs; P = 0.04). At discharge, the medication regime was changed in half of the patients. During subsequent visits to the outpatient clinic, two nonadherent patients had symptomatic hypotension, probably because of adherence. None of the patients visited the ED with a recurrent hypertensive crisis during the 1-year follow-up period.

Discussion

In this study, we showed that severely elevated BP is common in the ED and that the incidence is rising. Approximately half of the patients with severely elevated BP met the criteria of hypertensive urgency or hypertensive emergency, accounting for one in 200 ED visits. Hypertensive emergency was more prevalent than hypertensive urgency. As expected, patients with hypertensive emergency were older and had more comorbidities (e.g. diabetes, hypertension, previous stroke). In only 5% of the patients, suspicion of nonadherence was documented in the medical records, whereas in our prospective cohort, we observed nonadherence in 30.5% of the patients. This discrepancy has important clinical implications, as an intervention improving adherence might be more beneficial than extending drug therapy by increasing doses or adding drugs. This latter strategy may potentially lead to severe side effects such as hypotension, as was seen in two of the patients in the prospective study.

Table 4: Patient characteristics including one year follow-up data prospective study

	Total (n = 41)	**Adherent** (n = 30)	**Non-adherent** (n = 11)
Male	19 (46.3)	14 (46.7)	5 (45. 5)
Mean (SD) age	65 (11)	66 (12)	62 (11)
Mean (SD) SBP (mmHg)	198 (16)	196 (17)	202 (17)
Mean (SD) DBP (mmHg)	106 (15)	104 (15)	111 (14)
Mean (SD) BMI	29.0 (5)	30.0 (5)	25.3 (4)
Diabetes	10 (24)	8 (27)	2 (18)
Previous cardiovascular disease	22 (54)	17 (57)	5 (46)
Chronic kidney disease	10 (24)	5 (17)	4 (46)
Non-adherence earlier reported	6 (15)	3 (10)	3 (27)
Hypertensive urgency	20 (49)	13 (43)	7 (64)
Hypertensive emergency	12 (29)	8 (27)	4 (36)
Hospital admission	26 (63)	19 (63)	7 (64)
Change in drug regime after discharge (ED / hospital)	19 (48)	14 (47)	5 (50)
Number (SD) antihypertensive drugs[a]	2.9 (1.4)	2.7 (1.0)	3.7 (2.0)
Taking at least 3 antihypertensive drugs	22 (54)	14 (47)	8 (73)
Prescribed antihypertensive drugs			
ACE inhibitor	20 (49)	15 (50)	5 (46)
Angiotensin II receptor blocker	13 (32)	11 (37)	2 (18)
Calcium channel blocker	20 (49)	14 (47)	6 (55)
Diuretic	21 (51)	14 (47)	(64)
Beta blocker	25 (61)	17 (57)	8 (73)
Follow-up after one year			
Dead		2 (7)[b]	0 (0)
Alive, good BP regulation		19 (63)	4 (36)
Alive, poor BP regulation		6 (20)	7 (64)
Alive, BP regulation unknown		3 (10)	0 (0)

Values are numbers (percentages) unless stated otherwise. ACE: angiotensin-converting enzyme; BP: blood pressure; ED: emergency department; SD: standard deviation. a Student's t test between adherent and nonadherent group differed significantly (P value 0.04). b Both unrelated to blood pressure (cancer).

In our study, the incidence of hypertensive urgency and hypertensive emergency together (0.5%) is in line with most other studies, where reported incidences range from 0.45 to 3.0%.[93,95,99,106] The incidence of hypertensive emergency was higher than of hypertensive urgency, whereas most other investigators found a greater incidence of hypertensive urgency than hypertensive emergency.[95,99,106,107] This probably relates to the fact that our hospital is a tertiary referral centre for specialized treatment, such as thrombectomy for ischemic stroke,[108] craniotomy for intracerebral haemorrhage or thoracic surgery for aneurysms. Only one other study on hypertensive crisis in the ED found more hypertensive emergency than hypertensive urgency with comparable patient and hospital characteristics.[93]

We noted an increase in incidence of hypertension-related visits to the ED of 7.7% per year, which is probably because of the increase in hypertension in the general population.[109] This percentage is comparable to the increase reported by McNaughton *et al*. in 2015, who reported an increase of hypertension related emergency department visits of 5% per year in the period 2006 – 2012.[94]

Patients with hypertensive emergency presented most often with ischemic and haemorrhagic stroke, acute pulmonary enema and myocardial infarction. Their clinical symptoms mostly fitted the subtype of hypertensive emergency. Headache was the most common symptom and was, in most cases, a sign of hypertensive urgency and not of hypertensive emergency in line with earlier studies.[99,110] Approximately 5% of the patients with severe hypertension had no clinical symptoms of organ damage, but were diagnosed with either hypertensive urgency (29%) or hypertensive emergency (7%) after extensive testing. This implies that assessment of symptoms alone is insufficient to rule out hypertensive urgency and hypertensive emergency. Previous studies reported higher proportions of patients without symptoms, which may be partly explained by the BP criteria used.[92] Comparing hypertensive emergency and hypertensive urgency, we found that hypertensive emergency patients were older, had higher SBP and DBP, and more often smoked, which is in line with earlier studies.[92,100,101,106] Approximately two-third of patients with hypertensive emergency or hypertensive urgency had a previous history of hypertension, which is relatively low compared to percentages found in earlier studies (70 – 90%).[92,99-101] Despite the differences between hypertensive urgency and hypertensive emergency, no (combination of) factors could be identified that distinguishes hypertensive emergency from hypertensive urgency without the use of additional testing. Therefore, the standard workup, which includes blood tests and ophthalmoscopy, should always be followed in order to differentiate between hypertensive emergency and hypertensive urgency, if clinical signs do not yield the diagnosis hypertensive emergency. In our hospital, the guideline was not consistently followed. Especially ophthalmoscopy was performed in a low percentage of cases. It should be kept in mind that in hypertensive emergency, it might not have been necessary to confirm the diagnosis when another kind of organ damage was identified, but in hypertensive urgency it should have been 100% to rule out hypertensive emergency. This low percentage of following the guidelines is in line with an earlier study that found even lower numbers: in only 6% of all patients presenting with severe hypertension, all tests were performed as recommended in the local guideline.[91] Standard workup should include repeated measurements of blood pressure as blood pressure often lowers spontaneously and/or in response to pain or stress relief;[111] although repeated measurements were performed in most instances, enabling us to select patients with spontaneous blood pressure reduction as a separate category 'non-hypertensive urgency non-hypertensive emergency,' follow-up measurements were not always reported in the electronic patient record. Since carrying out this study, the American guideline has been altered to consider all severe hypertension not hypertensive emergency as 'markedly elevated blood pressure,' thus abandoning the terminology of hypertensive urgency. In this study, we employed the existing categorization according to the guidelines valid at the time.[96-98]

Many studies reporting about the incidence of hypertensive urgency and hypertensive emergency suggest that nonadherence is a contributing factor to the development of hypertensive urgency or hypertensive emergency, but studies directly assessing this possibility are limited. In a recent study, drug levels of all patients on antihypertensive drugs visiting the ED (for any reason) showed 28% nonadherence (undetectable drug levels), and nonadherence was associated with higher BP levels.[112] The assay used in this study, however, was validated using clinical samples from hospitalized patients obtained shortly after drug intake, and as a consequence, drug levels measured at time points more than 12 h after intake could have been false negative, overestimating the prevalence of nonadherence.[113]

In a study including patients with stroke, the odds ratio for developing a stroke as a result of nonadherence to antihypertensive drugs ranged from 1.7 to 2.7, depending on the number of years antihypertensive drugs had been prescribed.[99,103] A small prospective study defined nonadherence as a risk factor for the development of hypertensive crises, where nonadherence was defined solely on reporting by patients and physicians.[114]

Our study is the first study focusing on patients with severe hypertension in the ED using a well validated LC-MS/MS method, which is the most reliable method to assess adherence.[115] We found that 30.5% of the patients were indisputably nonadherent, when also taking into account the patients who self-reported nonadherence at inclusion. This rate is in line with earlier studies performed in uncomplicated hypertension and resistant hypertension.[116-122] Therefore, our findings imply that improving adherence is of major importance, especially as suspected nonadherence was documented in the electronic medical record in only 5% of patients in the retrospective study. Two out of nine patients who received follow-up in the outpatient clinic developed hypotension after the ED visit. These complications, presumably caused by using all previously and newly prescribed drugs, might be prevented by adequate assessment of adherence in the emergency department. Two observational studies indicate an improved BP control when providing feedback on undetectable drug levels.[123,124] Although this was not studied in a controlled way, it implies that immediate measurement and feedback at the ED might be an efficacious approach to improve adherence and consequently BP control.

When investigating the differences between the adherent and nonadherent patients, we found that nonadherent patients had been prescribed more antihypertensive drugs than adherent patients. Studies have shown that an increase in the number of prescribed drugs results in more nonadherence.[125,126] The drug for which most patients were nonadherent was spironolactone. Spironolactone is commonly used in resistant hypertension after the PATHWAY-2 trial.[127] Our findings suggest that the reason the BP target in these patients was not previously reached is nonadherence, whereas not reaching the BP target urges the physician to prescribe spironolactone.

Strengths and weaknesses

This study has strengths and limitations. The first strength of our retrospective study is the large number of patients for whom most of the relevant parameters were known. Secondly, the results from our retrospective analyses can easily be generalized to other countries, as the Dutch population is comparable with populations of most western countries, including the USA in terms of ethnicity, lifestyle, habits and disease incidence and prevalence. Our study population constituted of multiple ethnicities with patients born in more than 41 countries.

Our study also has limitations. First, in the retrospective study, we included only patients with both high SBP and DBP using cut-off points of at least 180 mmHg and DBP at least 110 mmHg, respectively. With this approach, we potentially missed patients with hypertensive urgency or hypertensive emergency with an isolated high SBP or DBP, resulting in an underestimation of the incidence. However, by applying both SBP and DBP, we limited the number of patients with increased BP because of pain or stress. In the prospective study, we chose threshold values of SBP at least 180 mmHg or DBP at least 120 mmHg, limiting direct comparison of the retrospective and prospective study. However, these threshold values did not influence the percentage of nonadherence. Also, there are no clearly defined cut-off values at which the risk of acute end-organ damage is absent or present. The acceleration of BP rise is more important than absolute BP values.

Secondly, because of the nature of care in the emergency setting, we encountered missing data. This may have led to underestimation of suspicion of nonadherence, although spontaneous report is more likely in presence than in absence of suspicion of nonadherence. However, lack of spontaneous reporting of suspected drug (non) adherence also gives important information on physicians' awareness of this problem. In addition, even when physicians are at least considering the chance of nonadherence as underlying cause, they tend to overestimate their patients' drug adherence.[128] Therefore, we think the retrospective study is representative for how the issue of drug adherence is handled in daily clinical practice. Finally, the study was executed in an urban hospital that also functions as a tertiary care centre. In that capacity, a proportion of the patients had a complex medical history with multiple comorbidities, and may therefore not be generalizable to secondary care centres, as also reflected by the higher incidence of hypertensive emergency than of hypertensive urgency.

Considering the prospective study, we were the first to prospectively investigate drug nonadherence in patients with a severely elevated blood pressure at the ED using a well validated LC-MS/MS. By ensuring that drug levels were analysed independent of obtaining informed consent, we were able to avoid a potential selection bias. The number of patients not giving and especially withdrawing consent was surprisingly low. However, this study also has several limitations. The study was underpowered to compare characteristics of adherent and nonadherent patients, as the proportion of nonadherence was lower than expected. Using our assay, we could measure seven antihypertensive drugs. We chose this specific selection of most commonly prescribed

antihypertensive drugs, because to use plasma drug levels in clinical practice, the assay needs to be extensively validated. Diuretics other than spironolactone were not measured as they are not detectable for 24 h after intake allowing measurement at a random time point (the ED visit). By not measuring diuretics and beta-blockers, drugs known to be associated with considerable nonadherence because of side effects, nonadherence might have been underestimated.[129] However, all measured drugs are in the top 100 of most used drugs in The Netherlands and all of the chosen ACE inhibitors and angiotensin II receptor blockers are available in fixed-dose combinations. Being nonadherent for one of the measured drugs implies that adherence to unmeasured drugs is also questionable. In addition, as both the nominator and the denominator of the calculation of nonadherence depend on the choice of antihypertensive drugs, this limitation did not lead to a bias. A final issue to discuss is white-coat adherence: in theory, patients could have taken their antihypertensive drugs just before going to the emergency department, but this might be more common during regular visits to the clinic than to the emergency department.

In conclusion, severely elevated BP is a common health problem and the incidence is increasing, resulting in frequent ED visits and high economic burden. We showed that all patients visiting the ED for suspicion of hypertensive emergency should receive a full workup, regardless of their clinical symptoms. We found in the prospective study that three in 10 patients were nonadherent for antihypertensive drugs, whereas in the retrospective study only one in 20 patient's physicians actively recorded nonadherence as a potential cause. Distinguishing between nonadherent and adherent patients is crucial, as treatment strategies differ. Therefore, ideally a point-of-care-test would be developed to enable direct assessment of adherence in order to adjust the treatment strategy accordingly.

Chapter 5

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Medically Unexplained Physical Symptoms in Patients Visiting the Emergency Department: an International Multicentre Retrospective Study

Abstract

Objective

The objective of this study was to assess the incidence and characteristics of patients presenting with physical symptoms that remain medically unexplained at the emergency department (ED).

Patients and methods

A retrospective chart study was carried out in three hospitals in The Netherlands and Belgium. All patients (age > 18 years) visiting the ED in 4 selected weeks in 2013 at the Erasmus University Medical Center (Erasmus MC) in Rotterdam, The Netherlands, and 1 selected week in 2013 at the Haaglanden Medical Centre, Westeinde HMC in The Hague, The Netherlands, and the University Hospital Ghent (UZG), Belgium, were included. Descriptive statistics were used for data analysis.

Results

A total of 2,869 patients (Erasmus MC 1,674, HMC 691, UZG 504) were included. Medically unexplained physical symptoms in the emergency department (EDMUPS) were present in 13.4% of all ED visits (Erasmus MC 12.5%, HMC 18.7%, UZG 9.1%). No EDMUPS were identified in trauma patients. When excluding trauma patients, EDMUPS were present in 18.5% (Erasmus MC 16.8%, HMC 26.5%, UZG 13.3%) of the visits. The characteristics of patients with and without EDMUPS differed significantly; patients with EDMUPS were more often younger, female, self-referred, frequent visitors, were prescribed less medication and more often had a psychiatric disease. Dutch and Belgian Hospital differed in the distribution of patients in triage categories and in the incidence of psychiatric illnesses.

Conclusion

Physical symptoms remain unexplained in a significant number of patients at the time of ED assessment.

Introduction

Medically unexplained physical symptoms (MUPS) are symptoms that cannot be fully explained by physical examination or by further testing.[130] Patients with persistent MUPS often have significantly reduced health-related quality of life with impaired physical, mental or social functioning.[131,132] To diagnose MUPS, a patient must experience physical symptoms for weeks, without underlying physical abnormalities found by a physician. MUPS are divided into clusters of symptoms. The secondary care system, (university) hospitals and psychiatric hospitals in The Netherlands use two clusters (i.e. pain-fatigue and cardiorespiratory complaints).

In primary care, about 30–50% of patients visiting a general practitioner (GP) have MUPS.[133,134] This percentage is approximately the same in secondary care, and MUPS occur within every medical specialty.[135,136] Patients with MUPS have up to two-fold higher healthcare consumption compared with patients whose complaints are fully medically explained. Also, their illnesses lead to more sick leave.[131,132] Preferred treatment strategies for patients with MUPS include a patient-centred approach, with a focus on symptom exploration, information on MUPS and reassurance rather than performing diagnostic investigations.[137,138] The GP should be responsible for case management, and clear communication between primary and secondary care is paramount.

GPs refer most patients with MUPS to outpatient clinics; however, patients also present at the emergency department (ED). The exact burden of MUPS in the ED (EDMUPS) is unknown.[138] Treatment strategies differ between the ED and (outpatient) clinic.[138] In the ED, the focus is often to rule out (serious) pathology in a brief time period, using additional examination, such as laboratory and radiographic studies. Not finding a viable somatic explanation for physical symptoms without the presence of alarming symptoms might lead to additional diagnostic tests, although guidelines suggest otherwise. This contributes towards higher healthcare costs.[138,139] Specific knowledge and tools to properly distinguish MUPS patients at the ED are lacking, and management of patients with EDMUPS remains challenging.[138] Therefore, the aim of this study is to determine the prevalence and characteristics of patients with EDMUPS.

Patients and methods

Study design

We performed an international multicentre retrospective study.

Setting

Data were collected from March to June 2014 at EDs from: 1) Erasmus University Medical Center, Rotterdam, the Netherlands (Erasmus MC), which is the largest university hospital of the Netherlands, with 1,320 beds and approximately 30,000 adult (≥ 18 years)

ED visits a year. It provides secondary and tertiary care. 2) Haaglanden Medical Centre Westeinde, The Hague, the Netherlands (HMC), is an 825-bed teaching hospital located in the city centre of The Hague with about approximately 56,000 adults ED visits a year. The hospital service area is mostly local, with a large population of immigrants with 99 different nationalities. Data were collected from July 2014 to March 2015 at the ED of 3) Ghent University Hospital in Ghent, Belgium (UZG) is a 1068-bed tertiary university hospital with approximately 35,000 adults visiting ED. The hospital service area is nationwide, and UZG offers complex regional care. All hospitals use the Manchester Triage System. In both countries, ambulance services are allocated to patients after contact with an emergency dispatch centre. Ambulance services can treat patients on-site, refer to a GP or transport patients to a hospital. Ambulance services also provide patient transport on GPs' request. The study was approved by the local Medical Ethic Boards of all hospitals.

Patients

Patients, 18 years and older, who visited the ED of the 1) Erasmus MC in the first week of February, May, August and November 2013, 2) HMC in the last week of January 2013 and 3) UZG in the first week of February 2013 were included in the study. The months in the Erasmus MC were selected to evaluate seasonal differences and public holidays. After initial evaluation of the data of the Erasmus MC, no difference in prevalence in terms of the season was found, and to obtain a sample size of minimum of 2,500 patients, we decided to only investigate 1 week, the first week of February, in the other hospitals. As the ED of HMC was reorganized in that month, we choose to investigate 1 week earlier. Patients were excluded when no data on their visit were available or if they left before contact with a physician.

Variables

The following data were retrieved from the electronic patient records: demographic data [i.e. age, sex, previous medical history, substance abuse (i.e. alcohol, smoking, illicit drugs)], frequent ED visit (defined as > 2 visits in last 2 years) and psychiatric diagnosis/history, as well as data on their actual ED visit [e.g. Manchester Triage System Triage class, referral (referred by a physician, ambulance, self-referral), date, time and duration of visit, treating specialist, trauma or non trauma, medical tests performed] and ED diagnosis were recorded. Data on treatment and aftercare [e.g. discharge disposition, medication at ED, prescription, discharge orders or explanations about the diagnosis given to the patient, correspondence (i.e. to the GP or other involved physicians), discharge orders to GPs and outpatient clinic appointments] were also recorded.

Data were extracted by one abstractor in the Netherlands and two abstractors in Belgium following standard operational procedures. Abstractors did not receive any additional training and blinding did not occur. Performance in the Netherlands was not monitored, but was evaluated by checking random samples. Performance in Belgium was not monitored or evaluated. EDMUPS were defined as presenting symptoms without an

adequate explanation despite adequate assessment of history and physical examination, diagnostic testing in the ED or during follow-up. In case of doubt, cases were discussed in consensus meetings. The follow-up period was the time between the ED visit and inclusion in the study (varying from 3 months to 2 years), and only data from the following admission, outpatient clinic appointment or second ED visit were used, if available. Patients for whom a descriptive diagnosis (e.g. atypical chest pain) or a known MUPS-syndrome (e.g. irritable bowel syndrome) was used, or when no diagnosis was made, and only the excluded diagnosis was stated ('rule-out medicine', e.g. no pulmonary embolism[138]) were classified as having EDMUPS. EDMUPS differs from the MUPS definition used by specialists in outpatient clinics or by GPs as it is based solely on the absence of a clarifying diagnosis after a single assessment by a physician at the ED, in contrast to the MUPS definition used by the Dutch healthcare organizations, which requires symptoms to be present for several weeks without a somatic explanation despite adequate assessment of medical history, physical examination and diagnostics. EDMUPS were clustered using two clusters: pain-fatigue, including complaints such as chronic fatigue, joint pain, or fibromyalgia and cardiorespiratory, including complaints such as thoracic pain, hyperventilation and palpitations. We hypothesized that EDMUPS fall within the spectrum of unexplained physical symptoms.

Statistical methods

Descriptive statistics were used for most categorical data. Categorical data were analysed using a χ^2-test. Continuous data, which were not normally distributed, were analysed using a Mann-Whitney (two groups with equal variances) or a Kruskal-Wallis test (three groups with equal variances). A P value less than 0.05 was considered significant. The prevalence of psychiatric diagnoses was described as an odds ratio. Data were analysed using SPSS Statistics 21 (IBM; IBM Corp., Armonk, New York, USA).

Results

Patients

A total of 3,199 patients, 18 years of age and older (Erasmus MC 1,812, HMC 761, UZG 626) visited EDs in the selected periods; 330 patients were excluded, resulting in the enrolment of 2,869 patients (Erasmus MC 1,674, HMC 691, UZG 504) in the study (*Figure 1*).

Patient characteristics

All patient characteristics per hospital are presented in *Table 1*. Patients visiting the ED were predominantly male (53.5%), with a mean age of 46 years (SD: 19.3, range: 18–97). There were more nontrauma patients (72.4%) than trauma patients (27.6%). Almost half were self-referrals (49.3%, range: 42.2–59.7%) and were triaged into the green triage category ranging from 2.0 to 35.9%. EDMUPS were present in 13.4% of all ED

Table 1: Patient characteristics of all patients per medical center			
	Erasmus MC (n = 1,674)	Haaglanden Medical Centre Westeinde (n = 691)	Ghent University Hospital (n=504)
Age			
Mean (range)	46 (18–97)	46 (18–94)	47 (18–93)
Median	45	44	43
Trauma/nontrauma			
Trauma patients	430 (25.6)	204 (29.5)	158 (31.3)
Nontrauma patients	1,244 (74.4)	487 (70.5)	346 (68.7)
EDMUPS	209 (12.5)	129 (18.7)	46 (9.1)
Sex			
Male	906 (54.1)	352 (50.9)	278 (55.2)
Female	768 (45.9)	339 (49.1)	226 (44.8)
Triage color			
Green < 120 min	549 (32.8)	248 (35.9)	10 (2.0)
Yellow < 60 min	809 (48.3)	272 (39.4)	79 (15.7)
Orange < 10 min	140 (8.4)	138 (20.0)	235 (46.6)
Red < 0 min	36 (2.2)	8 (1.2)	171 (33.9)
White, not-triaged	140 (8.4)	25 (3.6)	9 (1.8)
Referral			
Self-referral	709 (42.4)	404 (58.5)	301 (59.7)
Ambulance	310 (18.5)	94 (13.6)	82 (16.3)
Referred	655 (39.1)	193 (27.9)	121 (24.0)
Admission to ward			
Yes	630 (37.6)	144 (20.8)	226 (44.8)
No	1,044 (62.4)	547 (79.2)	278 (55.2)
Laboratory studies performed			
Yes	1,042 (62.2)	365 (52.8)	285 (56.5)
No	632 (37.8)	326 (47.2)	219 (43.5)
Radiographic studies performed			
Yes	1,144 (68.3)	355 (51.4)	299 (59.3)
No	530 (31.7)	336 (48.6)	205 (40.7)
Medication given at ED			
Yes	907 (54.1)	261 (37.8)	264 (52.4)
No	767 (45.9)	430 (62.2)	240 (47.6)

Prescription of medication at discharge			
Yes	1,005 (60.0)	426 (61.6)	224 (44.4)
No	669 (40.0)	265 (38.4)	280 (55.6)
Follow-up appointment			
Yes	930 (55.6)	360 (52.1)	219 (43.5)
No	744 (44.4)	331 (47.9)	285 (56.5)
Frequent visitors			
Yes	300 (17.9)	235 (34.0)	72 (14.3)
No	1374 (82)	465 (66.0)	432 (85.7)
Psychiatric disorder			
Yes	103 (6.1)	65 (9.4)	92 (18.3)
No	1,571 (93.9)	626 (90.6)	412 (81.7)

Values are represented as n (%) of patients. ED: emergency department: EDMUPS, medically unexplained physical symptoms in the emergency department.

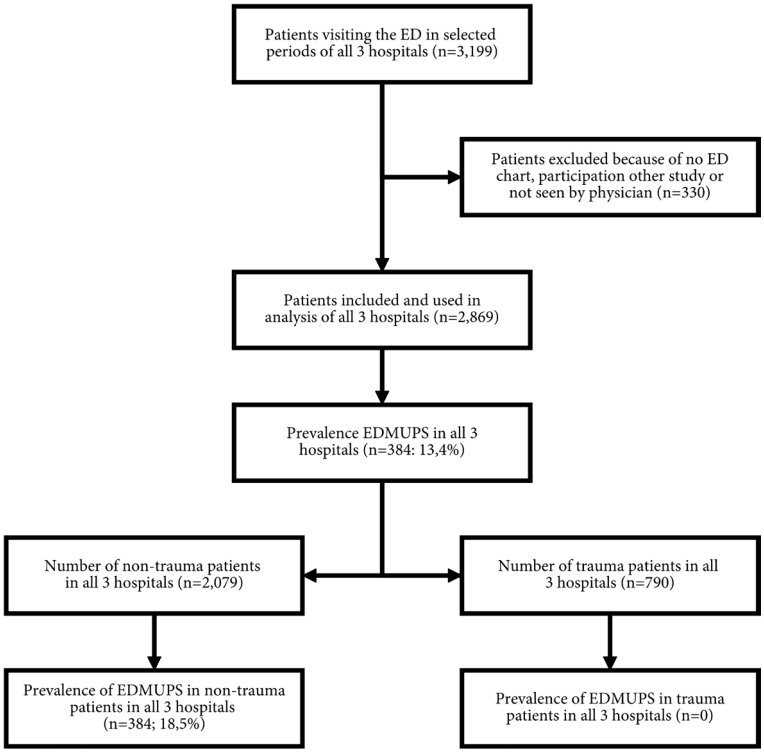

Figure 1: Flowchart showing the inclusion of study participants and the prevalence of EDMUPS.

ED: emergency department; EDMUPS: medically unexplained physical symptoms in the ED.

Table 2. Patient characteristics of patients with and without medically unexplained physical symptoms in the emergency department per medical center

	Erasmus MC			Haaglanden Medical Centre Westeinde			Ghent University Hospital		
	EDMUPS (n= 209)	Non-EDMUPS (n= 1,465)	P-value	EDMUPS (n= 129)	Non-EDMUPS (n= 562)	P-value	EDMUPS (n= 46)	Non-EDMUPS (n= 458)	P-value
Age									
Mean (range)	42 (18–86)	47 (18–97)	0.001	44 (18–92)	46 (18–94)	0.253	38 (18–77)	47 (18–93)	0.006
Median	40	47		43	44		38	45	
Sex									
Male	90 (43.1)	816 (55.7)	0.001	52 (40.3)	300 (53.4)	0.007	20 (43.5)	258 (56.5)	0.095
Female	119 (56.9)	649 (44.3)	<0.001	77 (59.7)	262 (46.6)	0.082	26 (56.3)	200 (43.7)	0.656
Triage color									
Green < 120 min	63 (30.1)	486 (33.2)		35 (27.1)	213 (37.9)		0 (0.0)	10 (2.2)	
Yellow < 60 min	127 (60.8)	682 (46.6)		59 (45.7)	213 (37.9)		9 (19.6)	79 (15.3)	
Orange < 10 min	10 (4.8)	130 (8.9)		31 (24)	107 (19)		22 (47.8)	213 (46.5)	
Red < 0 min	1 (0.5)	35 (2.4)		0 (0)	8 (1.4)		15 (32.6)	171 (34.1)	
White not-triaged	8 (3.8)	132 (9.0)		4 (3.1)	21 (3.7)		0 (0)	9 (1.8)	
Referral									
Self-referral	113 (53.6)	597 (40.8)	0.002	80 (62)	324 (57.7)	0.118	33 (71.7)	268 (58.5)	0.118
Ambulance	28 (13.4)	282 (19.2)		14 (10.9)	110 (19.6)		2 (4.3)	80 (17.5)	
Referred	69 (33)	586 (40)		35 (27.1)	128 (22.7)		11 (24)	110 (24)	
Admission to ward									
Yes	19 (9.1)	611 (41.7)	<0.001	14 (10.9)	130 (23.1)	0.002	11 (23.9)	215 (46.9)	0.003
No	190 (90.9)	854 (58.3)		115 (89.1)	432 (76.9)		35 (76.1)	243 (53.1)	
Laboratory studies performed									
Yes	161 (77)	881 (60.1)	<0.001	91 (70.5)	274 (48.8)	< 0.001	35 (76.1)	250 (54.6)	0.005
No	48 (23)	584 (39.9)		38 (29.5)	288 (51.2)		11 (23.9)	208 (45.4)	

Radiographic studies performed									
Yes	155 (74.2)	989 (67.5)	0.053	61 (47.3)	294 (52.3)	0.303	27 (58.7)	272 (59.4)	0.927
No	54 (25.8)	476 (32.5)		68 (52.7)	268 (47.7)		19 (41.3)	186 (40.6)	
MUPS cluster									
Cardio respiratory	118 (56.5)			50 (38.8)			18 (39.1)		
Pain-fatigue	91 (43.5)			79 (61.2)			28 (60.9)		
Medication given at ED									
Yes	70 (33.5)	837 (57.1)	<0.001	28 (21.7)	233 (41.5)	<0.001	15 (32.6)	249 (54.4)	0.005
No	139 (66.5)	628 (42.9)		101 (78.3)	329 (58.5)		31 (67.4)	209 (45.6)	
Prescription of medication at discharge of the ED									
Yes	87 (41.6)	918 (62.7)	<0.001	63 (48.8)	363 (64.6)	0.001	13 (28.3)	211 (46.1)	0.020
No	122 (58.4)	547 (37.3)		66 (51.2)	199 (35.4)		33 (71.7)	247 (53.9)	
Follow-up appointment									
Yes	68 (32.5)	862 (58.8)	<0.001	49 (38)	311 (55.3)	<0.001	19 (41.3)	200 (43.7)	0.758
No	141 (67.5)	603 (41.2)		80 (62)	251 (44.7)		27 (58.7)	258 (56.3)	
Frequent visitor									
Yes	59 (28.2)	241 (16.5)	<0.001	60 (46.5)	175 (31.3)	0.001	10 (21.7)	62 (13.5)	0.130
No	150 (71.8)	1,224 (83.5)		69 (53.5)	387 (68.9)		36 (78.3)	396 (86.5)	
Psychiatric diagnosis									
Yes	31 (14.8)	72 (4.9)	<0.001	22 (17.1)	43 (7.7)	0.001	6 (13)	86 (18.8)	0.337
No	178 (85.2)	1,393 (95.1)		107 (82.9)	519 (92.3)		40 (87)	372 (81.2)	

Values are represented as n (%). ED, emergency department; EDMUPS, medically unexplained physical symptoms in the emergency department; MUPS, medically unexplained physical symptoms.

visits (Erasmus MC 12.5%, HMC 18.7%, UZG 9.1%, P < 0.001). After excluding trauma patients, EDMUPS were present in 18.5% (Erasmus MC 16.8%, HMC 26.5%, UZG 13.3%) of patients (*Figure 1*). No difference was found in EDMUPS incidence between office hours (08: 00–18: 00) (11.4%) and outside office hours (13.3%) (P = 0.25). In the Erasmus MC, no seasonal difference in the incidence of EDMUPS was found (February 14.8%, May 13.2%, August 10.8% and November 10.7%, P = 0.203). A significant (P < 0.001) difference was found in the distribution of patients in triage allocation when comparing

the Dutch hospitals with UZG. Significantly more ED patients were categorized in the orange class, requiring more urgent management in the UZG compared with the Dutch hospitals. Also, the prevalence of psychiatric disorders was higher in the UZG compared with the Dutch hospitals.

Comparison of EDMUPS and non-EDMUPS patients

Patient characteristics of EDMUPS and non-EDMUPS patients are presented in *Table 2*. Patients with EDMUPS were more often female (57.6%, range: 56.3–59.7%, P < 0.001) and younger, with a mean age of 42 years (SD: 16.6, range: 18–92, P = 0.006). They were more often frequent visitors (35.4%) than patients without EDMUPS (21.4%) (P < 0.001). Overall, they were significantly more often self-referred, less likely to be subsequently admitted to a hospital ward and more intensely investigated. Self-referred patients mostly presented with symptoms fitting the pain-fatigue cluster, in contrast to referred patients, who mostly presented with symptoms fitting the cardiorespiratory complaints cluster. Furthermore, patients with EDMUPS were less likely to receive medication at the ED and to be discharged with a prescription. Only a small proportion received a follow-up appointment, although they were more frequent ED visitors. A psychiatric diagnosis was present in 15,3% of patients with EDMUPS. The most reported diagnoses were depression (32.2%), panic disorder (32.2%) and anxiety disorder (19.4%). In patients without EDMUPS, 8.2% had a psychiatric diagnosis (odds ratio = 2.01, 95% confidence interval: 1.47–2.74, P = 0.001). Patients with a psychiatric diagnosis received fewer follow-up appointments, but were more often frequent visitors of the ED. Follow-up data were not available for the Belgian hospital, except for patients who were hospitalized following the ED visit.

Discussion

This study shows that in a significant number of nontrauma patients visiting the ED, presenting symptoms remained unexplained, with clear differences in patient characteristics. Patients with EDMUPS are more often younger, female and self-referred, compared with patients with non-EDMUPS. This is in line with studies on MUPS.[135] Self-referred patients mostly presented with pain-fatigue symptoms, in contrast to referred patients, who mostly presented with cardiorespiratory symptoms. Differences between the participating hospitals were probably because of the locations of the hospitals, hospital type (secondary/tertiary referral) and number of self-referred patients.

Symptoms that remain unexplained are present in 25-50% of patients in general practice and specialist outpatient clinics, and were present in our study in approximately 18.5% of nontrauma patients visiting the ED.[133-136,140] In EDs, which are by definition focused on acute care, inappropriate (self)referrals might unnecessarily increase patient burden and costs in the ED. Giesen *et al*., [141] concluded that the majority of self-referrals to Dutch EDs should not be visiting the ED, but their GP. The differences in referral between two MUPS clusters suggest that GPs succeed in preventing referral of patients with pain-fatigue to

the ED, presumably by either treating them or by elective referral to outpatient clinics. However, it is difficult to rule out possible emergencies in patients with cardiorespiratory symptoms.[141] Patients with EDMUPS were more often frequent visitors of the ED.[133,142] In a study by Theadom *et al.*,[142] approximately 31.1% of the patients who were frequent visitors of the ED had unexplained symptoms, which is in line with our results. We also found a threefold higher likelihood of psychiatric disorders compared with nonfrequent visitors, and this was even larger when EDMUPS were present. This is comparable with other studies in the ED,[143-146] but was also found in studies in primary care and outpatient clinics.[136,144] Depression, anxiety disorders and panic disorders were the most frequent psychiatric diagnoses documented in the group with EDMUPS. Multiple studies showed a link between anxiety, depression, panic attacks and MUPS.[145,146] They also showed a comparable prevalence of psychiatric disorders compared with our data.[136] The higher prevalence of psychiatric disorders diagnosed or detected at UZG (18.3%) may be because of differences in healthcare organization.

Dutch acute psychiatric care is often organized on an ambulatory basis, whereas the ED of the UZG also has an acute psychiatry unit, and psychiatric assessment is more likely. As such, the percentage of psychiatric disorders in the Dutch hospitals (6.1 and 9.4%) might be an underestimate. Identification of the patients with EDMUPS, especially those who are likely to become frequent visitors, could lead to different treatment strategies. Better treatment strategies may not only increase quality of patient care; they may also have a beneficial effect on the workload of the EDs, and potentially reduce unnecessary examinations and thereby reduce costs. As there are many similarities between patient with EDMUPS and patients with MUPS in GP and outpatient clinic setting, it seems logical to apply strategies for patients with EDMUPS. It is more often not the demand of the patient for somatic intervention, but the combination of patient presentations and the physicians' response that leads to more somatic interventions.[147] Treatment of patients with MUPS differs from regular care and this group of patients benefits from regular contact and good communication by a trusted physician. Other studies showed that patients indicate that they provide cues on when they want somatic interventions and when they want to receive emotional support.[148] Focusing on the treatment of a psychiatric disorder can be useful for the resolution of physical symptoms.[140] The GP should therefore be the principal manager of patients with MUPS, and this should be clearly communicated to the GP and the patient. This strategy is acknowledged in the Dutch multidisciplinary guideline on MUPS, which stresses the importance of good communication through consultation letters. A quality letter contains the acknowledgment of a medically unexplained physical symptom and advice to the GP about follow-up. However, specialists' reply letters to GPs about MUPS patients often do not provide answers to referral questions or clear explanations about MUPS and perpetuating factors.[149] Another study showed that a training program for specialists in communicating with patients with MUPS is beneficial when treating MUPS patients.[137] This study has several limitations. First, retrospective data do not provide information on follow-up of all patients, and during follow-up presenting symptoms can be explained or may disappear. Therefore, we cannot indicate which percentage of patients with EDMUPS will eventually develop MUPS or in which patients symptoms

may be explained. In some cases, the follow-up period might be too short to correctly evaluate whether an explanation for the symptoms can be found. EDMUPS and MUPS are working diagnoses, and can be used in outpatient clinics. Unfortunately, there is no linked electronic health record in The Netherlands or Belgium. This makes the role of the GP important in communication and management of symptoms. Second, only visits to the hospitals included in the study were documented, without information on medical consumption in other hospitals in the time period assessed. This might lead to an underestimation of the percentage of frequent visitors as patients might visit other EDs. This study on patients with EDMUPS has multiple strengths as it focuses on patients visiting the ED, in contrast to the previous literature on MUPS in primary and secondary care. This study was carried out in three hospitals in two countries with different sizes and functions and even enabled a comparison of different healthcare systems. Nevertheless, similar patient characteristics were documented, indicating the validity of the findings.

Conclusion

Patients with MUPS represent a major burden to EDs as they do for primary and secondary healthcare. Further research should focus on the longitudinal follow-up of the natural evolution and use of medical services of this patient group.

Chapter 6

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Postural Orthostatic Tachycardia Syndrome (POTS): a Common But Unfamiliar Syndrome

Abstract

Postural orthostatic tachycardia syndrome (POTS) is a condition in which a change from a supine to an upright position causes an abnormally large increase in heart rate which may be accompanied by a variety of physical complaints. We report two cases illustrating the heterogeneity of this syndrome. We give an update on the aetiology of POTS, which is still poorly understood, and its overlap with other syndromes such as chronic fatigue syndrome. Clinicians should be aware of POTS, a fairly common clinical entity that can result in significant impairments to a patient's quality of life. Lifestyle measures (under which adequate fluid and salt intake, exercise) are a first line of treatment; if insufficient, pharmacotherapy can be considered to improve quality of life.

Introduction

Postural orthostatic tachycardia syndrome (POTS) is a condition in which a change from a supine to an upright position causes an abnormally large increase in heart rate.[150] A POTS diagnosis is made when patients meet all criteria shown in *Table 1*. Common complaints, not all explained by the increase in heart rate only, are light-headedness, palpitations, (pre-)syncope, fatigue, tremulousness and weakness or heaviness (especially of the legs).[151,152]

POTS is probably underdiagnosed due to the heterogeneity in both presentation and aetiology, and therefore the prevalence of POTS is still unsure. Three studies report a prevalence of approximately 170/100,000 in the United States.[153-155] Mean age of onset of POTS is approximately 30 years and most patients are between the ages of 20-40 years. There is a clear overrepresentation of women with a corresponding female:male ratio of 5:1.[155]

We describe two illustrative cases, followed by considerations regarding pathophysiology and treatment consisting of lifestyle advice. This advice may include psychological interventions which, if necessary, may be combined with pharmacotherapy.

Table 1: Criteria for the postural orthostatic tachycardia syndrome[150,165]

Heart rate increases ≥ 30 (40 in children 12-19 years) beats per minute from supine to standing (10 minutes)
Symptoms worsen with standing and improve with recumbence
Symptoms last ≥ 6 months
Absence of orthostatic hypotension (≥ 20 mmHg drop in systolic blood pressure)
Absence of other overt cause of orthostatic symptoms or tachycardia

Case Reports

Case 1

A 24-year-old Caucasian woman with an unremarkable medical history was referred to the outpatient clinic of internal medicine. Her referring cardiologist suspected POTS based on complaints of vertigo and postural-dependent sinus tachycardia; the patient had no severe orthostatic hypotension and a structurally normal heart as imaged by echocardiography. Her complaints, which also included flushing, malaise and concentration problems, started approximately three months earlier and improved when lying down and worsened when standing. Her sister and father had similar symptoms at the same age.

We performed a tilt table test. Her supine blood pressure was 141/84 mmHg and her heart rate was 111 beats per minute (bpm). After being tilted, physical complaints such as flushing and palpitations developed progressively and after seven minutes, the test was stopped. Her heart rate rose to 150 bpm while blood pressure increased slightly to 148/96 mmHg. At this point, blood tests were conducted. Serum noradrenaline level was 887 pg/

ml (baseline 292 pg/ml) and adrenaline level was 509 pg/ml (baseline 44 pg/ml). These complaints and findings, in absence of another explanation such as adrenal insufficiency, confirmed the diagnosis of POTS (*Table 1*). Since she had such a severe rise in heart rate and two first-degree relatives had similar symptoms, whole exome sequencing was performed after pretest counselling. No pathogenic variant, not even in the SLC6A2 gene (a gene that causes orthostatic intolerance), [156] was identified.

We advised lifestyle changes, including substantial fluid and salt intake, compression stockings and supervised physical reconditioning (horizontally; for example, cycling). Simultaneously, as part of the recommended dual policy of physical and psychological treatment, we referred her to a psychologist to discuss psychological factors that could contribute to her POTS symptoms.[152,157-159]

As her symptoms did not improve within weeks, we prescribed short-acting beta blocker propranolol (uptitrated to 40 mg three times a day) and fludrocortisone (62.5 mcg once daily), combined with extra salt (Sodium chloride tablets, 1000 mg three times a day). This resulted in good response, but the fludrocortisone led to severe insomnia. The patient herself suggested modafinil (100 mg bidaily) after reading Raj *et al*., [150] which was prescribed for her difficulty with concentration. This improved her so-called ''brain fog''.[150] For exceptional occasions such as her wedding, she was prescribed desmopressin (DDAVP) after a test-dose including control of sodium levels was conducted, which improved her symptoms substantially. Over time, and considering all lifestyle measures, her condition improved and medication could be tapered after six months to propranolol 40 mg three times a day and salt supplementation only. Currently, her symptoms are well under control with lifestyle measures and propranolol has been further tapered.

Case 2

A 44-year-old Caucasian male visited the general practitioner with complaints of syncope while standing. These complaints were present for approximately five to six months and started after an intentional weight reduction of 30 kg (weight at presentation: 95 kg, height: 1.97 m). Simultaneously, he developed paraesthesia of his legs. He was referred to an internist and a cardiologist for further investigation. The cardiologist excluded underlying cardiac pathology. The internist referred him to our hospital for further diagnostics, in particular, a tilt table test. This was performed, and showed an increase in heart rate from 58 bpm in supine position to 90 bpm when tilted, whereas his blood pressure remained around 154/98 mmHg. Noradrenaline rose to 229 pg/ml from a relatively low baseline level of 69 pg/ml. These measurements fit the criteria of POTS (*Table 1*).

The neurologist we consulted in our centre concluded the paraesthesia to be meralgia paresthetica of the right femoral cutaneous nerve and the left peroneal nerve, possibly triggered by the patient's weight loss. An association with POTS was excluded, although no biopsy was performed to rule out small fibre neuropathy.[160] We advised lifestyle changes, including intake of sufficient fluids and salts and prescribed sodium (Sodium

chloride tablets, 1000 mg three times a day). The symptoms of the patient resolved and no further pharmacotherapy was required.

Discussion

This paper describes two illustrative cases of patients with POTS. POTS, first described by Jacob Mendes Da Costa in 1871, is a clinical syndrome and not a distinct disease entity, and has clinical overlap with chronic fatigue syndrome and Ehlers-Danlos syndrome.[161] Clinical diagnostic criteria for POTS are provided in *Table 1*.

Pathophysiology

Under normal circumstances, heart rate and blood pressure remain stable or change only slightly and for a very short period of time in response to changing from a supine to an upright position due to a rapid response originating from the baroreceptors. In POTS patients however, heart rate increases to very high levels and for a longer time period. This is presumably due to different pathways. Hypovolemia is present in two-third of patients with POTS, potentially due to less responsiveness of the renin–angiotensin–aldosterone system.[162,163] Elevated (> 600 pg/ml) catecholamine levels upon standing are commonly recognized in patients with POTS.[164] Poor exercise tolerance and deconditioning is also present in the majority of cases. Although this could be a cause or a consequence of POTS, the fact that most patients benefit from exercise is an extra argument that deconditioning is a causal factor.[165] In addition to these common findings, two specific subtypes can be distinguished in most studies: the hyperadrenergic and the neuropathic subtypes, although in clinical practice this subdivision is less useful and difficult to differentiate.[150,158,165] A vast majority of POTS patients experience autonomic dysfunction in various autonomic domains.[166] Additional testing, such as measurement of catecholamines in response to standing or assessment of small fibre neuropathy, should be preserved for research purposes only or in specific indications – such as in case 2, where a relationship with the tremendous weight loss was likely.

Hyperadrenergic phenotype

A hyperadrenergic state, present in approximately 50% of patients with POTS, is due to excessive sympathetic discharge characterized by a supraphysiological rise in plasma levels of noradrenaline to 600 pg/ml or higher in response to standing as seen in case 1.[152,158,165] Blood pressure may fluctuate or increase heavily ("orthostatic hypertension") during prolonged standing. Symptoms of stress, emotional behaviour and cold pale skin may occur upon standing.[150] Likewise, the episodes can also be triggered by emotional stimuli and physical activity.[152] Earlier described hypovolemia may also attribute to the hyperadrenergic state. Hyperthyroidism or catecholamine secreting tumours should be ruled out as alternative diagnoses in patients presenting with this phenotype. In rare cases of familiar occurrence of POTS, a heterozygous variant in the SLC6A2 gene encoding the norepinephrine transporter has been found.[156]

Table 2: Diagnostic approach[150,158,165]	
Investigation	Diagnosis to be excluded
History focused on possible causes of orthostatic tachycardia, salt and fluid intake, impact on daily activities and family history	Underlying cardiac disease including arrhythmia such as inappropriate sinus tachycardia syndrome or conduction abnormalities[200]
Physical examination including stand test: BP and HR measurement supine and after 1, 3, 5 and 10 minutes of standing	Adrenal insufficiency (if suspicion, additional testing)
ECG	Triggers inducing tachycardia (drugs, diet)
Blood test for other causes of orthostatic intolerance: Hb TSH	 Anaemia Hypothyroidism or hyperthyroidism
On indication:	
(Nor)metanephrine (plasma or urine)	Pheochromocytoma
Tilt table test (most important indication: inability to stand)	If combined with catecholamines: autonomic failure
24-hour Holter monitoring, additional cardiac screening	Underlying cardiac disease
BP: blood pressure; HR: heart rate; ECG: electrocardiogram; Hb: haemoglobin; TSH: thyroid stimulating hormone.	

Hyperadrenergic states have also been suggested to be secondary to immune disorders associated with antibodies against components of the voltage-gated potassium channel complex.[152] Autoantibodies against the nicotinic acetylcholine receptor have been described to correlate with the severity of autonomic dysfunction in small patient cohorts.[164,167,168] Recent studies have shown elevated autoantibodies against adrenergic receptors (α1AR) in patients with POTS, resulting in a compensatory autonomic vasoconstriction and concurrent α1AR-mediated tachycardia.[169,170] Furthermore, another study showed Angiotensin II Type 1 Receptor autoantibodies (AT1R) in POTS patients.[171] However, these are small studies in selected patient populations and therefore further research is needed to establish the clinical implications.

Neuropathic phenotype

The other important mechanism found in POTS is presumably caused by (partial) peripheral sympathetic denervation leading to impaired peripheral vasoconstriction.[172] This denervation is thought to be a consequence of a small fibre neuropathy, which may be diagnosed by biopsy, impaired sweat testing or sudomotor axon reflex testing.[160,164] There is lack of vasoconstriction resulting in venous pooling in the lower limbs, which is reversed when the patient lies down as a result of gravity.[151,152] Considering these aspects, the second case is expected to have the neuropathic form of POTS potentially related to his weight loss [173,174] although biopsy was not performed. Indeed, in a small study over one third of patients fulfilled the criteria for POTS after bariatric surgery.[175]

Diagnostic approach

POTS patients present with atypical and rather common symptoms. The diagnostic approach is therefore challenging and based on four criteria (*Table 1*) while excluding other causes (*Table 2*). A key symptom for establishing the diagnosis of POTS within the differential diagnosis is worsening of symptoms while standing up. Since epidemiology and symptoms may overlap, inappropriate sinus tachycardia and vasovagal syncope must be distinguished from POTS, although these diagnoses are not mutually exclusive.16 Any condition or drug that could be causing orthostatic tachycardia, such as dehydration or pheochromocytoma, should be identified and adequately treated.[176] The tilt table test is commonly used for diagnosing POTS, although this is not strictly necessary: a simple stand test might be sufficient to confirm the diagnosis; the same is true for the measurement of catecholamines before and after tilting.[150,158,165]

Overlap with other conditions

There seems to be an overlap with fibromyalgia (FM) and other medically unexplained physical symptoms (e.g. chronic fatigue sleep disturbances).[152,177-179] POTS is found in up to 50% and 60% of patients with chronic fatigue syndrome (CFS) and FM, respectively.[154,180] In patients with CFS, abnormalities of the vascular and autonomic nervous system are common.[154,180] Similar to POTS patients, small fibre neuropathy also affects a majority of FM patients.[181,182] Given the similarities between symptoms of FM, CFS and POTS, it is reasonable to assume shared aetiology between these conditions.[177,180] This may involve so-called "somatic hypervigilance" or "central sensitization," in which relatively mild or routine sensory information is experienced more intensely or more distressing than usual.[159,183-186] This may also lead to a stronger physiological response to exercise, often reason to quit exercising.[187]

Treatment options

Currently, there is no standard treatment for POTS, and treatment strategies should be based on clinical presentation, the assumed underlying pathophysiology, potential overlapping syndromes, deconditioning and any psychological factors that can sustain symptoms. First-line POTS therapy consists of lifestyle recommendations. A multidisciplinary approach including physiotherapy and psychological support is recommended to optimize lifestyle treatment to avoid overmedicalization (*Table 3*).[152,157,158,165]

Since hypovolemia seems to play a major role in the majority of patients, fluid intake of at least 2-3 litres as well as 10 grams of salt per day (studies differ in their advice between 8-10 or 10-12 grams) should be advised to prevent hypovolemia.[150,165,176,188] A 24-hour urine measurement of sodium can be helpful since most patients often overestimate their current salt intake. Most patients may benefit from wearing support garments such as thigh-or waist-high tight support stockings in accordance with recommendations for orthostatic hypotension.[150,152] Patients should be encouraged to begin a gradual program

Table 3: Treatment options for POTS patients

Treatment option	Recommendation	Remarks	Level of evidence*[165]
Lifestyle			
Fluid intake Salt intake	At least 2- l daily Circa 10 grams daily	When hypovolemia suspected (majority of patients)	Expert opinion[150,152,158,165]
Physical conditioning	Preferably horizontal activity. 20-30 minutes, 3 times a week		Moderate[189-191]
Compression stockings	Waist-high style stockings (pressure 30 to 40 mmHg)		Expert opinion[150,152]
Psychological interventions	Focused on coping mechanisms and somatic hypervigilance		Expert opinion[152,157,165,192]
Pharmacological options			
Propranolol	20 mg daily	Only if blood pressure is sufficient High dose (≥80 mg) may worsen symptoms	Moderate[193]
Fludrocortisone	Start 50-62.5 mcg/day to max 300 mcg daily	When hypovolemia suspected. Caution in patients with migraine. Side effects include hypokalaemia, severe headaches and vertigo	Expert opinion[150,152,158,161]
Desmopressin	0.2 mg	Side effects include hyponatremia. Only for occasional usage	Moderate[194]
Ivabradine	Start 2.5 mg once or twice daily (lower than in case of heart failure)	Potentially beneficial for fatigue; may result in visual abnormalities	Weak[195]
Clonidine Methyldopa	0.1-0.2 mg bid or tid 125-250 mg bid	Hyperadrenergic phenotype; side effects include drowsiness, fatigue and worsening of mental clouding	Weak[201]
Pyridostigmine	30-60 mg tid	Side effects include gastrointestinal symptoms	Moderate[197,202]
Modafinil	100 mg bid	Potentially beneficial for "brain fog"; orthostatic tachycardia may be worsened	Expert opinion[150,152,165]
Midodrine	2.5 mg tid	Neuropathic phenotype; side effects include urinary retention due to prostatic hypertrophy	Moderate[203]

*bid: twice a day; tid: three times a day. * Scoring of evidence is as follows: moderate: one randomized controlled trial; weak: only small non-interventional studies; expert opinion: no specific studies in POTS, in most cases based on experience in orthostatic hypotension.*

of physical reconditioning under supervision of a dedicated physical therapist, working toward a goal of performing 20 to 30 minutes of aerobic activity (preferably horizontal, e.g. cycling) three times a week.[189-191]

Psychological treatment including psychotherapy can be helpful, both to improve coping mechanisms as well as to address the somatic hypervigilance.[157,192] In our centre, every POTS patient is offered a visit to a psychologist. The psychologist can assess to which extent psychological issues may be involved in the aetiology or maintenance of POTS.[157] Clinical trials to identify the most effective psychological treatment enabling more specific referral and treatment are needed.

Pharmacotherapy may be required for patients who remain symptomatic after three months of optimal lifestyle interventions, or for patients whose severe symptoms hamper life style modifications even at earlier stages. Several drugs have shown a positive effect in POTS treatment, although one should keep in mind that the highest level of evidence is moderate and most options are based on non-interventional studies or expert opinions only (*Table 3*). The most relevant options are shortly described below.

The best available evidence exists for low doses of short-acting beta blockers, in particular propranolol. It is mainly effective at lowering standing heart rate and improving complaints of palpitations.[152,157,158,165] Interestingly, in a direct comparison, propranolol was inferior to exercise therapy.[191] In this study, the combination of exercise and propranolol was not studied, contrasting with our recommendation to first optimize lifestyle before considering pharmacotherapy. High doses (≥ 80mg) of propranolol fail to show further improvement and may even worsen symptoms.[193] Fludrocortisone, a mineralocorticoid, can be used when hypovolemia is suspected, to enhance sodium retention and to promote intravascular volume expansion.[150] However, it can exacerbate headaches and vertigo, particularly in patients with migraine.[152] Incidentally, desmopressin can be used to reach rapid volume expansion.[194] Ivabradine, a selective sinus node inhibitor can slow heart rate without effecting blood pressure and seems to have a beneficial effect on fatigue.[195,196] When symptoms are severe due to high sympathetic nervous system activity, central sympatholytic agents, clonidine and methyldopa, can be prescribed. In patients who are refractory to other commonly-used medications, the use pyridostigmine, a peripheral acetylcholinesterase inhibitor, can be considered.[197] Stimulating agents such as modafinil or methylphenidate may be considered to improve concentration and reduce mental clouding, although its mechanism is unknown. One should keep in mind that modafinil may aggravate the orthostatic tachycardia since tachycardia is a well-known side effect, although this was not shown in a small trial focused on safety in patients with POTS.[150,198] The peripheral α1-adrenergic agonist midodrine may elicit vasoconstriction by reducing venous pooling, especially in neuropathic POTS.[172] As most POTS patients are between 20 and 40 years of age, its major side effect (e.g. urinary retention due to prostatic hypertrophy) is not an issue.[151,155]

Quality of life

POTS patients are limited in their physical activities and can become deconditioned over time.[152,161,191] Unsurprisingly, quality of life in patients with POTS is low. Benrud-Larssen *et al.* reported that patients with POTS and patients with congestive heart failure had comparable physical and psychological composite scores.[183] No correlation was found

between quality of life and the maximal increase in heart rate.[192] Despite the low quality of life, the prognosis of POTS is favourable, since 60% of the patients return with the given lifestyle and pharmacological options within five years to their level of functioning before onset; this should be emphasized to patients.[151,199] However, resolution of symptoms as illustrated in the patients above is not always the case, and may lead to a more complex and chronic condition frustrating both patient and physician.

Conclusion

In conclusion, POTS is a heterogeneous clinical syndrome that overlaps with multiple syndromes such as chronic fatigue syndrome and Ehlers-Danlos syndrome. The diagnosis can be made in most cases by a thorough history, physical examination and a limited amount of additional testing to rule out other causes of orthostatic intolerance. Currently, there is not one standard treatment, but a treatment plan should entail lifestyle recommendations and psychological treatment. Pharmacological treatment is reserved for the patients who remain symptomatic despite these interventions. Especially in current times of self-diagnosing and 'self-educated' patients who are familiar with this syndrome, clinicians should not only be well informed and aware of POTS, but also familiar with its multifactorial background and treatment options in order to optimize therapy options for their patients.

Chapter 7

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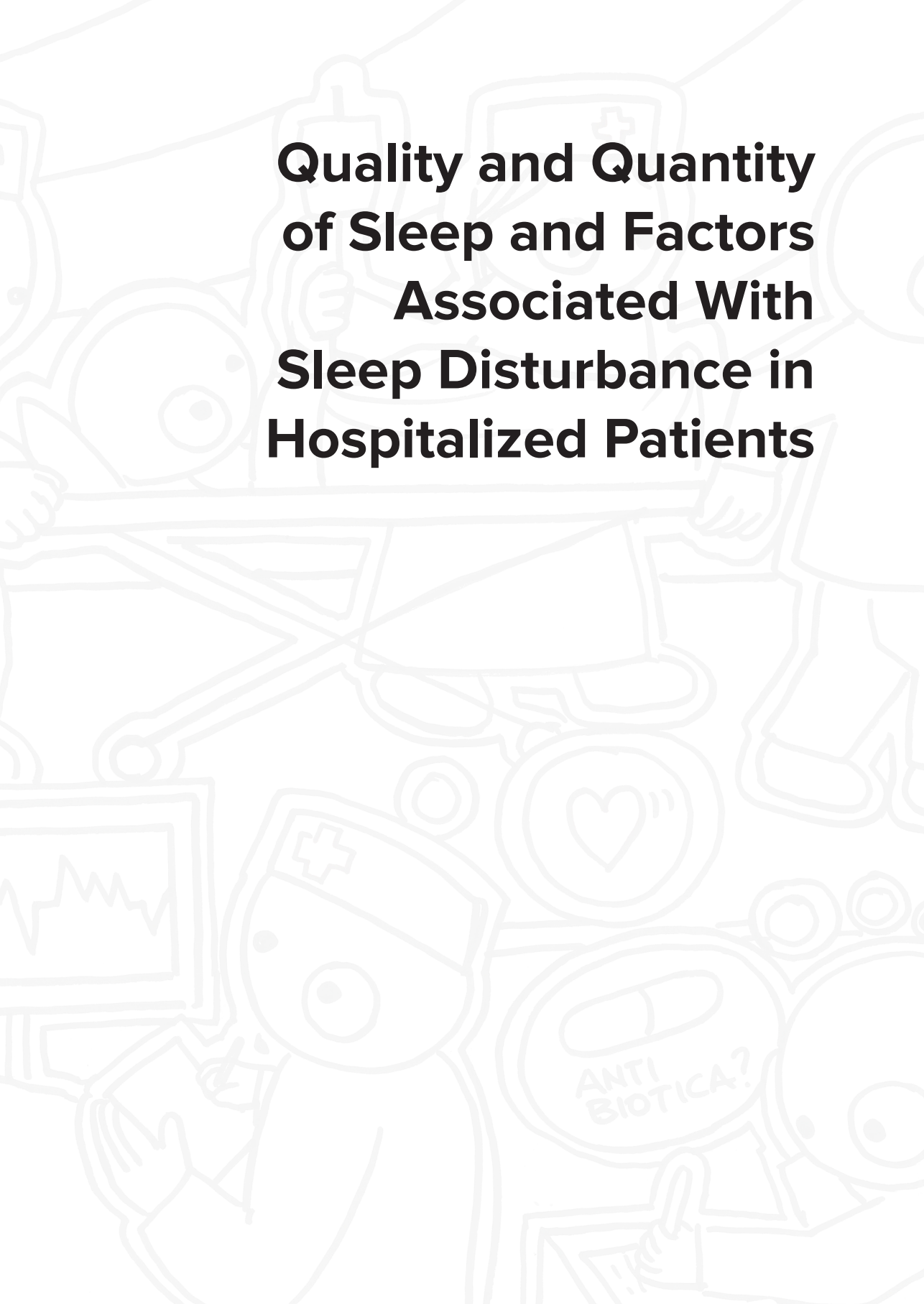
Quality and Quantity of Sleep and Factors Associated With Sleep Disturbance in Hospitalized Patients



Abstract

Importance

Although inadequate sleep has a proven negative association with health care outcomes, to date, no large-scale studies have examined sleep in general hospital wards.

Objectives

To assess the subjective quantity and quality of sleep and to identify the hospital-related factors associated with sleep disturbances in hospitalized patients.

Design

For this nationwide, single-day, multicentre, cross-sectional, observational study, which took place on February 22, 2017, all hospitals in the Netherlands were encouraged by word of mouth and conventional and social media to participate in this study. A total of 39 hospitals participated. Included patients were at least 18 years of age, were able to give informed consent, and had spent at least 1 night in a regular-care hospital ward.

Exposures

Hospitalization in a regular-care ward.

Main Outcomes and Measures

Quantity and quality of last night's sleep in the hospital compared with habitual sleep at home the month before hospitalization. The Consensus Sleep Diary and the Dutch-Flemish Patient-Reported Outcomes Measurement Information System (PROMIS) Sleep Disturbance item bank were used. Complementary questions assessed sleep-disturbing factors.

Results

A total of 2,005 patients were included (median age, 68 years; interquartile range, 57-77 years; 994 of 1,935 [51.4%] were male [70 patients did not identify their sex]). Compared with habitual sleep at home, the total sleep time in the hospital was 83 minutes (95%CI, 75-92 minutes; $P < .001$) shorter. The mean number of nocturnal awakenings was 2.0 (95%CI, 1.9-2.1) times at home vs 3.3 (95%CI, 3.2-3.5) times during hospitalization

(P < .001). Patients woke up 44 minutes (95%CI, 44-45 minutes; P < .001) earlier than their habitual wake-up time at home. A total of 1,344 patients (70.4%) reported having been awakened by external causes, which in 718 (35.8%) concerned hospital staff. All aspects of sleep quality measured using PROMIS questions were rated worse during hospitalization than at home. The most reported sleep-disturbing factors were noise of other patients, medical devices, pain, and toilet visits.

Conclusion and Relevance

This study demonstrated that the duration and quality of sleep in hospitalized patients were significantly affected and revealed many potentially modifiable hospital-related factors negatively associated with sleep. Raising awareness about the importance of adequate sleep in the vulnerable hospital population and introducing interventions to target sleep-disturbing factors may improve healing.

Introduction

Inadequate sleep has a negative association with general health and well-being.[204-207] Small studies [208-212] in selected patient populations suggest that sleep in hospitals is suboptimal. However, information about the quantity and quality of sleep in patients in general hospital wards is lacking. A good night's sleep improves cognitive and emotional functioning,[213] which is important during an often emotionally challenging stay in the hospital. Sleep is essential for adequate immune, metabolic, and endocrine functioning[204,214-216] and may have an association with healing and survival.[217] Studies[218,219] suggest that sleep deprivation is a possible key risk factor for development of delirium. Patient-related factors, such as pain, and hospital-related factors, such as noises from alarms or sleep interruptions attributable to medical procedures, may contribute to disturbance of sleep.[220-223] However, to date, no large-scale, multicentre studies have been performed to investigate how these factors are associated with sleep disturbance in hospitals. Identifying relevant and potentially modifiable hospital-related factors associated with sleep disturbances can be the key to introducing remedial measures. The primary aims of this nationwide, single-day study in the Netherlands were to assess the quantity and quality of sleep and to identify the hospital-related factors associated with sleep disturbances in hospitalized patients.

Methods

Study Design and Participants

This was a nationwide, single-day, multicentre, cross-sectional, observational study using the flash mob research (FMR) method, which allows the investigation of clinically relevant questions on a large scale in a short time.[224] Flash mob research is based on the concept of flash mobs: "a sudden and planned gathering of many people at a particular place that has been arranged earlier."[225] With the use of multiple hospitals, it is possible to obtain sufficient data with FMR in a short time. After preparing the study, the coordinators (H.M.W., E.S.v.d.E., J.A., F.H.B., E.J.W.v.S., and P.W.B.N.) invited acute care internists from hospitals throughout the Netherlands to participate in the study using word of mouth and conventional and social media. Hospitals were also recruited through the professional network of the members of the "Onderzoeks Consortium Acute Geneeskunde" Acute Medicine Research Consortium.[48] All participating hospitals received approval from their local ethics committees to obtain verbal informed consent with annotation in the patient record. Patient records were anonymized before the coordinators received them. The coordinating centre, the VU University Medical Centre in Amsterdam, the Netherlands, provided a standardized protocol, instructions on procedures, case report forms, and questionnaires. The study was performed on February 22, 2017, between 8 AM and 5 PM. To stimulate participation by health care workers and patients, conventional and social media provided some information before the study. However, to minimize observer and participant bias, release of the exact study date was embargoed until 6 AM February 22, 2017.

All patients at least 18 years of age, with any disease condition, able to give informed consent, and who spent at least the night before the data collection in a regular-care ward were eligible for enrolment. Patients from intensive care, coronary care, and stroke units were excluded.

Questionnaire

A Consensus Sleep Diary (CSD) was used to asses subjective sleep quantity.[226] In addition, after reaching consensus among the coordinating members, we selected 5 of 8 items from the Dutch-Flemish Patient-Reported Outcomes Measurement In- formation System (PROMIS), version 1.0, sleep disturbance item bank (Short Form 8a) and a sixth item from the complete PROMIS sleep disturbance item bank, which we believed were best suitable to measure sleep disturbance in hospitalized patients.[227,228] To measure the differences in sleep experiences in the hospital vs home, each item was asked twice: once with reference to the previous night at the hospital and once with reference to habitual sleep at home during the month before hospitalization. These items were complemented by questions about hospital-related, personal, and environmental factors that could have influenced sleep, including use of sleep medication.

Sleep Quantity

The CSD items assessed subjective estimates of the clock times of lights out (i.e. closing the eyes to fall asleep) and final awakening, sleep-onset latency (i.e. time taken to fall asleep), the number of awakenings, and the total duration of wake after sleep onset (i.e. time spent awake after going to sleep). The in- formation provided was used to calculate total sleep time (i.e. actual time spent asleep) and sleep efficiency (i.e. the proportion of sleep relative to the time between lights out and final awakening).

Sleep Disturbance

The included 5-point Likert-type PROMIS items assessed 2 positive (satisfying and refreshing) and 3 negative (restless, difficulty falling asleep, and feeling lousy when waking up) evaluations of sleep. Each item provided a statement and asked how well it suited the patient, from not at all to very much. A sixth item on general sleep quality was answered as very poor to very good. The items that assessed positive evaluations were re- coded in such a way that a higher score indicated more sleep disturbance. Because the time frame was adjusted for the design of this study, we did not calculate PROMIS T scores but only used raw summary scores (range, 0-24) that described overall sleep disturbance.

Disturbing Factors

The CSD items were complemented by questions on whether sleep was associated with a list of disease-related, hospital-related, personal, or environmental sleep-disturbing factors. An additional text field allowed patients to fill out other factors.

Statistical Analysis

Intrinsic to the FMR approach, no fixed sample size was set a priori. However, to obtain reliable and generalizable results and based on what was found feasible in a previous study, [224] we aimed to include at least 1,000 patients.

Categorical variables are summarized by percentages. Continuous variables are summarized by means and 95% CIs or medians and interquartile ranges (IQRs). Mean sleep quality and quantity were compared between hospital and home using mixed linear models with the patients' difference scores (hospital relative to home) as the dependent variable, with an intercept-only model for the fixed part and a random effect of hospital. Means were concluded to differ between hospital and home when the fixed intercept differed significantly from 0. To check whether differences in mean sleep quality and quantity between hospital and home varied across groups of patients, we added a fixed effect for the grouping variable to the mixed model. Transformations of the dependent variables were considered in case residuals and were not normally distributed. To assess the robustness of the conclusions based on mixed-model analysis to deviations from normality, additional sensitivity analyses were performed in which we compared the individual differences between groups using non-parametric tests (Mann-Whitney test and Kruskal-Wallis analysis of variance). The nonparametric tests ignored the clustering of patients within hospitals, but this clustering was found to be ignorable because the variance component for the random effect of hospital in the mixed models was often estimated to be 0. Normality of dependent variables and residuals from the mixed models was checked using normal probability plots. Analyses were performed with SPSS for Windows, version 21 (SPSS Inc.). $P < .05$ was considered to be statistically significant.

Results

An estimated potential population of approximately 2,500 patients was eligible for inclusion; however, some patients could not be included because they were too sick or could not grant consent because of cognitive disturbances (on clinical grounds). The questionnaire was completed by 2,005 patients in 39 of 93 Dutch hospitals (median age, 68 years; IQR, 57-77 years; 994 of 1,935 [51.4%] were male [70 patients did not identify their sex]). Nonsurgical specialties were best represented (1,536 [81.0%]) (*Table 1*). A total of 335 patients (16.7%) had been taking sleep medication at home (of which 189 [56.4%] were taking benzodiazepines) and 539 (26.9%) the previous night (of which 264 [49.0%] were taking benzodiazepines) (*Supplementary Table 1*).

The 1,427 patients (71.2%) who provided complete (home and at hospital) answers to all CSD questions were included in the sleep quantity analysis (*Figure 1*). The 578 excluded patients (28.8%) did not differ from the included patients with respect to

baseline characteristics (*Supplementary Table 2*).

Raw summary difference scores for the PROMIS questions could be calculated in 1,885 patients (94.0%) because of few missing answers in some patients. However, because many patients only forgot to fill out 1 of the 12 questions, we also chose to calculate the difference for each question separately (*Table 2*).

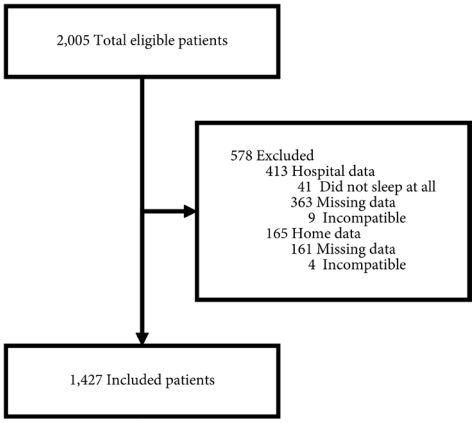


Figure 1: Inclusion Quantitative Sleep Measurements

Sleep Quantity

Table 3 summarizes the CSD measures of subjective sleep quantity. Mean total sleep time was 83 minutes (95%CI, 75-92 minutes) shorter during hospitalization (6 hours 4 minutes; 95%CI, 5 hours 56 minutes to 6hours 11 minutes) than at home (7 hours 27 minutes; 95%CI, 7 hours 21 minutes to 7 hours 33 minutes) (P < .001). The difference resulted primarily from earlier final awakening in the hospital of a mean of 44 minutes (95%CI, 44-45 minutes).There was a higher number of awakenings in the hospital 3.3 times (95% CI, 3.2-3.5 times) than at home (2.0 times; 95% CI, 1.9-2.1 times) (P < .001). Sleep efficiency was lower in the hospital (76%; 95% CI, 75%-77%) than at home (88%; 95% CI, 88%-89%) (difference, 12%; 95% CI, 14%-11%; P < .001).

Sleep Disturbance

Table 2 summarizes the PROMIS items of subjective sleep disturbance. For all 6 questions (*Supplementary Table 3* and *Supplementary Figure 1*), there was a significantly worse rating in the hospital (median, 9; IQR, 5-14) vs at home (median, 5; IQR, 3-9) (P <.001). Raw summary scores and differences in scores were not significantly associated with sex (male: mean, 9.5; 95% CI, 9.1-9.9; female: mean, 10.0; 95% CI, 9.6-10.4; P =.06), length of stay (1 day; mean, 10.5; 95% CI, 9.8-11.1; 2 days: mean, 9.6; 95% CI, 8.9-10.2; 3 days: mean, 9.7; 95% CI, 8.7-10.8; ≥ 4 days: mean, 9.7; 95% CI, 9.3-10.0; P = .14), or number of patients sleeping in the same room (single room: mean, 9.7; 95% CI, 9.2-10.3; double room: mean, 9.3; 95% CI, 8.8-9.9; triple room: mean, 10.0; 95% CI, 9.1-10.9; quadruple room: mean, 10.0; 95% CI, 9.6-10.5; 5-person room: mean, 10.4; 95% CI, 6.3-14.5; 6-person room: mean, 9.1; 95% CI, 6.7-11.5; > 6-person room: mean, 12.0; 95% CI, 0.4-23.5; P = .54). More sleep disturbance was experienced by patients admitted to a surgical unit (score, 10.5; 95% CI, 9.9-11.2) than patients in nonsurgical units (score, 9.6; 95% CI, 9.3-9.9) (P = .02), whereas there was no difference in sleep disturbance between these groups at home. Older patients experienced less sleep disturbance during hospitalization than younger patients. Sleep disturbance at home did not differ across age groups (> 36 years old: mean, 6.9; 95% CI, 6.0-7.8; 36-50 years old: mean, 7.0; 95% CI, 6.3-7.7; 51-65 years old: mean, 6.7; 95% CI, 6.3-7.2; 66-80 years old: mean, 6.5; 95% CI, 6.2-7.0; > 80 years old: mean, 6.6; 95% CI, 6.0-7.1; P = .84) (*Supplementary Table 4* and *Supplementary Figure 2*).

Table 1: Characteristics of 2,005 Patients

Characteristic	Finding[a]
Sex (n = 1,935)	
Male	994 (51.4)
Female	941 (48.6)
Age, y (n = 1,975)	
Median (IQR)	68 (57-77)
≤35	117 (5.9)
36-50	216 (10.9)
51-65	525 (26.6)
66-80	765 (38.7)
≥81	352 (17.8)
Length of stay (n = 1,773)	
Median (IQR)	4 (2-8)
1 Night	359 (20.2)
>1 Nights	1,414 (79.8)
No. of patients in room (n = 1,975)	
Median (IQR)	2 (1-4)
1	504 (25.5)
2	514 (26.0)
3	163 (8.3)
4	774 (39.2)
≥5	35 (1.8)
Ward type (n = 1,945)	
Acute admission unit	269 (13.8)
Regular ward	1676 (86.2)
Specialty (n = 1,897)	
Surgical specialties[b]	361 (19.0)
Nonsurgical specialties[c]	1536 (81.0)
Surgery (n = 1,981)	
Yes	451 (22.8)
No	1,530 (77.2)

Abbreviation: IQR: interquartile range. a: Data are presented as number (percentage) of patients unless otherwise indicated. All 2,005 patients answered the questions concerning demographics and sleep-disturbing factors. In 30 cases, the necessary demographic information could not be extracted mainly because we could not read the afor every question but only for the ones they did not respond to. b: Surgical specialties included cardiothoracic surgery, vascular surgery, plastic surgery, neurosurgery, ophthalmic surgery, general surgery, orthopaedics, urology, gynaecology, traumatology, anaesthesiology, and ear, nose, and throat. c: Nonsurgical specialties included cardiology, geriatrics, dermatology, gastroenterology, haematology, internal medicine, nephrology, neurology, oncology, psychiatry, pulmonology, and rheumatology.

Table 2: Subjective Sleep Disturbance Scores (PROMIS)[a]		
Item	Median (IQR)	Mean Difference (95% CI)
My sleep quality was		
Home (n = 1,958)	3 (2 - 3)	0.58 (0.52 to 0.64)
Hospital (n = 1,966)	2 (1- 3)	
I was satisfied with my sleep		
Home (n = 1,960)	3 (2 - 3)	0.60 (0.53 to 0.67)
Hospital (n = 1,961)	2 (1 - 3)	
My sleep was refreshing		
Home (n = 1,961)	3 (2 - 3)	0.63 (0.56 to 0.70)
Hospital (n = 1,969)	2 (1- 3)	
My sleep was restless		
Home (n = 1,951)	1 (0 - 2)	−0.45 (−0.52 to −0.38)
Hospital (n = 1,952)	1 (0 - 3)	
I had difficulty falling asleep		
Home (n = 1,957)	0 (0 - 1)	−0.51 (−0.59 to −0.44)
Hospital (n = 1,958)	1 (0 - 3)	
I felt lousy when I woke up		
Home (n = 1,952)	0 (0 - 1)	−0.24 (−0.30 to −0.18)
Hospital (n = 1,956)	0 (0 - 1)	
Raw summary score		
Home (n = 1,914)	5 (3 - 9)	−3.0 (−3.4 to −2.7)
Hospital (n = 1,921)	9 (5 -14)	

Abbreviations: IQR: interquartile range; PROMIS: Patient-Reported Outcomes Measurement Information System. a Every question was answered using a 5-point scale, scored as follows: 0: very poor/not at all; 1: poor/a little bit; 2: fair/somewhat; 3: good/quite a bit; and 4: very good/very much. A raw summary PROMIS sleep disturbance score was calculated after reverse coding the second and third items. A higher raw summary score indicates more subjective sleep disturbance (range, 0-24). Differences indicate hospital minus home scores. P < .001 for all comparisons.

Disturbing Factors

Sleep was negatively associated with at least 1 hospital-related factor in 1,276 patients (64.6%). Noise of other patients was the most common disturbing factor, interfering with sleep onset in 473 patients (23.6%). A total of 1696 patients (84.6%) reported at least 1 nocturnal awakening, and 65.8% of all reasons given were hospital related, including noise of other patients (453 [22.6%]) and being awakened by hospital staff (403 [20.1%]). Toilet visits were responsible for nocturnal awakenings in 434 patients (21.6%). Only 566 patients (28.2%) reported to have awakened spontaneously in the morning. Of patients who had not awakened spontaneously, hospital-related reasons were held responsible in 73.7% of the cases. In 718 patients (35.8%), it concerned awakenings by a member of the hospital staff (*Table 4*, and *Supplementary Table 5* and *Supplementary Figure 3*).

Table 3: Subjective Sleep Quantity and Timing Measures (Consensus Sleep Diary)[a]

Measure	Home	Hospital	Difference (95% CI), min	P Value
Lights out time	23:05 (23:01 to 23:08)	22:57 (22:52 to 23:01)	−8 (−9 to −8)	.002
Sleep onset	23:29 (23:25 to 23:33)	23:41 (23:35 to 23:46)	12 (12 to 12)	<.001
Sleep-onset latency, mean (95% CI), min	23 (21 to 25)	44 (40 to 47)	21 (21 to 21)	<.001
Wake after sleep onset, mean (95% CI), min	32 (29 to 34)	61 (57 to 65)	29 (29 to 29)	<.001
Final wake time	07:28 (07:24 to 07:32)	06:44 (06:40 to 06:48)	−44 (−45 to −44)	<.001
Sleep window	08:23 (08:18 to 08:28)	07:47 (07:42 to 07:52)	−36 (−36 to −36)	<.001
Total sleep time	07:27 (07:21 to 07:33)	06:04 (05:56 to 06:11)	−83 (−92 to −75)	<.001
Sleep efficiency, % (95% CI)	88 (88 to 89)	76 (75 to 77)	−12 (−14 to −11)	<.001

a: Home and hospital data are presented as mean clock time in hours: minutes (95% CI) unless otherwise indicated. Differences indicate hospital minus home scores. The summary measures are based on the 1,427 patients who provided compatible answers to all Consensus Sleep Diary questions.

Table 4: Sleep-Disturbing Factors

Sleep Variable[a]	No. (%) With ≥1 Reason	Sleep-Disturbing Factors, No. (%)[a] Hospital Related	Patient Related	Top 3 Sleep-Disturbing Factors[b]
Sleep-onset latency (n= 1,976)	1,276 (64.5)	4,144/6,334 (65.4)	2,190/6,334 (34.6)	Noise of other patients (23.6%), pain (19.9%), and noise of hospital equipment (19.4%)
Nocturnal awakenings (n = 2,004)	1,696 (84.6)	3,978/6,042 (65.8)	2,064/6,042 (34.2)	Other reason (36.4%), noise of other patients (22.6%), and awakened by hospital staff (20.1%)
Final awakening (n = 1,910)	1,344 (70.4)	3,234/4,389 (73.7)	1,155/4,389 (26.3)	Awakened by hospital staff (35.8%), other reason (11.6%), and noise of other patients (10.9%)

a: Hospital-related reasons include awakened by hospital staff, noise of other patients, noise of hospital staff, noise of medical instruments, uncomfortable bed or pillow, lights, transfer to new room, and other hospital-related answers to the open-ended question. Patient-related reasons include pain, anxiety, worrying about illness, dyspnoea, alarm clock, and other patient-related answers to the open-ended question. b: Percentages are the proportion of all patients (N=2,005) who experienced the sleep-disturbing factor. In the other factors category, 434 (59.5%) of nocturnal awakenings and 120 (51.4%) of final awakenings were caused by toilet visits; this was not an option included in the survey.

Discussion

To our knowledge, this nationwide, single-day, multicente, cross- sectional, observational, FMR study is the first large-scale study to examine the prevalence, severity, and factors negatively associated with sleep quantity and sleep quality in hospitalized patients. We found that hospitalized patients slept shorter times with more interruptions, woke up earlier, and experienced poorer sleep quality than at home. In two-thirds of cases, disturbances involved hospital-related factors, of which many seem modifiable.

In line with other studies,[212,220,223,229,230] we identified noises and awakenings by medical staff as the most important hospital-related sleep-disturbing factors. Although not included in the list of potential sleep disruptors, an important disturbing factor frequently mentioned by the patients was waking up for toilet visits. Continuous intravenous drips at night and extra diuretics may have contributed to an increased frequency of toilet visits in the hospital. Most of the sleep-disturbing factors found in our study seem easy to address by incorporating simple changes in nightly hospital routines. A recent pilot study[231] demonstrated an increase in total sleep time and subjective sleep quality after offering sleep hygiene education to nurses, introducing interventions to minimize light and noise disturbances, and reducing care-related disruptions and overnight fluids.

There was no significant difference in the association with sleep quantity and quality in patients sleeping in a single room compared with patients sleeping in a room with other patients. A probable explanation is that in most Dutch hospitals, the sickest patients are prioritized for sleeping in a single room because of scarcity and need for more care-related disruptions. Most of our population (57%) was older than 65 years and experienced fewer sleep disturbances in the hospital possibly because they are used to more disrupted sleep at home. In addition, sleep disturbance at home did not differ across age groups, possibly because the younger patients were also likely to have a high burden of co-morbidity affecting their sleep at home and in the hospital.

We used national newspapers and social media to promote the study, aiming to raise awareness about the existence of sleep disturbances in hospitals and stimulate future research. Future investigation on sleep optimization should focus on interventions such as dimmed lights in corridors and patient rooms, silent foot- wear, remote alarms in staff rooms and in the pockets of the nurses, and distribution of flight packages at admission that contain earplugs and eye masks. The possibility of introducing remote measurement of vital signs and nocturnal check-ups via webcams should also be explored. In addition, changing the timing and minimizing nursing activities early in the morning; avoiding unnecessary standard procedures, such as routine vital signs measurements, continuous intravenous drips at night, and diuretics in the afternoon, could potentially improve sleep. However, to our knowledge, most of these interventions have never been tested in general wards; therefore, prospective interventional studies are needed.

Strengths and Limitations

The main strength of the present study is that by using the FMR design we included a large heterogeneous sample of patients within 1 day. The hospitals were in different regions of the Netherlands and included academic, non-academic teaching, and nonteaching hospitals in urban and rural areas. Therefore, it was likely that we had a representative sample of the Dutch hospitals.

The study also had some limitations. For the subjective sleep quantity outcomes, almost one-third of the patients had to be excluded because of missing or incompatible data. There were no differences in the demographic characteristics of included and excluded patients; thus, we assumed that the included population was representative of the total study population. In addition, 41 patients reporting "not to have slept at all" the last night in the hospital were excluded because of missing exact time data. This exclusion may have led to an overestimation of sleep duration during hospitalization.

Furthermore, some admitted patients were not eligible for inclusion because of delirium or cognitive problems. Other patients were asleep when the questionnaires were distributed, possibly because they did not sleep enough at night. Some were too ill or exhausted, which may also have led to a conservative estimate of sleep problems during hospitalization.

A downside of using habitual sleep at home during the month before admission is the lack of information about the condition that the patients were in during that period. Habitual sleep pat- terns may have deviated from usual sleep patterns at home because of illnesses before admission. In addition, recall bias may have led to more positive estimates of in-home sleep and inflated the differences between in-home and in-hospital sleep ratings, which could have led to underestimation of sleep quantity and quality difference at home vs hospital.

Conclusions

This large-scale, multicentre study is the first, to our knowledge, to demonstrate compromised sleep quantity and quality in hospitalized patients and identified many potentially preventable hospital-related factors. Increasing awareness among health care workers of the importance of adequate sleep and introducing interventions that target sleep-disturbing factors in hospitals may lead to better sleep and better health outcomes.

Supplementary information

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Supplementary Table 1: Overview of use sleep medication

	Home (n=335)	Hospital(n=539)
Benzodiazepine	189 (56%)	264 (49%)
Melatonin	12 (4%)	6 (1%)
Antidepressant	10 (3%)	10 (2%)
Antipsychotic	3 (1%)	6 (1%)
Antiepileptic	1 (0%)	1 (0%)
Antihistamine	0 (0%)	8 (2%)
Opioid	8 (2%)	42 (8%)
Paracetamol	39 (12%)	61 (11%)
Other	18 (5%)	14 (3%)
Unknown by patient	55 (16%)	127 (24%)

Of 2,005 patients, 335 (17%) reported the use of sleep medication at home and 539 (26%) in the hospital. This table shows frequencies and proportions (n, %) of the different types of sleep medication that was reported by patients within these groups. Besides conventional sleep medication, patients indicated medicine like Paracetamol and opioids as medication to promote sleep.

Supplementary Table 2: Characteristics of patients included and excluded in analysis on subjective sleep quantity

	Included patients	Excluded patients
Sex		
Male	657 (47%)	260 (48%)
Female	734 (53%)	284 (52%)
Age		
<35	94 (7%)	23 (4%)
36-50	166 (12%)	50 (9%)
51-65	382 (27%)	143 (25%)
66-80	533 (38%)	232 (41%)
81+	234 (17%)	118 (21%)
Length of stay		
1 day	246 (20%)	113 (22%)
2 days	213 (17%)	91 (18%)
3 days	106 (8%)	34 (7%)
4+ days	693 (55%)	277 (54%)
Number of patients in room		
1	372 (26%)	132 (23%)
2	369 (26%)	145 (25%)
3	116 (8%)	47 (8%)
4	540 (38%)	234 (41%)
5	4 (0%)	5 (1%)
≥ 6	14 (1%)	1 (0%)
Specialty		
Non-surgical unit	1110 (82%)	426 (74%)
Surgical unit	246 (18%)	115 (20%)
Surgery		
Yes	319 (23%)	132 (23%)
No	1093 (77%)	437 (77%)
Sleep medication		
Yes	383 (27%)	156 (27%)
No	1044 (73%)	422 (73%)
Assistance filling out questionnaire		
Yes	403 (30%)	108 (19%)
No	953 (70%)	440 (76%)

n (%) of included or excluded patients within this specific variable

Supplementary Table 3: Distribution of answers to PROMIS sleep quality items

	Very poor (0)	Poor (1)	Fair (2)	Good (3)	Very good (4)	Median (IQR)	Difference (CI)
My sleep quality was…							
Home (n=1,958)	2 %	9 %	25 %	50 %	14 %	3 (2-3)	0·58 (0·52 - 0·64) p<·001
Hospital (n=1,966)	8 %	19 %	35 %	31 %	6 %	2 (1-3)	
	Not at all (0)	A little (1)	Somewhat (2)	Quite a bit (3)	Very much (4)	Median (IQR)	Difference (CI)
I was satisfied with my sleep.							
Home (n=1,960)	7 %	10 %	17 %	48 %	18 %	3 (2-3)	0·60 (0·53 - 0·67) p<·001
Hospital (n=1,961)	19 %	14 %	23 %	35 %	9 %	2 (1-3)	
My sleep was refreshing.							
Home (n=1,961)	9 %	11 %	22 %	46 %	12 %	3 (2-3)	0·63 (0·56 - 0·70) p<·001
Hospital (n=1,969)	22 %	19 %	24 %	30 %	5 %	2 (1-3)	
My sleep was restless.							
Home (n=1,951)	49 %	21 %	16 %	12 %	3 %	1 (0-2)	-0·45 (-0·52 --0·38) p<·001
Hospital (n=1,952)	35 %	22 %	17 %	18 %	9 %	1 (0-3)	
I had difficulty falling asleep.							
Home (n=1,957)	56 %	20 %	13 %	89 %	3 %	0 (0-1)	-0·51 (-0·59 --0·44) p<·001
Hospital (n=1,958)	40 %	21 %	13 %	15 %	11 %	1 (0-3)	
I felt lousy when I woke up.							
Home (n=1,952)	69 %	14 %	9 %	6 %	2 %	0 (0-1)	-0·24 (-0·30 --0·18) p<·001
Hospital (n=1,956)	57 %	20 %	10 %	9 %	4 %	0 (0-1)	

Every question is answered using a 5-point scale so a median and inter-quartile range (IQR) could be calculated. The 'difference' is the result of the mean at home minus hospital score.

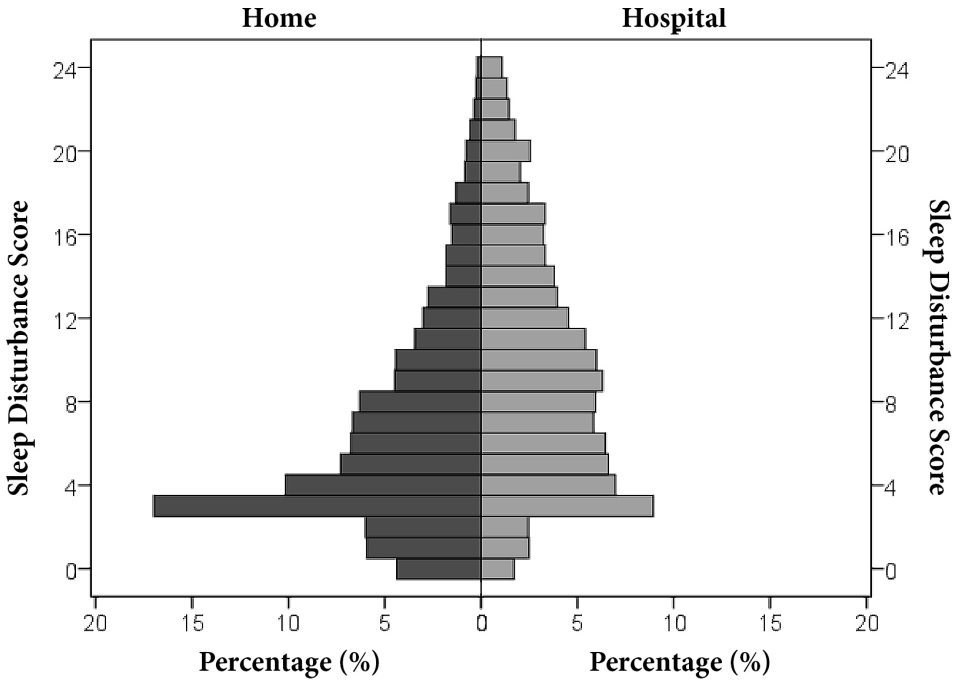
Supplementary Table 4: Differences in raw summary Sleep Disturbance scores between groups

	Hospital	Home
Sex		
Male	9.5 (9.1-9.9)	6.0 (5.7-6.4)
Female	10.0 (9.6-10.4)	7.4 (7.1-7.8)
Age		
<35	11.6 (10.6-12.7)	6.9 (6.0-7.8)
36-50	11.0 (10.2-11.8)	7.0 (6.2-7.7)
51-65	10.0 (9.5-10.6)	6.7 (6.3-7.2)
66-80	9.2 (8.8-9.6)	6.6 (6.2-7.0)
81+	9.1 (8.5-9.8)	6.6 (6.0-7.1)
Specialty		
Non-surgical unit	9.6 (9.3-9.9)	6.8 (6.5-7.1)
Surgical unit	10.5 (9.9-11.2)	6.3 (5.7-6.9)
Operation		
Yes	10.4 (9.8-10.9)	6.5 (6.0-7.0)
No	9.6 (9.3-9.9)	6.8 (6.4-7.1)
Sleep medication		
Yes	10.5 (10.0-11.0)	9.2 (8.7-9.8)
No	9.5 (9.2-9.8)	6.2 (5.9-6.5)
Assistance filling out questionnaire		
Yes	9.0 (9.7-10.3)	6.5 (6.0-7.0)
No	10.0 (8.5-9.5)	6.8 (6.5-7.1)

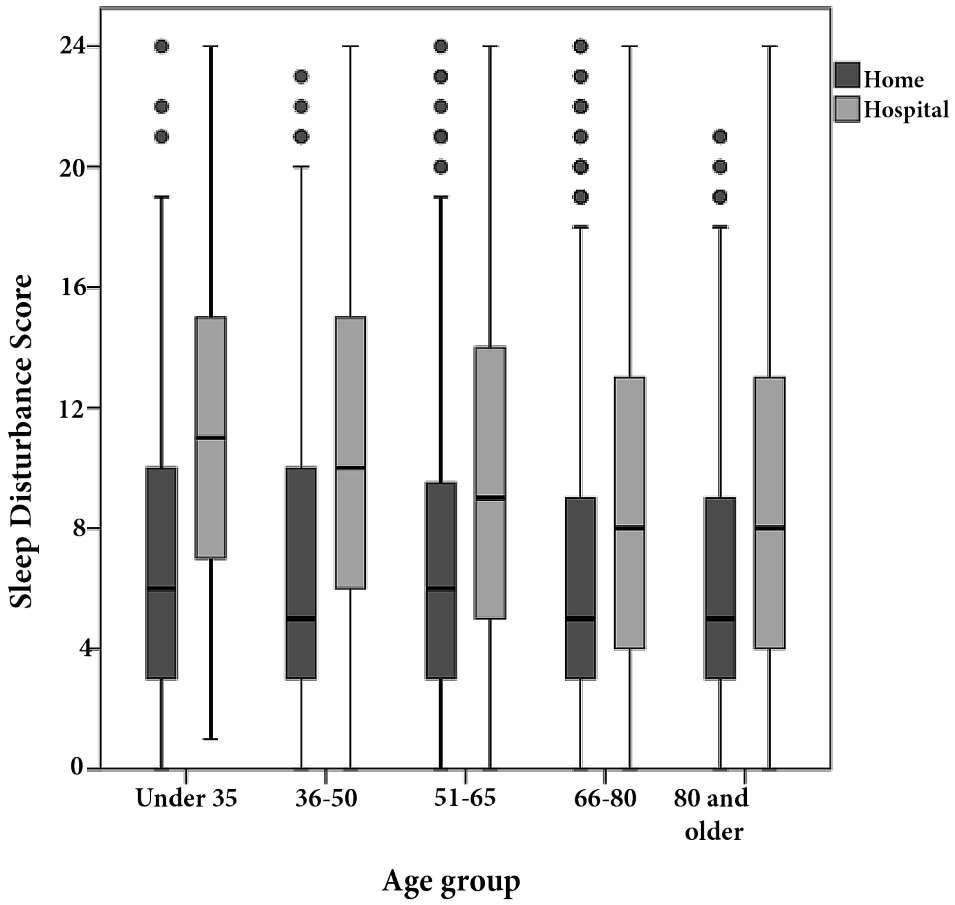
Mean and (95% CI) of raw summary PROMIS Sleep Disturbance scores (0-24) in different groups. A higher score indicates more sleep disturbance.

Supplementary Table 5: Listing of all disturbing factors		
Sleep Onset Latency (n=1,976)	Nocturnal Awakenings (n=2,004)	Final Awakening (n=1,910)
Noise of other patients (24%)	Other answer (36%)	Woken by hospital staff (36%)
Pain (20%)	Noise of other patients (23%)	Other answer (12%)
Noise of hospital equipment (19%)	Woken by hospital staff (20%)	Noise of other patients (11%)
Worrying about illness (17%)	Pain (20%)	Pain (11 %)
Other answer (17%)	Noise of hospital equipment (18%)	Lights (10%)
Uncomfortable bed/pillow (16%)	Uncomfortable bed/pillow (14%)	Noise of hospital staff (9%)
Woken by hospital staff (16%)	Lights (11%)	Noise of hospital equipment (7%)
Lights (15%)	Worrying about illness (10%)	Uncomfortable bed/pillow (6%)
Noise of hospital staff (11%)	Dyspnoea (10%)	Dyspnoea (5%)
Dyspnoea (11%)	Noise of hospital staff (10%)	Worrying about illness (5%)
Anxiety (6%)	Anxiety (5%)	Private alarm (4%)
Transfer (2%)	Transfer (2%)	Anxiety (3%)
		Transfer (1%)

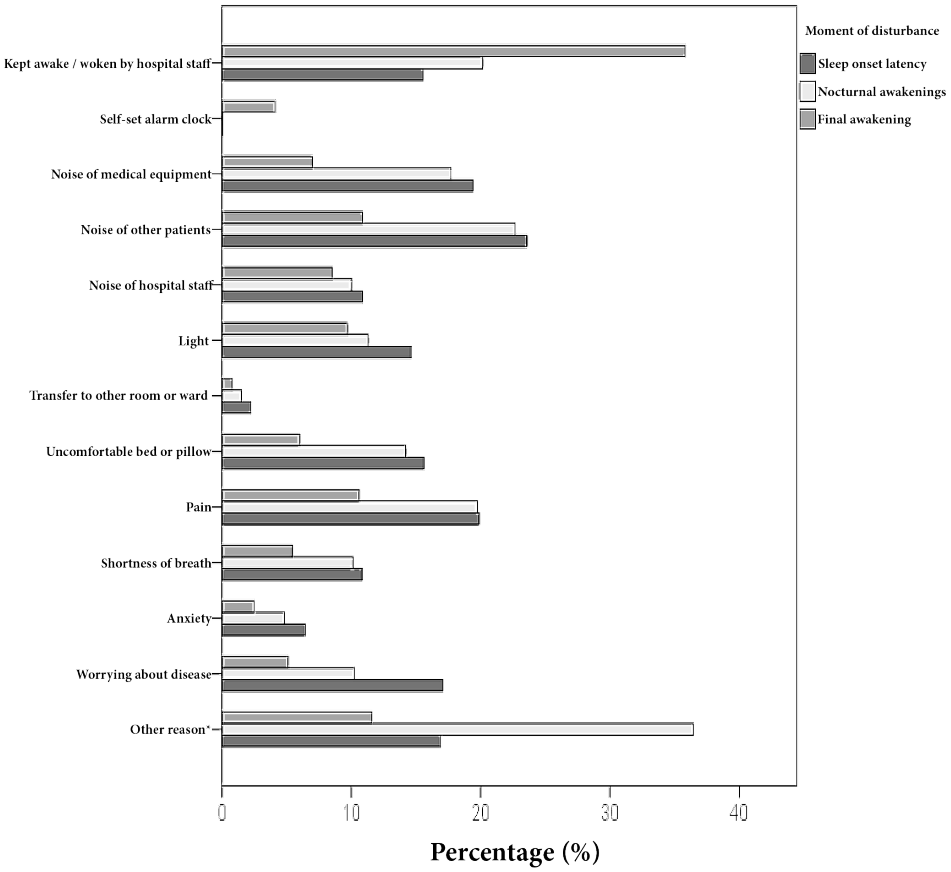
(%) Percentage of patients that suffered from this disturbing factor.



Supplementary figure 1: Distribution of raw summary Sleep Disturbance scores in the hospital and at home. *Distribution of the raw summary score of the six PROMIS questions on sleep disturbance (possible range 0 to 24). A higher score indicates more sleep disturbance.*



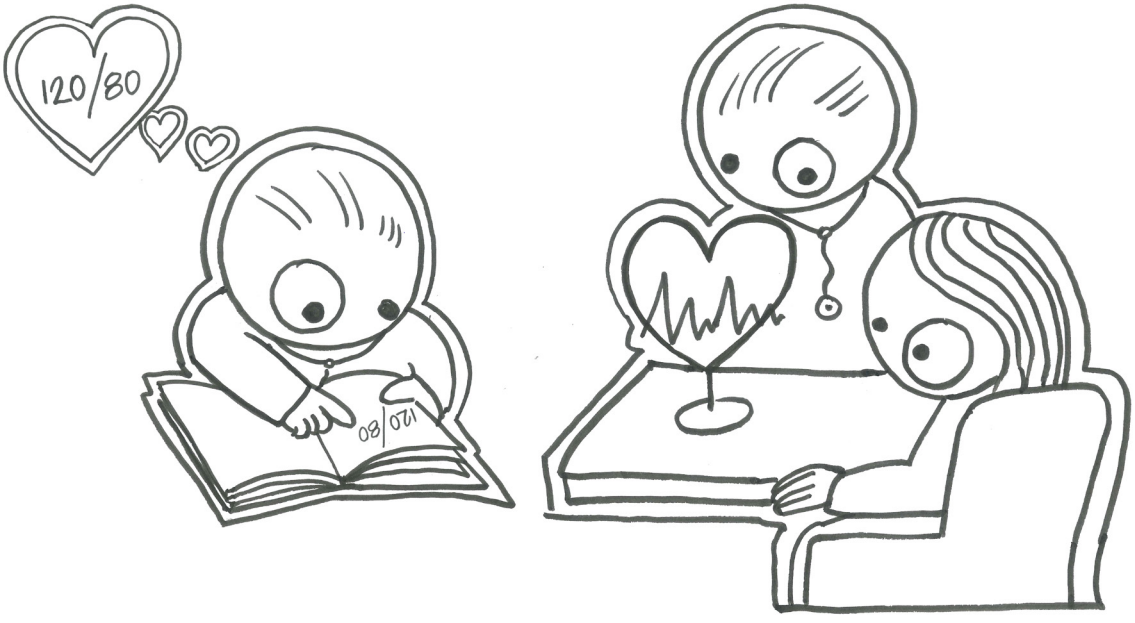
Supplementary figure 2: Raw summary Sleep Disturbance scores in the hospital and at home in different age groups.
Box-whisker plots of raw summary PROMIS Sleep Disturbance scores in different age groups. Higher scores indicate more sleep disturbance (possible range 0-24).



Supplementary figure 3: Overview of disturbing factors (before, during, after sleep onset).

Figure shows the proportion of all patients (n=2,005) who have chosen this specific reason. Other reasons: toilet visits, room temperature, no fresh air, uncomfortable sleeping posture, negative emotions, nausea, unknown environment, drains/IV lines/ urinary catheters, coughing, pruritus, noise in general, to many hours of rest during daytime.*

Prediction Models and Early Warning Scores



Chapter 8

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Prediction Models for Mortality in Adult Patients Visiting the Emergency Department: a Systematic Review

Abstract

We provide a systematic overview of literature on prediction models for mortality in the emergency department (ED). We searched various databases for observational studies in the ED or similar setting describing prediction models for short-term mortality (up to 30 days or in-hospital mortality) in a non-trauma population. We used the CHARMS-checklist for quality assessment. We found a total of 14,768 articles and included 17 articles, describing 22 models. Model performance ranged from AUC 0.63-0.93. Most articles had a moderate risk of bias in one or more domains. The full model and PARIS model performed best, but are not yet ready for implementation. There is a need for validation studies to compare multiple prediction models and to evaluate their accuracy.

Introduction

Rationale

It is important to provide timely and adequate care for patients in the emergency department (ED). Triage aids physicians in allocating their time and resources. Triage systems, such as the Manchester Triage Score and Emergency Severity Index can identify patients who require earlier treatment, but do not adequately forecast mortality.[232] There is an unmet need for models that objectively determine or forecast which patients have a high risk of mortality. In the case of ED crowding – where there are more patients than treatment rooms, and the waiting room is congested – this is even more important.[233] ED crowding has detrimental consequences for patients resulting in delay in treatment, increased in-hospital length of stay and increased mortality.[234,235]

Development and implementation of a prediction tool for mortality could be helpful to determine which patients benefit most from early treatment, especially during time pressured situations. This can lead to altered treatments regimens, intensified care and prevention of adverse outcomes. Currently, early warning scores (EWS) are used for mortality prediction at the ED, however they were not designed for this purpose.[236,237] Also, prediction models have been developed and validated for prediction of mortality. Presently, due to the diversity of these models, it is unclear which model is best at predicting mortality in patients presenting at the ED.

Objective

The aim of this systematic review was to give an overview of literature on the most commonly used scoring systems that predict short-term mortality (i.e. up to 30-day or in-hospital mortality) at the ED.

Methods

Study design

We performed a systematic review on prediction models of short-term mortality in the ED. The systematic review was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[238] The study protocol is registered in the International Prospective Register of Systematic Reviews (PROSPERO) under reference number CRD42017026119.

Eligibility criteria

The search was restricted to studies developing or validating a prediction model at EDs of European hospitals. This was done to minimize the effect of differences in healthcare systems on the EDs, making studies more comparable. Tools developed within a similar

setting as the ED, such as an Acute Medical Unit, were also included. Furthermore, the article needed to fulfil the following criteria: 1) the article described a model rather than merely individual predictors, 2) variables within the prediction models were measured at ED presentation, 3) the investigated outcome was short-term mortality (i.e. in-hospital mortality and up to a maximum of 30-day mortality), 4) the study derived or validated a model in a medical (non-trauma) population without selection for specific diseases (e.g. myocardial infarction) or symptoms (e.g. dyspnoea). Studies investigating the association of a triage system with mortality were excluded, as these studies were conducted for another purpose. Where an author published more than one article on the same prediction model, the article describing the model best or the article using the largest sample size was included. Only articles written in English with full-text availability were included.

Information sources

In attempt to identify all relevant studies, the following databases were searched: Embase.com, Medline Ovid, Cochrane CENTRAL, Web of Science Core Collection, and Google scholar. The latest comprehensive search was conducted on the 20th of June 2018.

Search

The search terms for searching the databases were 'prediction models', 'mortality' and 'Emergency Department' and related synonyms. The queries were developed for Embase.com, and syntax and thesaurus terms were afterwards adjusted for other databases. The search strategy was established by a biomedical information specialist (See *Appendix 1* for the complete syntaxes).

Study selection

Articles were deduplicated using EndNote for Windows (Thomas Reuters, version X7). Two investigators (A.F. and A.B.) independently reviewed all identified studies for inclusion based on title and abstract. Of the remaining records, full-text was assessed for eligibility by the same investigators. Any discordant results in the selection process were discussed in consensus meetings with a third investigator (J.A.).

Data collection process and data items

From each included article, the following data were extracted (if available): authors, year and journal of publication, country in which the study was performed, study period, study design, inclusion and exclusion criteria for the patient population, hospital setting (i.e. regional hospital, tertiary care hospital), patient characteristics (i.e. sex, mean age), sample size, the prediction model studied, variable selection of model, time of measuring variables, the outcomes studied, number of outcomes in the investigated population, handling of missing data, model assessment strategy, performance of the prediction model and whether a validation study was executed. If any of this data was missing, it

was marked as not specified (NS) in the characteristics table. Data were obtained by two researchers (A.F. and A.B.).

Risk of bias in individual studies

The quality of the included articles was assessed according to the Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies (CHARMS) checklist, which is a guideline that helps to critically evaluate the settings of a study and therefore helps to determine the reliability and applicability of the described prediction models and their outcomes.[239] Only derivation studies were assessed, because they can be evaluated on their predictor selection and model development. Using the CHARMS checklist, we assessed the risks for bias in the following domains: participant selection, predictor assessment, outcome assessment, model development and analysis. Each dimension was assigned a low, moderate or high risk of bias.

Summary measures, data synthesis and analysis

The main outcome was performance of the prediction models. The principle summary measure of model performance was the Area Under the Curve (AUC) in a Receiver Operating Characteristic (ROC) (i.e. how well the model discriminates high-risk from low-risk population). The AUC ranges from 0.5 (no discrimination ability) to 1.0 (perfect discrimination). An AUC > 0.8 is considered to be a reflection of good discrimination.[240] The calibration within model performance is also an area of interest (i.e. agreement between expected and observed outcomes). Methods to assess calibration were the Hosmer-Lemeshow goodness of fit test,[241] Schwarz Bayesian Information Criterion, Brier score or calibration slope. Patient characteristics reported in the articles were presented as mean with standard deviation (SD), median with interquartile range (IQR) or numbers with percentages. If possible, statistics not presented in the articles were calculated from the available data.

Results

Study selection

The electronic literature search identified 14,768 articles. After deduplication 8,099 records remained of which 78 were selected for full-text assessment. Finally, 17 articles were included in the qualitative synthesis of this systematic review (*Figure 1*). The latest search was conducted on 20 June 2018.

Study characteristics

Seventeen studies investigating 22 different prediction models were included for further analysis (*Table 1*). Ten studies focused on the development or validation of one model, while the remainder developed two or three models. Sample size ranged from 225 to

35,646 patients. Age was either noted as mean (SD), varying from 58.0 to 64.7 years, or as median (IQR), varying from 56 to 71 years. The ratio of male/female was similar in all articles, with percentage of male ranging from 46.1% to 57.7%. Mortality rates in the study population varied between 0.6% (40/6,947) and 12.7% (711/5,583). Missing data were not always reported, and neither was handling of missing data. Fifteen studies excluded cases with missing values or considered missing values to be normal. Only two studies used imputation techniques to replace missing values.[242,243]

Quality assessment

The quality of studies and susceptibility of bias between studies were assessed using CHARMS. Three studies did not extensively describe patient selection and therefore

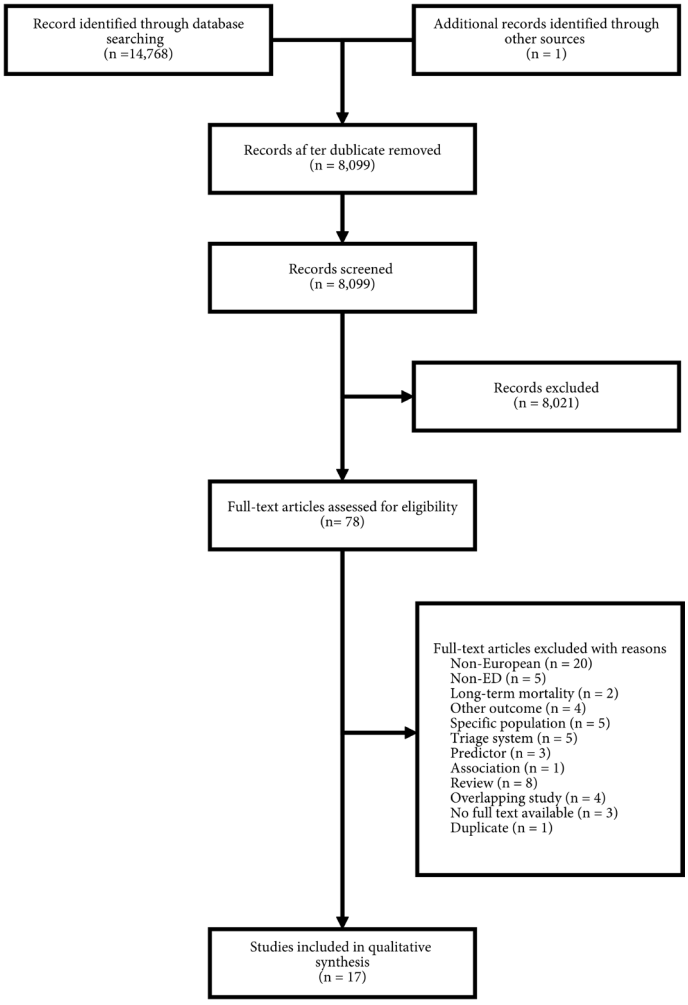

Figure 1: Flowchart for literature search

were considered as having moderate risk of bias.[236,244]

The Simple Clinical Score (SCS) and the Hypotension, Oxygen saturation, low Temperature, ECG changes and Loss of independence (HOTEL) score used subjective predictors (e.g. breathlessness), which can be difficult to reproduce. Therefore, the articles reporting these scores were assigned a moderate risk of bias in predictor assessment.[245-247] Studies that used predictors (e.g. laboratory values) that are not immediately available when a patient presents to the ED were also assigned a moderate risk for bias.[244,248-251]

In the appraisal of outcome two domains were assessed; description of outcome and description of loss of follow-up. Outcome was reported in all articles and resulted in low risk of bias. However, loss of follow-up was described in only five articles, resulting in a moderate risk of bias for the articles that did not provide these data.[242,243,245,252,253] Brabrand *et al.*[242] and Coslovsky *et al.*[243] described the development process of their models best. The study by O'Sullivan *et al.* did not describe the development process and was therefore considered having a high risk of bias.[248] Most articles entered all the variables with a strong predictive ability in a multivariate logistic regression analysis, however three studies used a backward stepwise regression procedure to identify the best prediction model.[242,243,254]

Studies including continuous variables in the prediction tool were less likely to have bias.[242,244,249] The majority of studies excluded patients with missing data and were therefore assigned a moderate risk of bias. Two studies used imputation methods to replace missing values.[242,243] Two other studies replaced missing values by normal values.[236,255]

Finally, the quality of analysis used in the articles was assessed. Seven articles did not provide a validation study and were therefore scored a high risk of bias.[236,248,250,252,254,256,257]

Five studies used internal validation,[243,245,246,253,255] resulting in a moderate risk. Four studies performed external validation and were scored as having a low risk of bias (*Table 2*).[242-244,247,251] Overall, none of the models scored a low risk of bias on all individual domains. Seven studies had a high risk on one of the domains within CHARMS.[236,248,250,252,254,256,257] The models by Coslovsky and Brabrand scored best with an overall low risk of bias on all domains.[242,243]

Variables included in the scoring systems

Median number of included predictors was 6 (IQR 5 – 8.5). Most prediction tools were primarily based on vital parameters (e.g. heart rate, oxygen saturation and body temperature). Eight models included laboratory results. Three prediction tools were solely based on biomarkers combined with patients' age and sex. [248,249,251] Predictors were categorized in patient characteristics, ED presentation, vital parameters, laboratory values, interventions and tests (*Table 3*).

Table 1: Study characteristics

Study	Country	Publication year	Study design	Study period	University hospital / Regional hospital	Settings	Study size, N	Population characteristics
Alam[252]	The Netherlands	2015	prospective observational cohort study	7th January 2013 - 15 February 2013	University hospital	ED	274	Mean age (SD): 60 (20) ♂ (%): 49.0
Brabrand[242]	Denmark	2015	prospective observational cohort study	1. October 2008 - February 2009, 2. February 2010 - May 2010, 3. March 2011 - July 2011	University hospital / Regional hospital	MAU	1. 2,608 2. 2,463 3. 2,210	Mean age (SD): 1. 62.4 (19.2) 2. 61.1 (19.4) 3. 63.0 (20.8) ♂ (%): 1. 52.1 2. 47.7 3. 46.1
Bulut[254]	Turkey	2014	prospective observational cohort study	October 2011 - April 2012	University hospital	ED	2,000	Mean age (SD): 61.41 (18.92) ♂ (%): 52.0
Coslovsky[243]	Switzerland	2015	prospective observational cohort study	October 2009 - October 2010	University hospital	ED, ICU	8,606	Mean age (SD): 58 (20) ♂ (%): 62.0
Cournane[250]	Ireland	2017	retrospective observational cohort study	2002 - 2016	Secondary care centre (large central teaching hospital)/ regional hospital	ED, AMUA	50,612	Median age (IQR): 62.1 (40.3-78.4) ♂ (%): 48.7

Duckitt[253]	UK	2007	prospective observational cohort study	1. July 2003 - November 2003 , 2. October 2005 - November 2005	Regional hospital (general)	EAU	1. 3,184 2. 1,102	Mean age (range): 1. 71 (17-106; range) †83 (32-99) 2. 73 (19-102; range) †81 (43-98) ♂ (%): 1. 48.0, † 46.0 2. 45.0, † 51.0
Goodacre[256]	UK	2006	retrospective observational cohort study	July 1996 - January 2001, sampled	University hospital	ED	5,583	Mean age: 63.4 ♂ (%): 57.7
Groarke[236]	Ireland	2008	prospective observational cohort study	30 day period; 8-19.00	Regional hospital (general)	MAU	225	Mean age (SD): 64.7 (19.1) ♂ (%): 51.6
Kellett (2006)[245]	Ireland	2006	prospective observational cohort study	17 February 2000 - 29 January 2004	Regional hospital	AMU	1. 6,736 2. 3,228	Mean age (SD): 1. 61.9 (20.3) 2. 62.1(20.2) ♂ (%): 1. 52.5 2. 50.1
Kellett (2008)[246]	Ireland	2008	prospective observational cohort study	17 February 2000 - 29 January 2004	Regional hospital	AMU	1. 6,947 2. 3,343	Mean age (SD): 1. 61.6 (20.4) 2. 61.9 (20.3) ♂ (%): 1. 52.7 2. 50.4

Table 1 (continued): Study characteristics

Study	Country	Publication year	Study design	Study period	University hospital / Regional hospital	Settings	Study size, N	Population characteristics
Kristensen[251]	Denmark	2017	prospective observational cohort study	1. 22 September 2009 - 28 February 2010 2. 4 September 2013 - 13 December 2013	University hospital	ED	1. 5,371 2. 5,738	Median age (IQR) 1. 63.8 (46.92-76.52) 2. 63.0 (46.0-76.0) ♂ (%): 1. 48.0 2. 49.4
Merz[257]	Bern	2011	prospective observational cohort study	11 June 2007 - 11 January 2008	University hospital	ED	4,388	Median age (IQR): 61.0 (44.3-74.1) ♂ (%): NS
Olsson[255]	Sweden	2004	prospective observational cohort study	October 1995 - November 1996	University hospital	ED	1,1751	Mean age (SD): 61.9 (20.7) ♂ (%): 48.4
O'Sullivan[248]	Ireland	2012	retrospective observational cohort study	1 January 2005 - 31 December 2010	Secondary care centre (large central teaching hospital)	ED, AMU	20,848	Median age (IQR): 56.5 (37.2-75.8) ♂ (%): 48.1
Silke[244]	Ireland	2010	prospective observational cohort study	1 January 2002 - 31 December 2007, 17 February 2000 - 29 January 2004	Secondary care centre (large central teaching hospital)/ regional hospital	ED, AMAU	10,712, 13,182, 3,597	Median age (IQR): 58.9 (37.9-75.6) ♂ (%): 48.1

Slagman[249]	Germany	2015	retrospective observational cohort study	15 February 2009 - 14 February 2010, 15 February 2011 - 14 February 2012	University hospital	ED	34,333, 35,646	Median age (IQR): 56 (38-71),† 71 (63-81) ♂ (%): 48.8
Straede[247]	Denmark	2014	prospective observational cohort study	2 October 2008 - 19 February 2009	Regional teaching hospital	MAU	1,080, 1,470	Mean age (SD): 62.4 (19.2), ♂ (%): 52.1

Characteristics of studies included for systematic review on prediction models for mortality for use in the ED (n=15). Abbreviations: AMAU, Acute Medical Assessment Unit; AMU, Acute Medical Unit; EAU, Emergency Assessment Unit; ED, Emergency Department; ICU, Intensive Care Unit; IQR, Interquartile range; MAU, Medical Assessment Unit; NS, Not specified; SD, Standard deviation; ♂, male; †, non-survivor.

Table 2: Risk of bias in the development studies

	Participant selection	Predictor assessment	Outcome assessment	Model development	Analysis
Alam (2015)[252]	L	L	L	M	H
Brabrand (2015)[242]	L	L	L	L	L
Bulut (2014)[254]	L	L	M	M	H
Coslovsky (2015)[243]	L	L	L	L	L
Cournane (2017)[250]	M	L	M	M	M
Duckitt (2007)[253]	L	L	L	M	M
Goodacre (2006)[256]	L	L	M	M	H
Groarke (2008)[236]	M	M	M	M	H
Kellett (2006)[245]	L	L	L	M	M
Kellett(2008)[246]	L	L	M	M	M
Kristensen (2017)[251]	L	L	M	M	L
Merz (2011)[257]	L	L	M	L	H
Olsson (2004)[255]	L	L	M	M	M
O'Sullivan (2012) [248]	L	L	M	M	H
Silke (2010) [244]	M	M	M	M	L
Slagman (2015) [249]	L	M	M	M	M

Risk of bias in the development studies. The risk of bias is assessed by the CHARMS checklist, which assesses the domains of participant selection, predictor assessment, outcome assessment, model development and analysis. The results are summarized as either low (L) risk of bias, moderate (M) risk of bias or high (H) risk of bias.

Outcomes

Outcomes were defined as mortality up to 30 days or in-hospital mortality. Further distinction was made in 24-hour mortality,[245-247] five-day mortality,[244] seven-day mortality,[242,244] and 30-day mortality.[245,247,248,250-252]

Model performance

Discrimination was described in all studies, except by Groarke et al.[236] Based on the reported sensitivity and specificity we approximated the AUC for this study. Eleven models provided an AUC < 0.8, of which five showed a poor discriminative ability (MEWS AUC=0.630, EWS AUC=0.68/0.656, RAPS AUC=0.64/0.652).[236,253-256] The MARS model had the best discriminative ability (AUC= 0.93, 95% CI [0.92-0.94].[244]

Calibration was measured for eleven models, of which eight used the Hosmer-Lemeshow goodness of fit test.[242,244,246,247,253,255] One article combined the calibration by the Hosmer-Lemeshow goodness of fit test with the Schwarz Bayesian Information Criterion,[246] and another article developed a calibration curve and reported the calibration slope and calculated the Brier score.[243] In two studies the Hosmer-Lemeshow goodness of fit test

Table 3: Variables within the prognostic models

Variables	NEWS	Full model Brabrand	PARIS	MEWS	REMS	Full model Coslovsky	Nurse risk estimate model	Worthing PSS	EWS	RAPS	SCS	HOTEL	VSS	aAISS	aAISS +comorbidity	MARS	MARS lab- only	Full model Slagman	EPICS	Full model Kristensen	Admission model Cournane
Patient characteristics																					
Age		x	x		x	x					x			x	x	x	x	x	x	x	x
Los of independence		x	x									x								x	
Diabetes											x										
Unable to stand unaided, or a nursing home resident											x										
Prior to current illness, spent some part of daytime in bed											x										
Comorbidities															x						
ED Presentation																					
APACHE II diagnostic category						x															
Breathless on presentation											x										
New stroke on presentation											x										
Coma without intoxication or overdose											x										
Altered mental status without coma, intoxication or overdose, and aged>50											x										
Seizures													x								

Table 3 (continued): Variables within the prognostic models

Variables	NEWS	Full model Brabrand	PARIS	MEWS	REMS	Full model Coslovsky	Nurse risk estimate model	Worthing PSS	EWS	RAPS	SCS	HOTEL	VSS	aAISS	aAISS +comorbidity	MARS	MARS lab- only	Full model Slagman	EPICS	Full model Kristensen	Admission model Cournane
Previous ED visit 12 months						x															
Vital parameters																					x
Body temperature	x			x				x	x		x	x				x					
Heart rate	x			x	x			x	x	x	x		x			x					
Systolic blood pressure	x	x	x	x				x	x	x	x	x	x								
MAP					x	x										x					
Capillary refill time						x															
Respiration rate	x	x	x	x	x			x	x	x	x		x			x					
Oxygen saturation	x				x			x	x		x	x	x								
SaO2/FiO2		x	x			x															
AVPU	x			x				x	x												
GCS					x	x				x			x								
Laboratory values																					
Albumin														x	x						
Troponin Positive														x	x						
Urea														x	x	x	x			x	x

RDW										x	x			x	x			
WCC										x	x	x	x	x				x
Sodium										x	x		x	x				x
Potassium										x	x	x	x	x		x		
Haematocrit												x	x			x		x
CRP														x	x	x		
Creatinine														x		x		
Platelets														x				
Sodium																x		
Interventions & tests																		
Mechanical ventilation					x						x					x		
Supplemental oxygen		x																
Abnormal ECG								x	x									
Other																		
Nurse risk estimate				x														

Variables in the prediction models within the articles. Abbreviations: APACHE II: Acute Physiologic Assessment and Chronic Health Evaluation II; AVPU: Alert, Verbal, Pain, Unresponsive; CRP: C-reactive protein; ECG: Electrocardiography; ED: Emergency Department; GCS: Glasgow Coma Scale; MAP: Mean arterial pressure; RBC: Red blood cell count; RDW: Red cell distribution width; SaO2/FiO2: pulse oximetry saturation / fraction of inspired oxygen; WCC: White cell count; NEWS: National early warning score; EWS: Early warning score; MEWS: Modified early warning score; SCS: Simple clinical score; HOTEL: Hypotension, oxygen saturation, low temperature, ECG changes, loss of independence; PARIS: Blood pressure, age, respiratory rate, loss of independence, peripheral oxygen saturation; REMS: Rapid emergency medicine score; RAPS: Rapid acute physiology score; PSS: Physiological scoring system; VSS: Vital sign score; AISS: Acute illness severity score; EPICS: Emergency processes in clinical structures; MARS: Medical admissions risk system; MTS: Manchester Triage System.

Table 4: Performance of the developed prediction models

Study	Prediction model	Mortality, N (%)	Discrimination, AUC (95% CI) / ±SE)	Calibration method	Calibration	Other performance measurements
24-hour mortality						
Kellett (2008)[246]	HOTEL	40 (0.6), 19 (0.6)	0.865 (0.793-0.937)	Schwarz BIC, HL GOF test	422.89, χ^2=1.49 (0.83)	NS
Kellett (2006)[245]	SCS	40 (0.6), 19 (0.6)	0.902 (±0.019)	NS	NS	NS
5-day mortality						
Silke[244]	MARS	648 (6.05), 171 (4.75)	0.93 (0.92-0.94)	HL GOF test	χ^2=5.66 (0.315)	NS
Silke[244]	MARS lab only	648 (6.05)	0.90 (0.89-0.90)	HL GOF test	χ^2=11.65 (0.167)	NS
7-day mortality						
Brabrand[242]	Full model	76 (2.5)	0.87 (0.82-0.93)	HL GOF test	P = 0.97	NS
Brabrand[242]	PARIS	76 (2.5)	0.86 (0.80-0.91)	HL GOF test	P = 0.42	NS
Silke[244]	MARS	788 (5.98)	0.91 (0.90-0.93)	HL GOF test	χ^2= 17.98 (0.02)	NS
30-day mortality						
Alam[252]	NEWS	11 (4.0)	0.768 (0.618-0.919)	NS	NS	NS
Kellett (2006)[245]	SCS	316 (4.7)	0.858 (±0.009)	NS	NS	NS
O'Sullivan[248]	aAISS	(4.8)	0.90 (0.89-0.90)	NS	NS	NS
O'Sullivan[248]	aAISS + co-morbidity	(4.8)	0.89 (0.88-0.89)	NS	NS	NS
Kristensen[251]	Full model	284 (5.3)	0.886 (0.861-0.911)	BS	BS 4.11 (3.54-4.70)	NS
Cournane[250]	Admission model	(4.6-7.0)	0.85 (0.85-0.86)	NS	NS	NS
In-hospital mortality						
Bulut[254]	MEWS	153 (7.65)	0.630 (0.608-0.727)	NS	NS	NS
Bulut[254]	REMS	153 (7.65)	0.707 (0.686-0.727)	NS	NS	NS
Coslovsky[243]	Full model	398 (4.6)	0.922 (0.916-0.927)	BS , CS	BS 0.028, CS 0.95	NS
Coslovsky[243]	Nurse risk estimate model	398 (4.6)	0.78	BS	BS 0.040	NS

Duckitt[253]	Worthing PSS	270 (8.0)	0.74 (0.71-0.77)	HL GOF test	P = 0.119	NS
Duckitt[253]	EWS	270 (8.0)	0.68 (0.65-0.71)	NS	NS	NS
Goodacre[256]	RAPS	711 (12.7)	0.64 (0.59-0.69)	NS	NS	NS
Goodacre[256]	REMS	711 (12.7)	0.74 (0.70-0.78)	NS	NS	NS
Goodacre[256]	Full model	711 (12.7)	0.81 (0.78-0.84)	NS	NS	NS
Groarke[236]	EWS	8 (3.6)	0.656 *	NS	NS	OR 2.19 (1.41-3.39)
Merz[257]	VSS	316 (7.2)	0.72 (0.53-0.91)	NS	NS	NS
Olsson[255]	RAPS	285 (2.4)	0.652 (±0.019)	NS	NS	NS
Olsson[255]	REMS	285 (2.4)	0.852 (±0.014)	HL GOF test	χ^2= 62 (< 0.0001)	NS
Slagman[249]	Full model	634 (1.8)	0.863 (0.848-0.877)	NS	NS	NS
Slagman[249]	EPICS	634 (1.8)	0.866 (0.853-0.878)	NS	NS	NS

*Performance of the developed prediction tools for mortality, divided by the time-frame of mortality. Abbreviations: AISS, Acute illness severity score; AUC, Area under the curve; BS, Brier score; CI, Confidence interval; CS, Calibration slope; EPICS, Emergency processes in clinical structures; EWS, Early warning score; HL GOF, Hosmer-Lemeshow goodness of fit; HOTEL, Hypotension, oxygen saturation, low temperature, ECG changes, loss of independence; MARS, Medical admissions risk system; MEWS, Modified early warning score; NEWS, National early warning score; NS, Not specified; OR, Odds ratio; PARIS, Systolic blood pressure, age, respiratory rate, loss of independence, peripheral oxygen saturation; PSS, Physiological scoring system; RAPS, Rapid acute physiology score; REMS, Rapid emergency medicine score; SCS, Simple clinical score; SE, Standard error; VSS, Vital sign score.*calculated from the available data.*

yielded a significant p-value in the derivation, which proves bad calibration (*Table 4, Figure 2 a-e*).[241]

Validation

Six studies performed an internal validation analysis, divided in temporal validation,[253] split-sample validation,[243,245,246,255] cross-validation[251] and bootstrap resampling validation.[243] External validation analysis was performed in five studies.[242,244,247,249,251] The AUC for all external validation studies was high, ranging from 0.837 and 0.960. Calibration within the validation studies was performed for twelve models, and only the PARIS model scored poorly in one validation dataset (*Table 5*).[242]

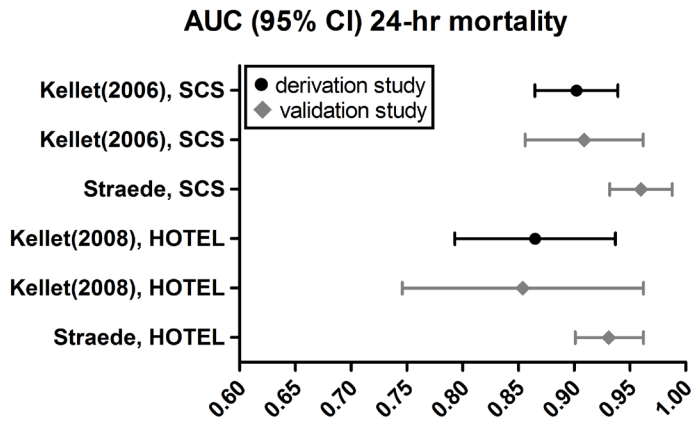

Figure 2 a: Discrimination performance of the models predicting 24-h mortality.

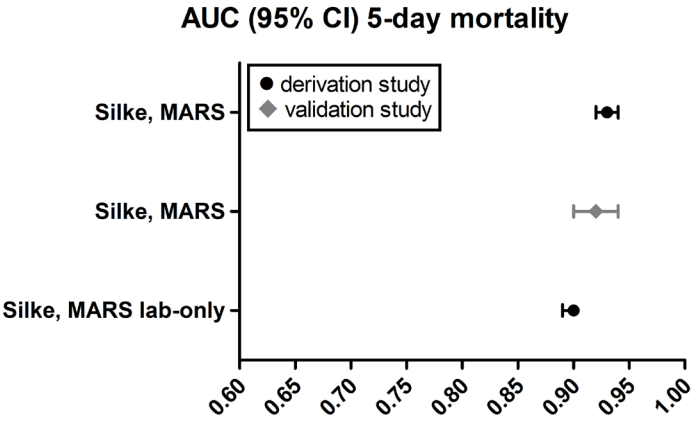

Figure 2 b: Discrimination performance of the models predicting 5-day mortality.

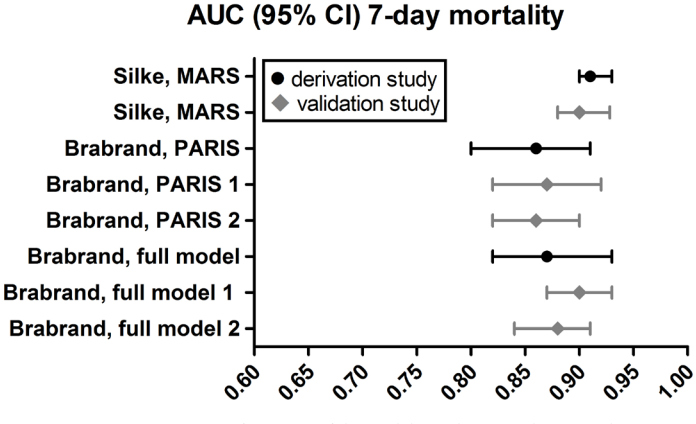

Figure 2 c: Discrimination performance of the models predicting 7-day mortality.

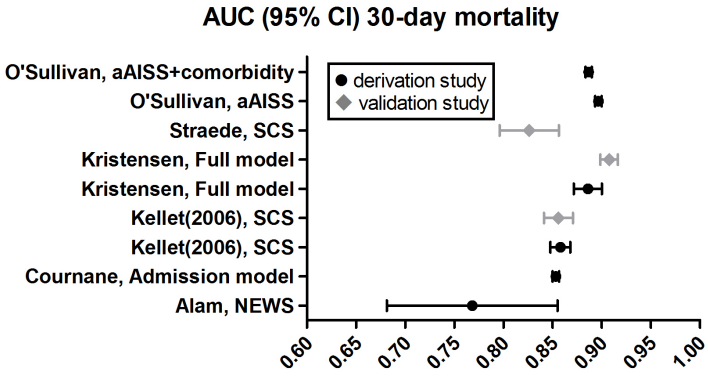

Figure 2 d: Discrimination performance of the models predicting 30-day mortality.

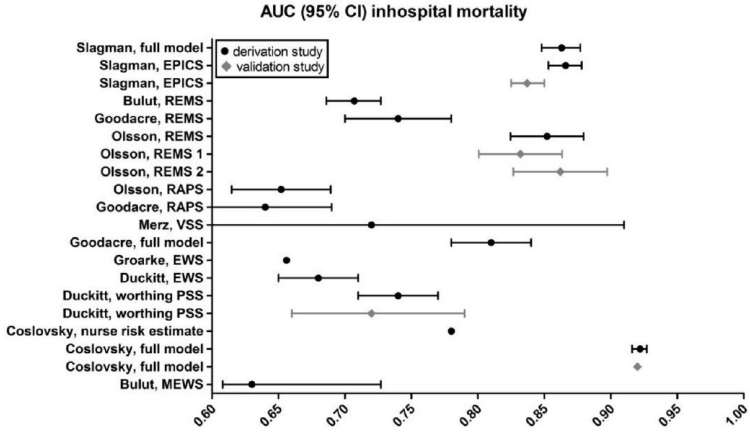

Figure 2 e: Discrimination performance of the models predicting inhospital mortality.

In all figures a distinction is made between derivation studies and validation studies. Abbreviations: AUC: Area under the curve; CI: Confidence interval; SCS: Simple clinical score; HOTEL: Hypotension, oxygen saturation, low temperature, ECG changes, loss of independence; MARS: Medical admissions risk system; PARIS: Systolic blood pressure, age, respiratory rate, loss of independence, peripheral oxygen saturation; aAISS: adjusted Acute illness severity score; NEWS: National early warning score; EPICS: Emergency processes in clinical structures; REMS: Rapid emergency medicine score; RAPS: Rapid acute physiology score; VSS: Vital sign score; EWS: Early warning score; PSS: Physiological scoring system; MEWS: Modified early warning score.

Table 5: Performance of the validated models

Study	Prediction model	Mortality, N (%)	Validation type	Discrimination, AUC (95% CI)/ (±SE)	Calibration method	Calibration
24 -h mortality						
Kellett (2008)[246]	HOTEL	19 (0.6)	split-sample validation	0.854 (0.746-0.962)	NS	NS
Kellett (2008)[246]	SCS	19 (0.6)	split-sample validation	0.909 (SE 0.027)	NS	NS
Straede[247]	SCS	26 (0.9)	external validation	0.960 (0.932-0.988)	HL GOF	χ^2=2.68 (0.998)
Straede[247]	HOTEL	26 (0.9)	external validation	0.931 (0.901-0.962)	HL GOF	χ^2=5.56 (0.234)
5-day mortality						
Silke [244]	MARS	171 (4.75)	external validation	0.92 (0.90-0.94)	HL GOF	χ^2=9.83 (0.278)
7-day mortality						
Brabrand[242]	Full model	1. 57 (2.0) 2. 111(4.3)	external validation	1. 0.90 (0.87-0.93) 2. 0.88 (0.84-0.91)	HL GOF	P = 1. 0.75 2. 0.33
Brabrand[242]	PARIS	1. 57 (2.0) 2. 111(4.3)	external validation	1. 0.87 (0.82-0.92) 2. 0.86 (0.82-0.90)	HL GOF	P =1. 0.74 2. <0.001
Silke[244]	MARS	216 (5.11)	external validation	0.90 (0.88-0.928)	HL GOF	χ^2=4.46 (0.814)
30-day mortality						
Kellett (2006)[245]	SCS	145 (4.5)	split-sample validation	0.856 (SE 0.013)	NS	NS
Straede[247]	SCS	196 (6.4)	external validation	0.826 (0.774-0.879)	HL GOF	χ^2=4.00 (0.947)
Kristensen[251]	Full model	234 (4.1)	cross-validition /external validation	0.908 (0.892-0.923)	BS	3.40 (3.08-3.72)
In-hospital mortality						
Coslovsky[243]	Full model	398 (4.6)	bootstrapping / split-sample validation	0.920	CS	CS 0.935 (split sample)
Coslovsky[243]	Nurse risk estimate model	398 (4.6)	bootstrapping	negligible difference	BS	negligible difference
Duckitt[253]	Worthing PSS	85 (8.0)	temporal validation	0.72 (0.66-0.79)	HL GOF	P = 0.565

Olsson[255]	REMS	285 (2.4)	split-sample validation	1. 0.832 (± 0.016) 2. 0.862 (±0.018)	HL GOF	χ^2= 1. 35.3 2. 31.7
Slagman[249]	EPICS	765 (2.1)	external validation	0.837 (0.825-0.850)	NS	NS

Performance of the different validation prediction tools for mortality, divided by the time-frame of mortality. Abbreviations: AUC, Area under the curve; BS, Brier score; CI, Confidence interval; CS, Calibration slope; EPICS, Emergency processes in clinical structures; HL GOF, Hosmer-Lemeshow goodness of fit; HOTEL, Hypotension, oxygen saturation, low temperature, ECG changes, loss of independence; MARS, Medical admissions risk system; NS, Not specified; PARIS, Systolic blood pressure, age, respiratory rate, loss of independence, peripheral oxygen saturation; PSS, Physiological scoring system; REMS, Rapid emergency medicine score; SCS, Simple clinical score; SE, Standard error; VSS, Vital sign score.

Discussion

In our systematic review we described models that predict short-term mortality of patients visiting the ED. To our knowledge, none of these models are currently implemented for mortality prediction in clinical practice. We assessed the methodological quality of the prediction models for discrimination, calibration and validation, where available. The discrimination of the models, presented by the AUC, ranged between average and excellent, with the majority having a good discriminatory performance. The MARS model had the highest performance, followed by the model by Coslovsky *et al*. and the SCS.[243-245] To determine the level of agreement between the expected and observed outcome, calibration is paramount. Calibration was assessed in seven studies, and was good in four, which shows that these models are suitable for validation.[242-244,246,251,253,255]

Validation is needed before a model can be implemented in clinical practice, and external validation is preferred. Of the nine articles that described validation, only five used external validation. Internal validation was performed either using a split-sample, cross-validation or a bootstrap resampling technique. One study used bootstrap resampling,[243] which is considered the best method, as it provides a true representation of the population without loss of patients.[258] In the studies that provided validation, the performance in all models was satisfying, and the highest performance was for the HOTEL score (AUC=0.960).[247] The PARIS model had insufficient calibration for the validation in one of the two validation cohorts.[242] This means that the model was not generalizable to one of the studied cohorts.

When we assessed the quality of the prediction models, the models by Coslovsky and Brabrand scored best with an overall low risk of bias on all the assessed domains.[242,243] Only in the analysis domain high risk of bias was found, and this is explained by a lack of validation in these studies.[236,248,250,252,254,256,257] Some of the CHARMS criteria within the domains were missing in all studies. First, most studies lacked information on missing data or excluded patients with missing information. Excluding these patients, however, might limit not only the correctness, but also the usability of the model. In daily practice, the parameters of a model are not always available.[259] There are multiple options to

address the issue of missing data. Missing values can be replaced by imputation, by the mean or by a normal value dependent on the type of missing data. It is also possible to assign a special category to missing values which correlates to a certain regression coefficient (thus mortality risk). Multiple imputation is considered to be the best method, since it gives reliable results without losing data.[12,260] Unfortunately, just two articles used imputation methods to address missing values.[242,243]

Second, most articles did not describe loss of follow-up. However, it is questionable whether there is much influence of this loss of mortality data, since only short-term mortality (with a maximum of 30 days) was studied. Third, the number of variables that can be used in a model depends on the number of events (i.e. mortality) encountered in the study cohort. To limit overfitting in a model, there should be at least ten events per variable in order to include a parameter in a model.[261] The events per variable were only explicitly mentioned by Brabrand *et al.*[242] Fourteen studies had enough events in relation to their number of variables.[243-249,253-257] However, the studies of Groarke and Alam had less than ten events per variable.[236,252] This could have been addressed by using a larger sample with more events.

The SCS, PARIS and full model of Coslovsky had a high performance of the model with good validation and low risk of bias.[242,243,245] However, a model should also be usable in clinical practice with a relevant predicted outcome. The relevance of a tool that predicts 24-hour mortality seems limited, as these patients presumably are more critically ill upon ED presentation. A model that uses parameters with low interrater and intrarater variability is reproducible and generally implementable. This can best be achieved by using objective measurements. Objective measurements also allow automatic calculation of the scores and the subsequent risks in an electronic patient file, and may even trigger alarms. Not all models met this prerequisite, as the SCS uses a patient's complaint of subjective breathlessness as a parameter.[245]

For immediate and effective use a model should use parameters that are readily available and easily obtained. Eight of the models included in this systematic review used laboratory values as predictors, which entails a waiting time, and thereby delay in prediction.[244,248-251] Six models used parameters requiring (collateral) history, such as loss of independence, confinement to bed, and comorbidities.[242,243,245-248] In patients with an altered or lowered consciousness this information is not always available, which subsequently influences the results of the model. Furthermore, parameters such as the presence of seizures and APACHE II diagnostic category require both diagnostic testing, which takes time, and require patients to be in one of these diagnostic categories, which is not always the case. Therefore these parameters are not applicable to all patients, and thus are the models not generalizable to the general ED population. We believe that in specific patient populations parameters like APACHE II diagnostic category will perform better than merely vital parameter. However, Coslovsky *et al.* showed that the effect of APACHE II category was less than vital signs, such as MAP (OR = 0.57 vs OR=0.93).[243] Last, models with complex calculations require applications ("apps") or calculation programs, which could cause a delay in the risk calculation.

We found that for clinical use in the ED the RAPS, REMS, NEWS and EWS are most suited, since they use routinely acquired vital parameters, which meets the requirements of early, easily obtainable and objective predictors. However, the AUC of these models is lower compared to the PARIS and full score.

Future model development should ideally combine good model performance with clinical applicability. The use of a prospective cohort study design is warranted as it allows optimal predictor selection and outcome measurement.[262] Before implementation, a model should be externally validated to prove generalizability. Large datasets allow head-to-head comparison of multiple models in order to detect the best model. Most importantly, pre- and post-implementation measurements should be performed to determine if introduction of a mortality prediction tool leads to earlier identification of patients at risk, with subsequent faster initiation of treatment and a decrease in mortality as a final result. If introduction of a prediction tool at the ED finally does not yield these effects, its further implementation in clinical practice warrants of little use.

Our study has several strengths and limitations. Strengths of this study include the comprehensive search strategy and the methodological quality assessment with CHARMS, and both were executed by two researchers. There are also several limitations. First, in our review we identified highly heterogeneous studies, making it unfeasible to perform a formal meta-analysis. This heterogeneity makes it difficult to reliably rank different models, as the different models all have their merits and flaws. Second, selection bias might be present. We attempted to minimize this risk by using two researchers to select the studies. Third, despite we only selected European studies, practice and organization between countries can differ. External validation might make these results more generalizable, however, as external validation was mostly done in the same country, these risks remain.

Conclusion

In conclusion, we provide an extensive overview of literature concerning prediction models for mortality in the ED for an unselected medical population. In general, the models performed well to excellent. Models with more and difficult obtainable parameters performed better. Most studies had bias due to the reporting of missing values, handling of missing data and lack of validation. These issues should be taken into account in future models. At this time, the PARIS model and the full-model of Brabrand *et al.* are the best performing models, however, these models require additional information such as loss of independence. The EWS and NEWS use readily available parameters, but have lower performance. Therefore, the perfect model has yet to be developed.

Appendix 1: Search strategy for systematic review of the identification of prediction models for mortality in the Emergency Department

Records identified in various databases				
		04-01-2017		19-06-2018
	Total	Unique	Total	Unique
Embase.com	4,066	3,977	4,909	4,824
Medline Ovid	4,551	1,310	4,917	1,482
Web-of-science	3,603	1,242	4,516	1,585
Cochrane	114	24	231	83
Google scholar	300	204	200	125
Total	**12,634**	**6,757**	**14,768**	**8,099**

Embase.com

('prediction'/exp OR 'predictive value'/exp OR 'predictive validity'/exp OR 'prediction and forecasting'/de OR 'predictor variable'/exp OR (predict*):ab,ti) AND (mortality/exp OR survival/exp OR survivor/de OR 'fatality'/de OR (('intensive care'/exp OR 'intensive care unit'/exp) AND ('hospital admission'/exp OR 'hospitalization'/de)) OR (mortalit* OR surviv* OR fatal* OR ((admission* OR admit*) NEAR/3 (icu OR intensive-care*))):ab,ti) AND ('emergency care'/exp OR 'emergency patient'/exp OR 'emergency ward'/exp OR 'emergency health service'/exp OR ((emergen* NEAR/3 (ward* OR department* OR patient* OR service* OR admiss* OR admit* OR hospital* OR call*))):ab,ti) AND ('cohort analysis'/exp OR 'follow up'/exp OR 'longitudinal study'/de OR 'retrospective study'/de OR 'prospective study'/de OR 'evaluation study'/de OR model/de OR 'disease model'/de OR 'population model'/de OR 'process model'/de OR simulation/exp OR algorithm/de OR 'validation process'/exp OR 'sensitivity and specificity'/exp OR 'scoring system'/exp OR 'decision tree'/de OR (model OR simulat* OR cohort* OR (follow* NEXT/1 up*) OR followup* OR longitudinal* OR retrospectiv* OR prospectiv* OR evaluation* OR algorithm* OR validat* OR sensitivit* OR specificit* OR score* OR (decision NEXT/1 tree*)):ab,ti) NOT ([Conference Abstract]/lim OR [Letter]/lim OR [Note]/lim OR [Editorial]/lim) AND [english]/lim NOT ((child/exp OR childhood/exp OR adolescent/exp OR adolescence/exp) NOT (adult/exp OR adulthood/exp)) NOT (pediatrics/exp OR (picu OR nicu OR picus OR nicus OR pediatric* OR paediatric*):ab,ti)

Medline ovid

("Predictive Value of Tests"/ OR "Forecasting"/ OR (predict*).ab,ti.) AND (exp mortality/ OR

mortality.xs. OR survival/ OR survivors/ OR (("Critical Care"/ OR "Intensive Care Units"/) AND ("Patient Admission"/ OR "hospitalization"/)) OR (mortalit* OR surviv* OR fatal* OR ((admission* OR admit*) ADJ3 (icu OR intensive-care*))).ab,ti.) AND ("Emergency Medical Services"/ OR "emergencies"/ OR exp "Emergency Service, Hospital"/ OR ((emergen* ADJ3 (ward* OR department* OR patient* OR service* OR admiss* OR admit* OR hospital* OR call*))).ab,ti.) AND (exp "cohort studies"/ OR "evaluation study"/ OR exp "Models, Statistical"/ OR "Computer Simulation"/ OR "Models, Theoretical"/ OR Algorithms/ OR "Validation Studies"/ OR exp "sensitivity and specificity"/ OR "Decision Trees"/ OR (model OR simulat* OR cohort* OR (follow* ADJ up*) OR followup* OR longitudinal* OR retrospectiv* OR prospectiv* OR evaluation* OR algorithm* OR validat* OR sensitivit* OR specificit* OR score* OR (decision ADJ tree*)).ab,ti.) NOT (letter OR news OR comment OR editorial OR congresses OR abstracts).pt. AND english.la. NOT ((exp child/ OR exp Infant/ OR adolescent/) NOT (exp adult/)) NOT (exp pediatrics/ OR (picu OR nicu OR picus OR nicus OR pediatric* OR paediatric*).ab,ti.)

Cochrane

((predict*):ab,ti) AND ((mortalit* OR surviv* OR fatal* OR ((admission* OR admit*) NEAR/3 (icu OR intensive-care*))):ab,ti) AND (((emergen* NEAR/3 (ward* OR department* OR patient* OR service* OR admiss* OR admit* OR hospital* OR call*))):ab,ti) AND ((model OR simulat* OR cohort* OR (follow* NEXT/1 up*) OR followup* OR longitudinal* OR retrospectiv* OR prospectiv* OR evaluation* OR algorithm* OR validat* OR sensitivit* OR specificit* OR score* OR (decision NEXT/1 tree*)):ab,ti)

Web-of-science

TS=(((predict*)) AND ((mortalit* OR surviv* OR fatal* OR ((admission* OR admit*) NEAR/3 (icu OR intensive-care*)))) AND (((emergen* NEAR/2 (ward* OR department* OR patient* OR service* OR admiss* OR admit* OR hospital* OR call*)))) AND ((model OR simulat* OR cohort* OR "Follow up" OR followup* OR longitudinal* OR retrospectiv* OR prospectiv* OR evaluation* OR algorithm* OR validat* OR sensitivit* OR specificit* OR score* OR (decision NEAR/1 tree*))) NOT ((child* OR infan* OR adolescen* OR newborn* OR neonat*) NOT (adult* OR older* OR elder* OR (aged NEAR/3 (person* OR patient*)))))

Google scholar

Prediction|predictivemortality|survival|fatal|fatality|"icu|care admission"|"admitted**icu|intensive"|"admitted*icu|intensive""emergency ward|department|patient|service" model|simulation|cohort|"follow up"|evaluation

Chapter 10

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Predicting Mortality in Patients With Suspected Sepsis at the Emergency Department: a Retrospective Cohort Study Comparing qSOFA, SIRS and National Early Warning Score

Abstract

Objective

In hospitalized patients, the risk of sepsis-related mortality can be assessed using the quick Sepsis-related Organ Failure Assessment (qSOFA). Currently, different tools that predict deterioration such as the National Early Warning Score (NEWS) have been introduced in clinical practice in Emergency Departments (ED) worldwide. It remains ambiguous which screening tool for mortality at the ED is best. The objective of this study was to evaluate the predictive performance for mortality of two sepsis-based scores (i.e. qSOFA and Systemic Inflammatory Response Syndrome (SIRS)-criteria) compared to the more general NEWS score, in patients with suspected infection directly at presentation to the ED.

Methods

We performed a retrospective cohort study. Patients who presented to the ED between June 2012 and May 2016 with suspected sepsis in a large tertiary care centre were included. Suspected sepsis was defined as initiation of intravenous antibiotics and/or collection of any culture in the ED. Outcome was defined as 10-day and 30-day mortality after ED presentation. Predictive performance was expressed as discrimination (AUC) and calibration using Hosmer-Lemeshow goodness-of-fit test. Subsequently, sensitivity, and specificity were calculated.

Results

In total 8,204 patients were included of whom 286 (3.5%) died within ten days and 490 (6.0%) within 30 days after presentation. NEWS had the best performance, followed by qSOFA and SIRS (10-day AUC: 0.837, 0.744, 0.646, 30-day AUC: 0.779, 0.697, 0.631). qSOFA (≥2) lacked a high sensitivity versus SIRS (≥2) and NEWS (≥7) (28.5%, 77.2%, 68.0%), whilst entailing highest specificity versus NEWS and SIRS (93.7%, 66.5%, 37.6%).

Conclusions

NEWS is more accurate in predicting 10- and 30-day mortality than qSOFA and SIRS in patients presenting to the ED with suspected sepsis.

Introduction

Sepsis is a syndrome characterized by both signs of infection and manifestations of a systemic host response.[16] Sepsis is the primary cause of mortality from infection. The definition of sepsis has changed throughout the last decades. In February 2016 the Third International Consensus Definition for Sepsis (Sepsis-3) replaced the Sepsis-2 definition dating from 2001.[16,34,36] Sepsis is currently defined as a "life-threatening organ dysfunction caused by a dysregulated host response to infection", in which organ dysfunction is represented by an increase of at least two points in the Sequential Organ Failure Assessment (SOFA) score.[16] The Systemic Inflammatory Response Syndrome (SIRS) score, which was part of the definition in Sepsis-1 and -2, has been abandoned.

The quick Sepsis-related Organ Failure Assessment (qSOFA) was introduced with the new Sepsis-3 definition.[305] However, not all medical societies support this new definition.[49,306] The qSOFA consists of three parameters (i.e. low systolic blood pressure (≤ 100 mmHg), tachypnoea (≥ 22 /minute) and altered mental status (Glasgow Coma Scale (GCS) < 15 / AVPU<Alert)), with a maximum score of three points. qSOFA is a bedside prompt to identify patients with a suspected infection who are at greater risk for a poor outcome. It is a simplified score based on the SOFA score. Early identification of these patients potentially results in earlier adequate treatment and a decrease in mortality. qSOFA aims to prognosticate the course of sepsis and intends to predict sepsis-related mortality and adverse events; a score of two points or higher gives a three to 14-fold increase in in-hospital mortality.[305] The qSOFA score is claimed to be more accurate than SOFA in departments outside the intensive care unit (ICU), however the use of qSOFA in the Emergency Department (ED) is questionable.[305,307-310] The authors of Sepsis-3 also consider qSOFA as a prompt to identify possible infection.[16]

In many patients admitted to the ED with sepsis the severity of their illness is not directly clear. The presence of a life-threatening infection can easily be overlooked. The use of screening tools in the ED can aid in early recognition of patients with sepsis, resulting in early initiation of effective and complete treatment. This requires screening tools with a high sensitivity. SIRS has been criticized for being too sensitive, while lacking specificity in recognizing sepsis, and it is therefore not an ideal screening tool. As qSOFA performed better than SIRS in hospitalized patients, it has been proposed that qSOFA is preferred to SIRS. Alternatively, early warning scores, such as the National Early Warning Score (NEWS), are already recommended for use in the ED, and should therefore also be considered.[311] NEWS was introduced in 2012 by the Royal College of Physicians, who aimed to provide a standardized early warning score. This score is used for early detection of patients at risk for deterioration but is not specific for sepsis. NEWS comprises of seven parameters (i.e. respiratory rate, oxygen saturation, supplemental oxygen, body temperature, systolic blood pressure, heart rate, AVPU score) with a maximum of twenty points. In clinical practice cut-off values of 1–4, 5–6 and ≥ 7, respectively for low, medium and high risk are used. NEWS was primarily developed for use on the wards, however NEWS was also tested for use in the ED and in the prehospital setting.[312,313] For use in the ED a cut-off value of ≥ 7 is suggested.

Table 1: Variables within NEWS, qSOFA and SIRS criteria

	NEWS[a]							qSOFA[b]			SIRS[c]		
	3	2	1	0	1	2	3	1	0	1	1	**0**	**1**
Body temperature (˚C)	≤35.0		35.1–36.0	36.1–38.0	38.1–39.0	≥39.1					<36.0	36.0–38.0	>38.0
Heart rate (bpm)	≤40		41–50	51–90	91–110	111–130	≥131					≤90	>90
Systolic blood pressure (mmHg)	≤90	91–100	101–110	111–219			≥220	≤100	>100				
Respiratory rate (per minute)	≤8		9–11	12–20		21–24	≥25		<22	≥22		≤20	>20
Oxygen saturation (%)	≤91	92–93	94–95	≥96									
Supplemental oxygen		Yes		No									
AVPU score				A/15			V,P,U		A	V,P,U			
GCS							<15		15	<15			
WBC (*10⁹/L)											≤4.0	4.0–12.0	>12.0

Variables within the National Early Warning Score, quick Sepsis-related Organ Failure Assessment and Systemic Inflammatory Response Syndrome criteria. Each variable is measured and summed up. a: NEWS ranges from 0 to 20, wherein 1 to 3 points are given for aberrant values in the following variables: body temperature, heart rate, systolic blood pressure, respiratory rate, oxygen saturation, supplemental oxygen and AVPU score. b: qSOFA ranges from 0 to 3, in which 1 point is assigned to abnormal values in the following variables: systolic blood pressure, respiratory rate and AVPU score. c: SIRS ranges from 0 to 4 points, wherein 1 point is allocated to aberrant values in the following variables: body temperature, heart rate, respiratory rate and WBC. The asystemic inflammatory response syndrome;˚C: degrees centigrade; bpm, beats per minute; mmHg: millimetre of mercury; AVPU: alert, verbal, pain, unresponsive; WBC: white blood cell count.

The aim of this study was to determine the prognostic value of qSOFA in predicting mortality in comparison to SIRS and NEWS in patients presenting to the ED with suspected sepsis.

Methods

Study design and setting

This was a retrospective cohort study nested in a large anonymous database of patients visiting the ED of the Erasmus University Medical Center, Rotterdam, the Netherlands (Erasmus MC), which is the largest tertiary referral centre in The Netherlands. The ED is an open access department with approximately 30,000 annual visits. Patients are strongly encouraged to see a general practitioner before visiting the ED. The database of the ED consists of all patients presenting to the ED. This database holds information of patients from January 2012 and onwards, on both clinical and vital parameters, laboratory results, other diagnostic procedures and treatments. The data was extracted from the electronic health records every two weeks through May 2017. Random samples were manually checked for concordance.

Selection of participants

In our consecutive cohort, we included patients with suspected sepsis visiting the ED between June 1st 2012 and May 31st 2016. Suspected sepsis was defined as either the initiation of non-prophylactic intravenous antibiotic therapy during their ED visit or the collection of any culture (i.e. blood cultures, urine cultures, wound cultures, throat swabs, sputum cultures and cultures of cerebrospinal fluid) or viral diagnostics (i.e. polymerase chain reaction (PCR) on blood and stool samples, on throat swabs and on cerebrospinal fluids) during the index visit. Rapid diagnostic testing for viral or bacterial infections was not possible during the study period. Patients who presented with symptoms directly related to trauma were excluded. A comprehensive search in the database identified all patients who met this definition.

Measurements and outcomes

Demographic data (i.e. age, sex), vital parameters (i.e. blood pressure, body temperature, respiratory rate, peripheral oxygen saturation, consciousness level according to AVPU scale or GCS), laboratory testing performed, acuity level according to Manchester Triage System (MTS) category, and supplemental oxygen therapy were derived from the database.

The AVPU scale is a system to score the mental status and is an acronym of 'Alert, Verbal, Pain, Unresponsive'.[314] When AVPU was not scored, GCS was used, and vice versa. Only the first vital parameters were retrieved as the aim of the study was to assess the ability of the different prompts to screen for short-term mortality at ED presentation. White blood

cell count was retrieved for all patients when available. Data on all-cause mortality was obtained from patient records and 10- and 30-day mortality was calculated. Mortality data was retrieved from the patient records, which are linked to municipal mortality data. Subsequently, we assessed whether mortality was directly sepsis-related or not.

We calculated qSOFA, SIRS and NEWS and formed groups using cut-off values most indicative for poor outcome (qSOFA ≥ 2, SIRS ≥ 2, and NEWS ≥ 7) (*Table 1*).[34,305,311] The Medical Ethics Committee of the Erasmus MC reviewed the study and deemed exempt.

Statistical analysis

Data was summarized using mean, median, interquartile range (IQR) and standard deviation (SD) when appropriate. Missing or clinically implausible data was replaced by multiple imputation. This method is valid even when large sets of data are missing.[315] Missing values within the parameters were imputed five times using non-missing parameters. Furthermore, imputation was based on a distribution of the observed data to preclude that implausible values would replace the missing value. After imputation, five complete datasets were available. In each dataset the SIRS, qSOFA and NEWS scores were recalculated using the imputed variables. Whenever possible, results were pooled. When pooling was not possible, single imputation was used. The primary outcome was all-cause mortality within 10- and 30-days after ED presentation.

Patient characteristics were compared using the two-sampled t-test, Mann-Whitney U test, and chi-squared test based on the distribution of the data. Univariate regression analysis was used for association between the different parameters and 10- and 30-day mortality to determine which variable is the best predictor. This predictor is characterized by the largest LRχ^2 and a high explained variance (i.e. R^2 close to one).

Logistic regression was used to obtain the odds for 10- and 30-day mortality based on individual scores. The predictive performances of qSOFA, SIRS, and NEWS were expressed as discrimination (area under the Receiver Operating Characteristic-curve) and calibration. Calibration represents how

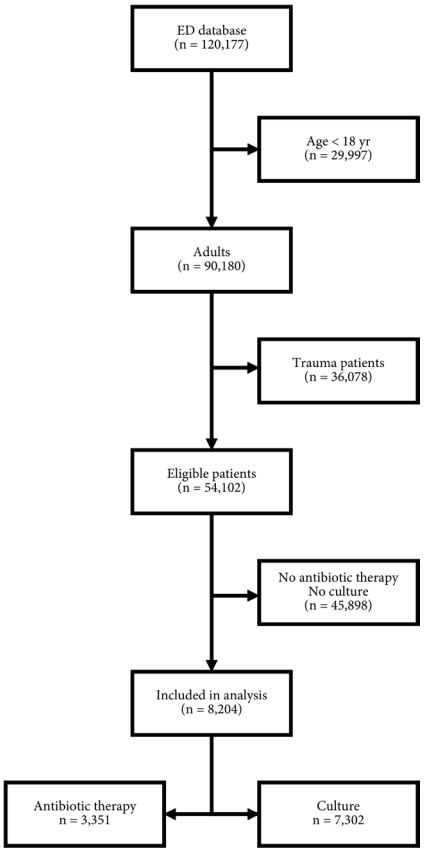


Figure 1. Subject inclusion flowchart.

mortality predictions resemble the observed mortality, which was measured by the Hosmer-Lemeshow goodness-of-fit test and expressed as a χ^2-value and accessory P value. Subsequently, sensitivity, specificity and positive- and negative predictive values were calculated for the different cut-off points. The Youden's J statistic was calculated to assess the optimal cut-off point for the different scores. A P value < 0.05 was considered statistically significant. Analyses were undertaken using Statistical Package for the Social Science (SPSS) version 21 and R statistics version 3.1.3. (2015-03-09).

Results

Patient characteristics

A total of 120,177 ED visits in 75,428 unique patients were recorded between June 1st 2012 and May 31st 2016. 21,326 patient records were excluded as their ED visits were related to trauma, leaving 54,102 patients for analysis. 3,351 patients received intravenous antibiotic therapy in the ED. Bacterial cultures and viral diagnostics were collected from 7,302 patients during their ED visit. In total, 8,204 patients were analysed (*Figure 1*). The majority of patients were male (55.9%), and the median age was 57.0 (IQR 41.0–67.0). In total, 74.6% of patients were hospitalized (*Table 2*). 10-day and 30-day mortality was 3.5% (286) and 6.0% (490), respectively. Of the 490 deceased patients, 64,7% died in the hospital. Patients who died were significantly older, and had higher heart rates, lower systolic blood pressures, lower oxygen saturation and higher respiratory rates during ED presentation. 18,4% of the deceased patients had positive cultures. The cause of death could be retrieved from the patient records in all 490 deceased patients. In 63.4% of patients their death was directly related to sepsis.

Performance of the models

Univariate regression analysis showed that oxygen therapy during ED presentation—a variable within NEWS—was the best predictor for mortality ($LR\chi^2 = 335.73$), although the explained variation was low ($R^2 = 0.110$). Other strong predictors included systolic blood pressure and mental status (*Table 3*).

NEWS performed substantially better than qSOFA and SIRS in predicting both 10-day mortality (AUC [95% CI]: 0.837 [0.812, 0.861], 0.744 [0.708, 0.78] and 0.646 [0.613, 0.679] respectively) and 30-day mortality (0.779 [0.755, 0.804], 0.697 [0.667, 0.726] and 0.631 [0.605, 0.656] respectively) (*Figure 2 and Figure 3*).

Calibration for NEWS showed a $\chi^2 = 10.743$ and p-value = 0.217, compared to $\chi^2 = 6.915$ and p-value = 0.032 for qSOFA, and $\chi^2 = 22.827$ and P value = 0.004 for SIRS. The non-significant P value indicates that the mortality rates between the observed and the predicted values were statistically equivalent.

qSOFA showed the highest specificity, followed by NEWS and SIRS. Sensitivity was highest in SIRS, followed by NEWS and qSOFA. Using Youden's J statistic, the optimal

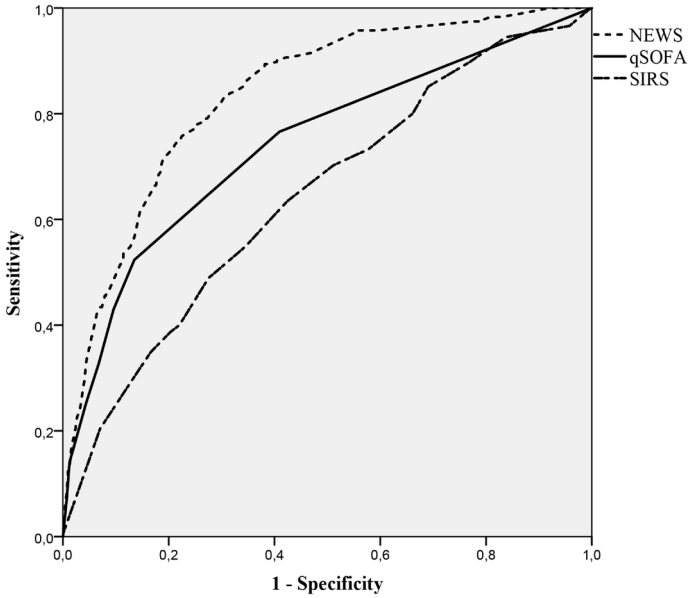


Figure 2. ROC curve 10-day mortality.

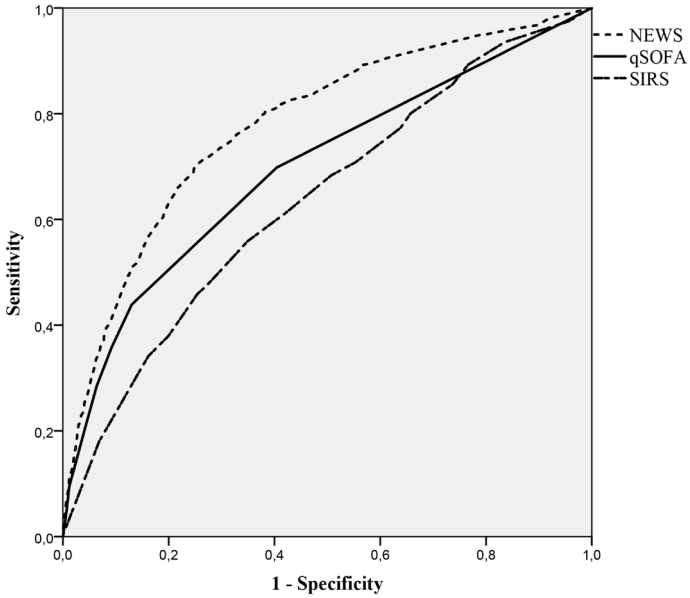


Figure 3. ROC curve 30-day mortality.

Table 2: Patient characteristics

	N (% missing)	All patients	Died < 10 days	Died < 30 days	Alive	P-value
N (%)		8,204	286 (3.5)	490 (6.0)	7,714 (94.0)	
Male, N (%)	8,204 (0)	4,581(55.8)	182 (63.6)	321 (65.5)	4,260 (55.2)	<0.0001[a]
Age, median (IQR)	8,204 (0)	57.0 (41–68)	68.0 (58.75–78)	67.0 (58–77.25)	56.0 (41–67)	<0.0001[b]
Body temperature in ˚C, mean (SD)	7,945 (3.2)	37.6 (1.3)	36.9 (1.7)	37.2 (1.5)	37.7 (1.2)	<0.0001[c]
HR in bpm, mean (SD)	7,858 (4.2)	97.9 (21.4)	103.7 (26.5)	104.9 (26.1)	97.5 (21.0)	<0.0001[c]
SBP in mmHg, mean (SD)	7,764 (5.4)	131.7 (26.1)	119.6 (36.2)	121.3 (34.0)	132.3 (25.4)	<0.0001[c]
RR per minute, mean (SD)	4,796 (41.5)	21.3 (8.5)	25.0 (9.1)	24.5 (9.1)	21.0 (8.3)	<0.0001[c]
Oxygen saturation in %, mean (SD)	7,578 (7.6)	96.0 (3.6)	93.9 (5.9)	93.9 (5.6)	96.2 (3.4)	<0.0001[c]
AVPU, N (%)	6,643 (19.0)					<0.0001[d]
Alert		6,104 (91.9)	152 (64.7)	291 (72.6)	5,813 (93.1)	
Verbal		385 (5.8)	39 (16.6)	57 (14.2)	328 (5.3)	
Pain		69 (1.0)	12 (5.1)	16 (4.0)	53 (0.8)	
Unresponsive		85 (1.3)	32 (13.6)	37 (9.2)	48 (0.8)	
Supplemental oxygen, N (%)	8,204 (0)	2,472 (30.1)	223 (78.0)	338 (69.0)	2,134 (27.7)	<0.0001[a]
Laboratory testing performed, N (%)	8,204 (0)	6,980 (86.9)	251 (87.8)	437 (89.2)	6,690 (86.7)	0.118[a]
WBC in $*10^9$/L, mean (SD)	7,036 (14.2)	11.8(12.9)	17.0 (30.7)	15.4 (24.2)	11.6 (11.6)	<0.0001[c]
SIRS≥2, N (%)	4,387 (46.5)	2,940 (67.0)	178 (62.2)	298 (78.6)	2,642 (65.9)	<0.0001[a]
qSOFA≥2, N (%)	4,318 (47.4)	369 (4.5)	59 (20.6)	87 (17.8)	282 (7.0)	<0.0001[a]
NEWS≥7, N (%)	4,243 (48.3)	1,895 (44.7)	135 (77.1)	212 (70.0)	1,683 (42.7)	<0.0001[a]
MTS, N (%)	7,786 (5.1)					<0.0001[d]
Immediate		168 (2.2)	47 (18.2)	53 (11.8)	115 (1.6)	
Very urgent		1,002 (12.9)	87 (33.7)	148 (32.9)	854 (11.6)	
Urgent		5,451 (70.0)	115 (44.6)	230 (51.1)	5,221 (71.2)	
Standard		1,144 (14.7)	9 (3.5)	19 (4.2)	1,125 (15.3)	
Non urgent		16 (0.2)	0 (0.0)	0 (0.0)	16 (0.2)	
Admission, N (%)	8,204 (0)	6,117 (74.6)	273 (95.5)	455 (92.9)	5,662 (73.4)	<0.0001[a]

Patient characteristics. Abbreviations: N: number; SBP: systolic blood pressure; RR: respiratory rate; HR: heart rate; AVPU: Alert, Verbal, Pain, Unresponsive); WBC white blood cell count; SIRS: systemic inflammatory response syndrome; qSOFA: quick sepsis-related organ failure assessment; NEWS: national early warning score; MTS: Manchester Triage System; IQR: interquartile range (25–75 percentile); SD: standard deviation; bpm: beats per minute; mmHg: millimetres of mercury; L: litre;˚C: degrees centigrade. a: Chi-squared test b: median test c: independent samples t-test d: Mann-Whitney U test.

Table 3: Univariate regression on the outcome 30-day mortality

		$LR\chi^2$	R^2
SIRS	Body temperature	0.51	0.000
	Heart rate	24.05	0.008
	Respiratory rate	28.13	0.013
	WBC	60.50	0.022
qSOFA	Respiratory rate	22.50	0.010
	Systolic blood pressure	133.49	0.045
	AVPU	142.03	0.060
NEWS	Oxygen therapy	335.73	0.110
	Oxygen saturation	44.54	0.016
	Respiratory rate	30.32	0.014
	Body temperature	17.13	0.006
	Systolic blood pressure	103.87	0.035
	Heart rate	43.04	0.015
	AVPU	144.17	0.059

30-day mortality univariate regression. The best parameter in the univariate model has the highest likelihood function ($LR\chi^2$). R^2 is the proportion of the variance in outcome 30-day mortality explained by the univariate model.

cut-off points for 10-day mortality were qSOFA ≥ 1, SIRS ≥ 2 and NEWS ≥ 7, and for 30-day qSOFA ≥ 1, SIRS ≥ 3 and NEWS ≥ 7 (*Table 4*).

Discussion

In this retrospective observational study of patients visiting the ED with a suspected sepsis we found that NEWS was superior to qSOFA and SIRS in predicting 10- and 30-day mortality for both discrimination and calibration. The different prompts all have different sensitivities and specificities for mortality. qSOFA has the highest specificity and lowest sensitivity, SIRS has the lowest specificity and highest sensitivity. NEWS has both an intermediate sensitivity and specificity, but is the best overall predictor in distinguishing high risk from low risk patients. NEWS has a lower sensitivity resulting in a significant number of false negatives, i.e. not all the patients who eventually died were identified with NEWS. NEWS was the only model with a good agreement between the expected and observed outcomes, i.e. calibration. However, none of the prediction models succeeded to fulfil all performance assessments, which would ideally be the case. Subsequent measurements of NEWS (e.g. hourly) will potentially identify patients who deteriorate during the stay in the ED and may improve sensitivity. We conclude that at presentation to the ED NEWS can be used as an alternative screening tool for patients with suspected sepsis who are at risk for deterioration, multi-organ failure, and subsequently death.

Our findings support the increasing data that suggests that the NEWS score is a useful screening tool in the ED, although its use has not fully been validated in the ED setting. Jo *et al*. studied the NEWS combined with serum lactate in predicting mortality in the general adult ED population and found an excellent discrimination (AUC = 0.96) for predicting two-day mortality.[316] The NEWS score as measured in the prehospital setting showed good correlation ($P < 0.001$) with hospital disposition.[317] Our study confirms the findings by Churpek *et al*. which support the introduction of the NEWS score in the ED.[318] However, they studied patients outside the ICU and not only ED patients. And they primarily measured the performance of the different prompts based on the worst vital signs. NEWS had the highest performance in predicting in-hospital mortality in ED patients compared to qSOFA and SIRS (AUC = 0.77, AUC = 0.69 and AUC = 0.65 respectively). We used vital parameters at presentation in the ED and found similar results. In the Churpek *et al*. study a NEWS threshold of ≥ 7 is suggested.[318] This threshold is also recommended by the Royal College of Physicians.[311] We were able to confirm this threshold using our data. In a cohort study by Sbiti-Rohr *et al*. in patients with community-acquired pneumonia, the NEWS score in the ED was significantly higher for those who died within 30 days after presentation than for survivors.[319] These results are similar to a study of patients presenting to the ED with acute dyspnoea; survivors had significantly lower NEWS scores at ED presentation.[320]

The NEWS was also studied in patients suspected of sepsis. Corfield *et al*. found that an increased NEWS on arrival at the ED was associated with mortality in patients who met the sepsis criteria as defined by Bone *et al*. (odds ratio 1.95 to 5.64).[321]

Most prediction scores include measurements which are subject to interpretation. A study on the interrater agreement of GCS assessed at the ED yielded low agreement.[322] Semler *et al*. showed that in hospitalized patients recorded respiratory rates were higher than directly observed measurements. Also, the recorded rates were more likely to be 18 or 20 breaths/minute.[68] We expect that parameters that are not acquired automatically are subject to confounding by disease severity and were more likely to be measured and noted when one would expect a deviant result.[323,324] Therefore, for the proper use of the NEWS, qSOFA and SIRS these measurements should be routinely performed in a structural way.

Specific scoring systems are used as an alternative to the NEWS to predict sepsis-related mortality in ED patients. The SIRS criteria, as introduced by Bone in 1992, were studied as a prediction tool for mortality and most studies show that an increase in SIRS items reflects an increased risk of mortality, ranging from 1.4% to 12% when no SIRS criteria were met and increasing to approximately 36% for four SIRS items.[325,326] In Sepsis-3, the qSOFA was introduced as a simple tool to detect deterioration and predict mortality in departments outside the ICU. Simultaneously, SIRS criteria were abandoned from the new sepsis definition after criticism of its low specificity. The qSOFA≥ 2 resembles a three to 14-fold increase in mortality risk.[305]

qSOFA has been challenged as a prompt in the ED to identify patients with an increased risk for sepsis-related mortality ever since its introduction. Despite a high specificity (84–96%), the qSOFA has low sensitivity (13–53%).[308,327] This low sensitivity can be explained by the fact that the qSOFA is composed of vital parameters representing late symptoms of deterioration (e.g. altered mental status due to inadequate perfusion of the brain).[49,328] In addition, qSOFA was derived in a cohort of critically ill patients, in which 11% of the patients were admitted in the ICU.[305] These patients represent a selected population compared to all patients who visit the ED, therefore, selection bias may be present. Furthermore, qSOFA was developed on the most aberrant results in serial vital parameter measurements. This approach may ameliorate the ability to predict mortality, but it restricts the utility as a prompt for early identification of patients at risk directly at ED presentation. All these arguments mainly affect the sensitivity and can influence the predictive performance of qSOFA. To increase sensitivity, Park *et al*. proposed the use of the qSOFA cut-off point of ≥ 1 instead of 2 for patients in the ED, resulting in an increase in sensitivity from 53.0% to 82.0%. This is in line with our findings. Changing the cut-off to 1 would increase the usability of qSOFA as a screening tool at cost of specificity. However, NEWS still has a higher sensitivity and a better predictive performance.

Strengths and limitations

This study has a number of strengths and limitations. The major strength of our study is that we used a large consecutive dataset with many relevant parameters directly derived from electronic patient records with mortality data directly acquired from municipality data.

Our study also has several limitations. The first limitation of this study is its retrospective design using data from a single tertiary care centre. In our centre we treat many patients with congenital and acquired immunodeficiencies (e.g. patients with organ or bone marrow transplantation, chemotherapy), which may limit the generalizability. The database contained missing values, which were replaced by multiple imputation. Multiple imputation has also been used in other sepsis-related studies.[305,308,329] Respiratory rate was most frequently missing and, as mentioned earlier, availability of respiratory rate might be an indicator of confounding by indication, as it is more often measured in patients who are deemed more critically ill.[323]

A second limitation is the definition of the study population. As there is no gold standard for defining an infection, the study population was difficult to determine. We based our inclusion criteria on the definition of Seymour *et al*.[305] but modified the criteria to incorporate the largest group of patients who were suspected for infection and at risk for sepsis. Both microbial diagnostics and initiation of antibiotics were used as a proxy for a clinically suspected sepsis. These inclusion criteria could possibly bias against people with viral disease, as no antibiotics given and cultures are not routinely performed. However, in the most critically ill patients cultures are taken and antibiotics are started empirically in clinical practice, regardless of the suspected pathogen (e.g. virus, bacteria). Furthermore, we also included viral cultures such as throat swabs and stool cultures, but

these were a minority as compared to blood cultures (289 and 46 vs. 6,552). Therefore, the chance of bias due viral sepsis is limited.

Last, to determine the best screening tool at presentation in the ED, we chose to use only the first recorded vital signs for calculation of NEWS, qSOFA and SIRS. We are aware that rapid changes in vital parameters could be indicative for a higher risk for mortality and that people may deteriorate during their ED visit. However, the duration of ED stay is intended to be very limited. Choosing to only use the first vital parameters may limit the predictive ability of the different models. However, in clinical practice the first vital parameters are used to determine the severity of the patient's condition and, therefore, to triage patients in urgent and non-urgent. Using first available parameters in this study actually reflects clinical practice and in our opinion is a valid method to test predictive performance upon ED presentation, with results comparable to using the worst vital parameters.[318]

Conclusions

In conclusion, the NEWS is more accurate in predicting 10- and 30-day mortality than qSOFA and SIRS in patients suspected of sepsis on initial presentation to the ED. Our finding suggests that the introduction of the NEWS in the ED with subsequent measurements should be further studied. This will potentially aid the early detection of all patients at risk for deterioration in the ED including those at risk of sepsis-related mortality.

Supporting information

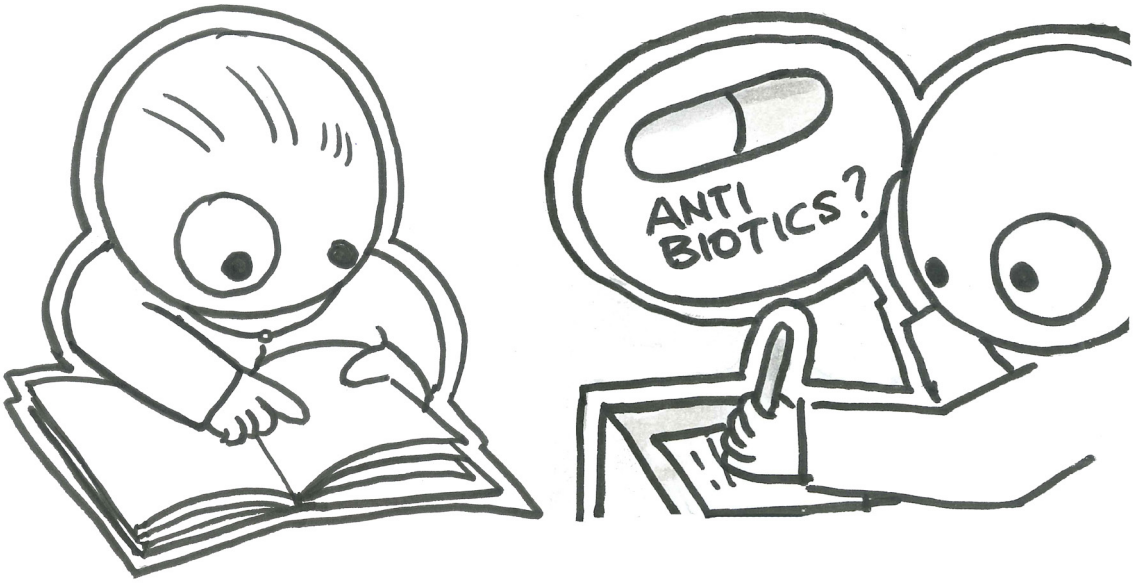
Supporting Table 1: Sensitivity (95% CI), specificity (95% CI), positive predictive value, negative predictive value and Youden's index for different cut-off values for 10- and 30-day mortality.

10-day mortality	Sensitivity [95% CI] [%]	Specificity [95% CI] [%]	PPV [%]	NPV [%]	Youden's index
SIRS					
≥1	98.0 [95.5-99.2]	12.2 [11.5-12.9]	3.9	99.4	0.102
≥2‖	80.4 [75.3-84.9]	37.3 [36.2-38.4]	4.4	98.1	0.177¶
≥3	50.4 [44.4-56.3]	67.0 [66.0-68.0]	5.2	97.3	0.174
4	15.0 [11.1-19.7]	90.8 [90.2-91.4]	5.5	96.7	0.058
qSOFA					
≥1	77.2 [72.0-82.0]	59.1 [58.0-60.2]	6.5	98.6	0.362¶
≥2‖	33.1 [27.8-39.0]	93.3 [92.7-93.8]	15.3	97.4	0.264
3	7.8 [4.9-11.4]	99.3[99.1-99.5]	28.2	96.7	0.071
NEWS					
≥3	98.3 [96.0-99.4]	17.8 [17.0-18.7]	4.2	99.7	0.161
≥4	94.5 [91.1-96.8]	26.0 [25.0-27.0]	4.5	99.2	0.205
≥5	89.1 [85.0-92.5]	42.1 [41.0-43.2]	5.3	99.1	0.312
≥6	82.1 [77.2-86.4]	57.0 [56.0-58.1]	6.5	98.9	0.391
≥7‖	76.3 [70.9-81.0]	65.9 [64.8-66.9]	7.6	98.7	0.421¶
≥8	59.6 [53.5-65.2]	77.1 [76.2-78.0]	8.7	98.1	0.367
≥9	45.8 [40.0-51.8]	84.0 [83.2-84.8]	9.5	97.7	0.298
≥10	35.1 [29.4-40.8]	89.4 [88.7-90.1]	10.8	97.4	0.245
≥11	22.8 [18.0-28.0]	94.5 [94.0-95.0]	13.2	97.1	0.173
≥12	9.4 [6.3-13.4]	98.3 [98.0-98.6]	17.3	96.7	0.078
≥13	9.4 [6.3-13.4]	98.3 [98.0-98.6]	17.3	96.7	0.078
≥14	4.2 [2.2-7.2]	99.3 [99.1-99.5]	17.9	96.6	0.035
≥15	1.2 [0.2-3.0]	99.7 [99.6-99.8]	14.1	96.5	0.009
≥16	0.3 [0.0-1.9]	99.9 [99.8-100.0]	15.4	96.5	0.003

30-day mortality	Sensitivity [95% CI] [%]	Specificity [95% CI] [%]	PPV [%]	NPV [%]	Youden's index
SIRS					
≥1	96.3 [94.3-97.8]	12.4 [11.7-13.2]	6.5	98.1	0.087
≥2‖	77.2 [73.2-80.8]	37.6 [36.5-38.7]	7.3	96.3	0.148
≥3	48.1 [43.7-52.7]	67.3 [66.2-68.4]	8.5	95.3	0.154¶
4	14.9 [11.9-18.4]	90.9 [90.2-91.5]	9.4	94.4	0.058
qSOFA					
≥1	69.9 [65.7–74.0]	59.5 [58.0-60.2]	10.0	96.9	0.294¶
≥2‖	28.5 [24.6-32.8]	93.7 [92.7-93.8]	22.6	95.3	0.222
3	5.5 [3.7-7.9]	99.3 [99.1-99.5]	34.0	94.2	0.048
NEWS					
≥3	95.6 [93.3-97.1]	18.1 [17.2-19.0]	7.0	98.5	0.137
≥4	90.6 [87.7-93.0]	26.3 [25.3-27.3]	7.3	97.8	0.169
≥5	83.0 [79.4-86.3]	42.5 [41.4-43.6]	8.5	97.5	0.255
≥6	75.5 [71.4-79.3]	57.6 [56.5-58.7]	10.2	97.3	0.33
≥7‖	68.0 [63.6-72.1]	66.5 [65.4-67.6]	11.5	97.0	0.345¶
≥8	55.0 [50.6-59.6]	77.8 [76.8-78.7]	13.7	96.4	0.328
≥9	42.0 [37.6-46.5]	84.5 [83.7-85.3]	14.9	95.8	0.266
≥10	31.3 [27.1-35.5]	89.8 [89.1-90.5]	16.5	95.3	0.211
≥11	20.9 [17.3-24.7]	94.8 [94.3-95.3]	20.7	94.9	0.158
≥12	14.7 [11.7-18.1]	96.8 [96.4-97.2]	22.6	94.6	0.114
≥13	8.1 [5.9-11.0]	98.5 [98.2-98.8]	25.3	94.3	0.066
≥14	3.9 [2.4-6.0]	99.4 [99.2-99.6]	28.5	94.1	0.033
≥15	1.0 [0.3-2.4]	99.7 [99.6-99.8]	20.0	94.0	0.007
≥16	0.4 [0.1-1.5]	99.9 [99.8-100.0]	11.3	94.1	0.004

Sensitivity (95% CI), specificity (95% CI), positive predictive value, negative predictive value and Youden's index for different cut-off values for 10- and 30-day mortality. ‖ are the predefined cut-off values which are most indicative for a poor outcome. ¶ representing the optimal cut-off points. Abbreviations: CI: confidence interval; PPV: positive predictive value; NPV: negative predictive value; SIRS: systemic inflammatory response syndrome; qSOFA: quick sepsis-related organ failure assessment; NEWS: national early warning score.

Predictors of Antibiotic Susceptibility



Chapter 11

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Euro Surveill. 2015; 20(47):pii=30074.

International Travel and Acquisition of Multidrug Resistant *Enterobacteriaceae:* a Systematic Review

Abstract

International travel is considered to be an important risk factor for acquisition of multidrug-resistant *Enterobacteriaceae* (MRE). The aim of this systematic review was to determine the effect of international travel on the risk of post-travel faecal carriage of MRE. Secondary outcomes were risk factors for acquisition of MRE. A systematic search for relevant literature in seven international databases was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Articles needed to report on 1) foreign travel, 2) screening of asymptomatic participants, 3) antimicrobial susceptibility data and 4) faecal *Enterobacteriaceae* carriage. Two researchers independently screened the abstracts, assessed the full article texts for eligibility and selected or rejected them for inclusion in the systematic review. In case of disagreement, a third researcher decided on inclusion. Eleven studies were identified. In all studies, a high prevalence (> 20%) of carriage of MRE after international travel was found. The highest prevalence was observed in travellers returning from southern Asia. Foreign travel was associated with an increased risk of carriage of MRE. Further research is needed to assess if this leads to an increase in the number of infections with MRE. Systematic review registration number: PROSPERO CRD42015024973.

Introduction

Rationale

Worldwide, the number of international travellers has grown from 25 million in 1950 to 1,087 million in 2013.[330] According to the World Tourism Organization, this number is expected to increase by an average of 3.3% a year.[330] Of the international travellers visiting developing countries, 22–64% have self-reported health problems and about 8% require medical care during or after travel.[331,332] Healthy travellers may be exposed to a broad range of microorganisms while travelling, including drug-resistant *Enterobacteriaceae*, which may subsequently be introduced into their home country.[333,334]

Enterobacteriaceae are Gram-negative bacteria that are part of the human body's normal commensal flora, called microbiota. *Enterobacteriaceae*, such as *Escherichia coli* and *Klebsiella* species, are capable of causing both healthcare-associated and community-acquired infections.[335] Multidrug-resistant *Enterobacteriaceae* (MRE), including extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae* (ESBL-E) and plasmid-mediated Amp C-producing *Enterobacteriaceae* (pAmp C-E) are emerging worldwide.[336] Cases of carbapenemase-producing Enterobacteriaceae (CPE) are also reported more frequently.[337]

Since 2003, community carriage rates of MRE have increased dramatically in various regions, such as South-East Asia, the Western Pacific and the Eastern Mediterranean.[336] During visits to such areas, travellers might acquire MRE and become asymptomatic carriers of MRE. In their home country, they may cause spread in the community and contribute to worldwide emerging antimicrobial resistance.[335,338,339] Acquired MRE in the digestive tract are considered apathogenic, however carriage of such *Enterobacteriaceae* have resulted in clinically relevant infections.[337] International travel has been reported as a risk factor for urinary tract infections caused by ESBL-E.[340,341] The question arises if these observations warrant clinicians being aware of MRE in recently returned otherwise healthy, international travellers who seek medical attention even for unrelated conditions.

Objectives

The aim of this systematic review was to determine the effect of international travel on the risk of acquisition of faecal carriage of MRE. A secondary objective was to determine risk factors for acquisition of drug resistance.

Methods

Protocol and registration

A specific protocol was designed and used to conduct the study. The study is registered

Embase.com ('Gram negative bacterium'/exp OR 'Gram negative infection'/de OR Enterobacteriaceae/de OR Escherichia/exp OR Klebsiella/exp OR Salmonella/exp OR Shigella/exp OR Yersinia/exp OR 'Enterobacteriaceae infection'/exp OR ('Gram negative' OR Enterobacteri* OR (Enter* NEXT/1 bacteria*) OR Enterobacter* OR Escherichia* OR 'e coli' OR Klebsiella* OR Salmonell* OR Shigell* OR Yersinia*):ab,ti) AND (travel/de OR 'traveller diarrhoea'/de OR aviation/exp OR (travel* OR touris* OR turista OR aviation OR 'air transport' OR airport*):ab,ti) AND ('antibiotic resistance'/exp OR 'multidrug resistance'/de OR 'drug resistance'/de OR 'antibiotic sensitivity'/de OR 'bacterial colonization'/exp OR 'bacterium carrier'/de OR (resistan* OR coloni* OR ((antibiotic* OR antimicrob*) NEAR/3 sensitivit*) OR susceptib* OR carriage* OR carrier*):ab,ti) NOT ([animals]/lim NOT [humans]/lim)
MEDLINE (OvidSP) (exp "Gram-Negative Bacteria"/ OR exp "Gram-Negative Bacterial Infections"/ OR Enterobacteriaceae/ OR exp Escherichia/ OR exp Klebsiella/ OR exp Salmonella/ OR exp Shigella/ OR exp Yersinia/ OR exp "Enterobacteriaceae infections"/ OR ("Gram negative" OR Enterobacteri* OR (Enter* ADJ bacteria*) OR Enterobacter* OR Escherichia* OR "e coli" OR Klebsiella* OR Salmonell* OR Shigell* OR Yersinia*).ab,ti.) AND (travel/ OR "Travel Medicine"/ OR exp aviation/ OR (travel* OR touris* OR turista OR aviation OR "air transport" OR airport*).ab,ti.) AND (exp "Drug Resistance, Microbial"/ OR exp "Drug Resistance, Multiple"/ OR "drug resistance"/ OR "bacterium carrier"/ OR (resistan* OR coloni* OR ((antibiotic* OR antimicrob*) ADJ3 sensitivit*) OR susceptib* OR carriage* OR carrier*).ab,ti.) NOT (exp animals/ NOT humans/)
Cochrane Library (('Gram negative' OR Enterobacteri* OR (Enter* NEXT/1 bacteria*) OR Enterobacter* OR Escherichia* OR 'e coli' OR Klebsiella* OR Salmonell* OR Shigell* OR Yersinia*):ab,ti) AND ((travel* OR touris* OR turista OR aviation OR 'air transport' OR airport*):ab,ti) AND ((resistan* OR coloni* OR ((antibiotic* OR antimicrob*) NEAR/3 sensitivit*) OR susceptib* OR carriage* OR carrier*):ab,ti)
Web of Science TS = (((("Gram negative" OR Enterobacteri* OR (Enter* NEAR/1 bacteria*) OR Enterobacter* OR Escherichia* OR "e coli" OR Klebsiella* OR Salmonell* OR Shigell* OR Yersinia*)) AND ((travel* OR touris* OR turista OR aviation OR "air transport" OR airport*)) AND ((resistan* OR coloni* OR ((antibiotic* OR antimicrob*) NEAR/3 sensitivit*) OR susceptib* OR carriage* OR carrier*)))
Scopus TITLE-ABS-KEY((("Gram negative" OR Enterobacteri* OR (Enter* W/1 bacteria*) OR Enterobacter* OR Escherichia* OR "e coli" OR Klebsiella* OR Salmonell* OR Shigell* OR Yersinia*)) AND ((travel* OR touris* OR turista OR aviation OR "air transport" OR airport*)) AND ((resistan* OR coloni* OR ((antibiotic* OR antimicrob*) W/3 sensitivit*) OR susceptib* OR carriage* OR carrier*)))
PubMed ((Gram negative[tiab] OR Enterobacteri*[tiab] OR Entero bacteria*[tiab] OR Enteric bacteria*[tiab] OR Enterobacter*[tiab] OR Escherichia*[tiab] OR e coli[tiab] OR Klebsiella*[tiab] OR Salmonell*[tiab] OR Shigell*[tiab] OR Yersinia*[tiab])) AND ((travel*[tiab] OR touris*[tiab] OR turista[tiab] OR aviation[tiab] OR air transport*[tiab] OR airport*[tiab])) AND ((resistan*[tiab] OR coloni*[tiab] OR ((antibiotic*[tiab] OR antimicrob*[tiab]) AND sensitivit*[tiab]) OR susceptib*[tiab] OR carriage*[tiab] OR carrier*[tiab])) AND publisher[sb]
Google Scholar "Gram negative"|Enterobacteriaceae|Escherichia|Klebsiella|Salmonella|Shigella|Yersinia travel|traveller|tourist|tourism|resistance|resistant|colonization|colonisation|susceptibility|carriage |carrier
Box: Search strategy for systematic review of the acquisition of multidrug-resistant Enterobacteriaceae in international travel

in the international prospective register of systematic reviews (PROSPERO) under registration number CRD42015024973.

Search strategy and selection criteria

The systematic review was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[342] The following databases were searched, attempting to identify all relevant studies: Embase, MEDLINE, Web of Science, Scopus, Cochrane Library, PubMed and Google Scholar. The latest search was conducted on 17 August 2015.

The topic search terms used for searching the databases were 'Gram negative bacteria', 'Gram negative bacterial infections', 'Enterobacteriaceae', 'Escherichia', 'Klebsiella', 'Campylobacter', 'Salmonella', 'Shigella', 'Yersinia', 'travel', 'traveller', 'tourist', 'tourism', 'turista', 'aviation', 'air transport', 'airport', 'colonisation', 'carriage', 'carrier', 'susceptibility' and '(multiple) drug resistance'.

The queries differed per database searched and were developed with help of a biomedical information specialist (Box). Articles written in English, German, French and Dutch were included.

For inclusion the article needed to fulfil the following criteria: 1) It needed to be related to foreign travel 2) report on screening in asymptomatic participants 3) present antimicrobial susceptibility data and 4) report on faecal *Enterobacteriaceae* carriage. We used the following exclusion criteria: case reports, reviews, meta-analyses, veterinary medicine, in vitro studies and studies regarding symptomatic patients. The reference lists of reviews were screened to identify studies possibly missed by the search.

Two researchers (R.H. and J.A.) independently performed the screening of the abstracts. Any discordant result was discussed in consensus meetings. After screening the abstracts, the full text of the articles was assessed for eligibility by the same two researchers and selected or rejected for inclusion in the systematic review. In case of disagreement a third researcher (A.V.) decided on inclusion.

Data collection process

The following data (if available) were extracted from each article: year of publication, country of the study, study period, study design, microorganism studied, study population, study size, age, sex, sample time before and after travel, duration of travel, travelling in pairs or groups, symptoms during travel, countries visited, MRE prevalence before travel, MRE prevalence after travel, MRE resistance acquired during travel, resistance to other antibiotic drugs of acquired MRE, risk factors for acquisition (among which travel to predefined United Nations geographical regions: southern Asia, Asia except southern Asia, Africa, South and Central America, North America, Europe and Oceania,[343] method of MRE susceptibility determination, phenotypic approaches,

genotypic characterization of post-travel MRE isolates, molecular typing of post-travel MRE isolates, duration of MRE colonization and MRE transmission to household contacts. To obtain missing data, authors of the articles were contacted.

Quality assessment

We assessed the methodological quality and the risk of bias in individual studies that may affect the cumulative evidence, using tools for assessing quality and susceptibility to bias in observational studies as recommended in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement.[344,345]

Data synthesis and analysis

As a result of the design of the studies (cohort studies) and the heterogeneity in patient populations (e.g. travellers, healthcare workers and healthcare students), a formal meta-analysis was not possible. Therefore, the study results were summarized to describe the main outcomes of interest. The principle summary measure was percentage of MRE acquisition during travel, defined as ESBL-E or pAmp C-E. Furthermore, risk factors for acquisition of drug resistance were assessed. If possible, percentages not presented in the articles were calculated from the available data.

Results

Study selection

A total of 2,398 studies were identified through database searching after duplicates had been removed (*Figure 1*). After screening of titles and summaries, 36 articles were selected for full-text assessment. Eleven articles were included in the qualitative synthesis of the systematic review (see *Figure 1* for reasons for exclusion).[346-356]

Study characteristics

Eleven prospective cohort studies, conducted in Northern and Western Europe, Australia and the United States (US) were included.[346-356] The characteristics of these studies are shown in *Table 1*. Nine studies investigated travellers visiting a travel or vaccination clinic, one study hospital staff and contacts, and one study healthcare students working or studying abroad. The number of study participants ranged from 28 to 574. The median age of travellers in the individual studies varied between 25 and 66 years, with the youngest group being healthcare students. In all studies, the majority of travellers were female (range: 55–78%). The proportion of participants who were lost to follow up varied from 3.8% (4/106) [18] to 30% (12/40).[350] The mean duration of travel was similar in all studies (14–21 days). In the study by Angelin *et al*. on healthcare students, median length of stay was 45 days (range: 13–365 days).[351] In four studies, follow-up samples of MRE carriers were collected at six months after returning from travel, and in one of these

studies, samples were collected monthly in the first three months with further follow-up until 12 months after return.[354] Ten studies used a phenotypic method for susceptibility testing, with genotypic confirmation of ESBL positivity by PCR. [346-351,353-356] One study used a PCR-based approach.[352] In one study, only isolated *E. coli* were included, whereas the other studies included all isolated *Enterobacteriaceae*, which mainly consisted of *E. coli*. [346-356]

Acquisition of multidrug-resistant Enterobacteriaceae

Faucal carriage of MRE varied from 1 to 12% before travel and acquisition of MRE from 21% to 51% (*Table 2*). [346-350,352-356] In the study by Kuenzli *et al*. on travellers to the Indian subcontinent only, a much higher MRE acquisition rate of 69% was demonstrated.[355]

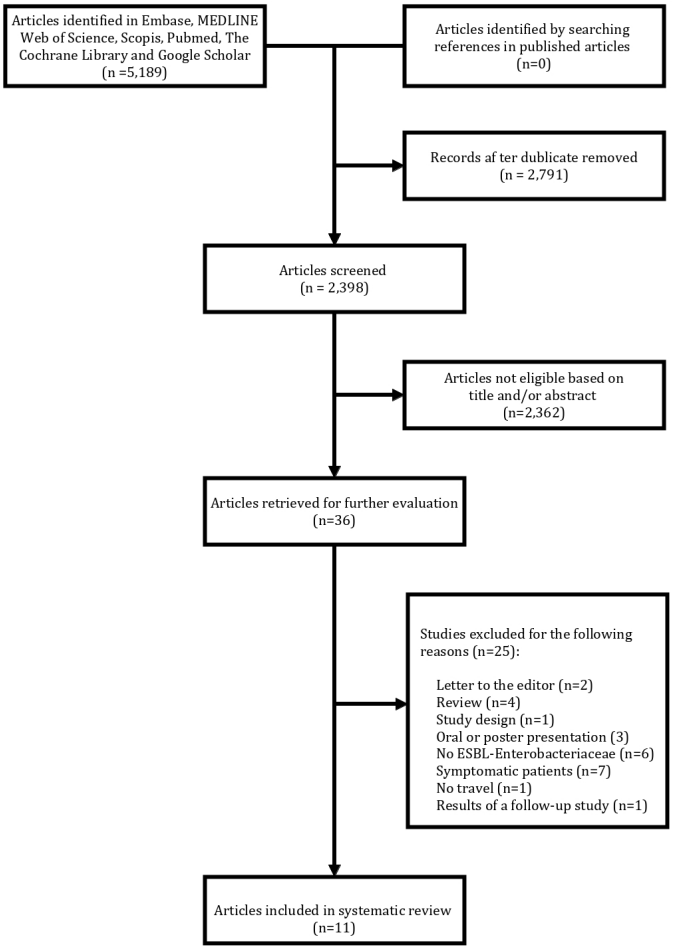

Figure 1: Flowchart for literature search on the acquisition of multidrug-resistant Enterobacteriaceae in international travel. *ESBL: extended-spectrum beta-lactamase.*

Table 1: Characteristics of prospective cohort studies included for systematic review of the acquisition of multidrug-resistant *Enterobacteriaceae* in international travel (n = 11)

Study	Country	Study period	Population characteristics	Study size[a]	Median age in years (range or SD)	Women (%)	Identification of MRE-positive organisms in post-travel isolates	Sample method used	Sample time (range) before/after travel	Mean duration of travel in days (range)	Total number of co-travellers participating in study	Follow-up of resistant isolates
Tängdén[346]	Sweden	November 2007 January 2009	Travel clinic	100	43 (2–84)	55	*Enterobacteriaceae* 100% (24/24) *E.coli*	Stool	Unknown	14 (1–26)	23	6 months
Kennedy[347]	Australia	January 2008 April 2009	Hospital staff and contacts	102	45 (17–77)	62	*E.coli*	Rectal or perianal swab	Within 2 weeks before and after	21 (9–135)	Unknown	6 months
Östholm-Balkhed[348]	Sweden	September 2008 April 2009	Vaccination clinic	231	54 (18–76)	59	*Enterobacteriaceae* 90% (104/116) *E.coli*[b]	Stool sample	15 (1–114) days/3 (0–191) days	16 (4–119)	Unknown	None
Kantele[349]	Finland	March 2009 February 2010	Travel clinic	430	40 (0–77)	61	*Enterobacteriaceae* 97% (94/97) *E. coli*[b]	Stool sample	Before and first (or second) stool after	19 (4–133)	83	None
Weisen-berg[350]	US	July 2009 February 2010	Travel clinic	28	66 (41–83)	68	*Enterobacteriaceae* 100% (7/7) *E. coli*[b]	Stool sample	1 week before / 1 week after	16 (8–24)	Unknown	None
Angelin[351]	Sweden	April 2010 January 2014	Healthcare students	99	25 (15–20)	78	*Enterobacteriaceae* 100% (36/36) *E. coli*[c]	Stool sample	Close to de-parture/ 1 to 2 weeks after returning	45[d] (13–365)	Unknown	None
von Winters-dorff[352]	NL	November 2010 August 2012	Travel clinic	122	43 (18–72)	58	Not done	Stool sample	Before and immediately after	21 (5–240)	Unknown	None

Paltansing[353]	NL	March 2011 September 2011	Travel clinic	370	33 (19–82)	63	*Enterobacteriaceae* 92% (146/158) *E. coli*[c]	Rectal swab	Immediately before and after	21 (6–90)	None	6 months
Ruppé[354]	France	February 2012 April 2013	Vaccination centres	574	36 (SD 13)	61	*Enterobacteriaceae* 93% (491/526) *E. coli*[b]	Stool sample	Within 1 week before and after	20 (15–30)	None	12 months
Kuenzli[355]	Switzerland	December 2012 October 2013	Travel clinic	170	41 (30–53)	56	*Enterobacteriaceae* 98% (157/161) *E. coli*[b]	Rectal swab	1 week before/ directly after	18 (5–35)	Unknown	None
Lübbert[356]	Germany	May 2013 April 2014	Travel clinic	205	34 (3–76)	57	*Enterobacteriaceae* 92% (58/63) *E. coli*[b]	Stool sample	Before/ within 1 week after	21 (3–218)	22	6 months

E.coli: Escherichia coli; MRE: multidrug-resistant Enterobacteriaceae; SD: standard deviation. NL: the Netherlands; US: United States of America a: Number of travellers who provided pre- and post-travel swab. b: Data of MRE-positive isolates newly acquired during travel. c: Data of MRE-positive isolates post-travel. d: Healthcare students, median duration of stay.

Table 2: Risk of multidrug-resistant Enterobacteriaceae in travellers (n = 11 studies)

Study	Method of MRE determination	Phenotypic approaches	Results genotypic characterization post- travel MRE isolates	Results molecular typing of post-travel MRE isolates	MRE prevalence pre-travel% *(ratio)*	MRE prevalence post-travel *% (ratio)*	New MRE acquisition during travel *% (ratio)*[a]	Persistent newly acquired MRE carriage 6 months after travel *% (ratio)*	Results univariate /multivariate risk factor analysis for MRE acquisition	MRE in non-travelling household contacts *% (ratio)*
Tängdén[346]	Phenotypic approach with genotypic confirmation by PCR	Enrichment broth, selective media AST: Etes, MRE confirmation: disc diffusion	TEM (n = 11), SHV (n = 3), CTX-M group1 (n = 14) of which CTX-M-15 (n = 13), CTX-M-1 (n=1), CTX-M group 4 (n = 10) of which CTX-M-9 (n = 3), CTX-M-14 (n = 5), CTX-M-27 (n = 2)[b]	No data	1 (1/105)	No data	24 (24/100)	24 (5/21)	Gastroenteritis; travel to India[c]	No data
Kennedy[347]	Phenotypic approach with genotypic confirmation by PCR	Enrichment broth, selective media, AST: Vitek2, MRE confirmation: disc diffusion	TEM or SHV (n = 4), CTX-M group 1 (n = 12), CTX-M group 9 (n = 6), and pAmp C genes(n=4)[d]	No data	2 (2/106)	22 (22/102)	21 (21/100)	6 (1/18)	Gastroenteritis; use of antibiotics; travelling to Asia, South America and/or Middle East/Africa[e, c]	No data
Östholm-Balkhed[348]	Phenotypic approach with genotypic confirmation by PCR	Selective media, AST: Etest, MRE confirmation: Etest	TEM-19 (n = 1), SHV (n = 6), CTX-M-15-like (n = 36), CTX-M-14-like (n = 36), CTX-M-27-like (n = 5), CTX-M-53-like (n=5), CTX-M-1/61 like (n = 3), CTX-M-2 like (n = 2), CTX-M-3-like (n = 1), pAmpC genes (n = 15), no genes detected (n = 13)[b]	No data	2 (6/251)	31 (72/231)	30 (68/226)	No data	Age; diarrhoea or other gastrointestinal symptoms; travel to Asia, Africa (north of equator), Indian subcontinent[f]	No data
Kantele[349]	Phenotypic approach with genotypic confirmation by PCR	Selective media, AST: Vitek2, MRE confirmation: disc diffusion	79% CTX-M-type (CTX-M-1 and CTX-M-9 most prevalent), other common strains TEM and OXA (data not published)[b]	No data	1 (5/430)	22 (93/430)	21 (90/430)	No data	Traveller's diarrhoea; age; use of antibiotics for traveller's diarrhoea[f]	No data

Weisenberg[350]	Phenotypic approach with genotypic confirmation by PCR	Selective media, AST: Vitek2, MRE confirmation: disc diffusion	SHV-12 (n = 1), CTX-M-14 (n = 3), CTX-M-15 (n = 2), no gene detected (n = 1)[b]	MLST typing 7 MDR *E. coli* isolates: ST 39, 8 (n = 2), 37, 399, 437, 83	4 (1/28)	25 (7/28)	26 (7/27)	No data	No data	No data
Angelin[351]	Phenotypic approach for detection of ESBL, pAmp C and phenotypic approach with genotypic characterization for detection of OXA-48/OXA-181	Selective media, AST: disc diffusion, MRE confirmation: Etest (ESBL), disc diffusion (pAmpC)	No data	No data	7 (7/99)	36 (36/99)	35 (35/99)	No data	Travel to the South-East Asia region (India, Nepal, Vietnam, Indonesia, Sri Lanka); antibiotic treatment during travel[g]	No data
von Wintersdorff[352]	Metagenomic approach (detection *bla*CTX-M)	No data	*bla* CTX-M (n = 41)[d]	No data	9 (11/122)	34 (41/122)	32 (36/111)	No data	Travel to Indian subcontinent[f]	No data
Paltansing[353]	Phenotypic approach with genotypic characterization by microarray	Enrichment broth, selective media, AST: Vitek2, MRE confirmation: disc diffusion	SHV (n = 1), CTX-M group 1 (n = 110) of which CTX-M-1-like (n = 4), CTX-M-3-like (n = 1), CTX-M-15-like (n = 85), CTX-M-32-like (n = 20), CTX-M-group 9 (n = 42), CTX-M-group 2 (n = 2), CTX-M-group 8/25 (n = 1), pAmpC genes (n = 3)[d]	MLST typing: 146 MDR *E. coli* isolates: most prevalent ST 38 (n = 17), ST10 (n = 10), ST131 (n = 9)	9 (32/370)	36 (133/370)	33 (113/338)	17 (19/113)	Travel to South or East Asia[f]	18 (2/11)
Ruppé[354H]	Phenotypic approach with genotypic confirmation by PCR	Enrichment broth, selective media, AST: disc diffusion	Predominant CTX-M-type (95.4%) among which CTX-M-group 1 predominated (83.7% of all CTX-M), OXA-181 (n = 2), NDM-1 (n = 1)[b]	No data	12 (81/700)	No data	51 (292/574)	After 1 month 34 (83/245); after 2 months 19 (45/236); after 3 months 10 (24/233); after 6 months 5 11/230); after 12 months 2 (5/227)	Travel to Asia or sub-Saharan Africa; beta-lactam use during travel; diarrhoea during travel; type of travel[f]	No data

Table 2 (continued): Risk of multidrug-resistant Enterobacteriaceae in travellers (n = 11 studies)

Study	Method of MRE determination	Phenotypic approaches	Results genotypic characterization post- travel MRE isolates	Results molecular typing of post-travel MRE isolates	MRE prevalence pre-travel% *(ratio)*	MRE prevalence post-travel *% (ratio)*	New MRE acquisition during travel *% (ratio)*[a]	Persistent newly acquired MRE carriage 6 months after travel *% (ratio)*	Results univariate /multivariate risk factor analysis for MRE acquisition	MRE in non-travelling household contacts *% (ratio)*
Kuenzli[355]	Phenotypic approach with genotypic screening by microarray and confirmation by PCR/DNA sequence analysis	Enrichment broth, selective media, AST: Vitek2, MIC for meropenem and ertapenem: Etest, MRE confirmation: disc diffusion, modified Hodge test	TEM-1-like (n = 33), SHV238S/240K (n = 7), SHV238S (n = 1), SHV-5/12-like (n = 1), SHV-2/3-like (n = 1), CTX-M-15-like (n = 48), CTX-M group 9 (n = 1), CTX-M group 1 (n = 24), predominant ESBL gene was CTX-M-15 (80 representative *E. coli* isolates analysed) [b], NDM-1 (n = 1)	80 representative *E. coli* isolates analysed by rep-PCR: not clonally related. MLST performed on 34 randomly selected *E. coli* isolates: only 3 pandemic strains found (ST131 n = 2; ST648 n = 1)	3 (5/175)	No data	70 (118/170)	No data	Travel to India, Bhutan or Nepal; visiting friends and relatives; consumption of ice cream and pastry;, length of stay[f]	No data
Lübbert[356]	Phenotypic approach with genotypic confirmation by PCR	Selective media, AST: micro broth dilution method, MRE confirmation: Etest	SHV-12 (n = 1), CTX-M group 1 (n = 37) of which CTX-M-15 (n = 33), CTX-M-55 (n = 4), CTX-M group 9 (n = 19) of which CTX-M-14 (n = 9), CTX-M-27 (n = 1), CTX-M-65 (n = 1)[b]		7 (14/205)	31 (63/205)	30 (58/191)	9 (3/35)	Travel to India or South-East Asia; gastroenteritis[c]	No data

AST: antibiotic susceptibility testing; bla: beta-lactamase; CTX-M: cefotaximase; E. coli: Escherichia coli; ESBL: extended-spectrum beta-lactamase; KPC: Klebsiella pneumoniae carbapenemase; MLST: Multilocus sequence typing; MDR: multi-drug resistant; MRE: multidrug-resistant Enterobacteriaceae; NDM: New Delhi metallo-beta-lactamase; OXA: oxacillinase; pAmp C: plasmid-borne AmpC; PCR: polymerase chain reaction; PFGE: pulsed-field gel electrophoresis; rep-PCR: repetitive extragenic palindromic PCR; SHV: Sulphydryl variable; TEM: Temoniera. a: Percentage of MRE-positive post-travel samples in those travellers whose pre-travel sample was MRE-negative. b: Acquired genes detected in post-travel MRE isolates. c: Univariate statistics. d: Prevalent genes detected in post-travel MRE isolates. e: Risk factors for resistance to gentamicin, ciprofloxacin and/or third generation cephalosporins. f: Multivariable logistic regression analysis; participants ESBL-positive before travel were excluded. g: Binary regression analysis. h: Carbapenemase-positive isolates were included in the definition MRE.

The risk of acquisition of MRE varied with the geographical region (*Table 3*). [346-350,352-356] Travel to southern Asia posed the highest risk (range: 29–88%), followed by other Asian countries (18-67%) and Northern Africa (range: 31-57%). Acquisition of MRE after travelling to sub-Saharan Africa (range: 0-49%) or South and Central America (range: 0–33%) was less frequent, and three studies did not observe any acquisition of MRE after travel to South or Central America (*Table 3*). Acquisition of MRE after travel to North America, Europe and Oceania was rare. Results of the genotypic characterization of MRE isolated after travel are presented in *Table 2*, the majority of the genes belonged to the CTX-M type.

Risk factors for acquisition of multidrug-resistant Enterobacteriaceae

Besides travel destinations, other risk factors for acquiring MRE were age, use of antibiotics during travel (beta-lactam use) and gastroenteritis or other gastrointestinal symptoms (*Table 2*). The study of Kantele *et al*., designed to study these risk factors as primary outcome, showed that travel diarrhoea (adjusted odds ratio (AOR) = 31.0; 95% confidence interval (CI): 2.7–358.1)) and antibiotic therapy for travel diarrhoea (AOR = 3.0; 95% CI: 1.4–6.7) proved to be the most important risk factors for acquiring MRE.[350] In the study of Kuenzli *et al*. in which only travellers to southern Asia were included, risk factors for MRE acquisition were length of stay, visit to family or friend and consumption of ice cream or pastry (*Table 2*).[355] Angelin *et al*. found a significant association for travel to the South-East Asia region (OR = 30; 95% CI: 6.3–147.2), and antibiotic treatment during travel (OR = 5; 95% CI: 1.1–26.2), but found no association with travellers' diarrhoea or patient-related healthcare work.[351]

Resistance of multidrug-resistant Enterobacteriaceae to other antibiotic drugs

Resistance of post-travel MRE isolates to various antibiotics was determined in nine studies (*Table 4*).[346-348,350-353,355,356] In the study by Wintersdorff *et al*., a PCR-based approach was used, therefore it was not possible to determine which microorganism carried the resistance genes.[352] The resistance data to other antibiotic drugs in the study by Kennedy *et al*. were not part of the publication, but were provided on request.[347] Antimicrobial resistance was high for ciprofloxacin, varying from 31% to 57%, and for cotrimoxazole, varying from 49% to 86%.[346-348,350-353,355,356] Aminoglycoside resistance was high for gentamicin (range: 17-50%) and tobramycin (range: 18-59%) and low for amikacin (range: 2-5%). [346-348,350-353,355,356] Carbapenemase-producing *Enterobacteriaceae* were observed in four travellers who had all visited India (in the study by Ruppé *et al*., two OXA-181 and one New Delhi metallo-beta-lactamase 1 (NDM-1), and in the study by Kuenzli *et al*., one NDM-1 but this strain was not included in the resistance results).[354,355] Resistance to nitrofurantoin, colistin and fosfomycin was only analysed in some of the studies (*Table 4*).[347,348,350-352,355]

Table 3: Proportion of travellers who acquired multidrug-resistant Enterobacteriaceae, by travel destination (n = 11 studies)

Study	Southern Asia% (ratio)	Asia except southern Asia% (ratio)	Northern Africa% (ratio)	Sub-Saharan Africa% (ratio)	South and Central America% (ratio)	North America% (ratio)	Europe% (ratio)	Oceania% (ratio)
Tängdén[346] a, b	78 (7/9)	29 (10/34)	33 (4/12)	4 (1/23)	0 (0/7)	0 (0/2)	13 (2/16)	-
Kennedy[347] a, c	57(8/14)	25 (21/85)	33 (1/3)	0 (0/2)	20 (1/5)	20 (2/10)	14 (3/21)	0 (0/2)
Östholm-Balkhed [348] a, b	71(10/14)	43 (26/60)	57 (17/30)	21 (15/71)	16 (5/31)	0 (0/15)	0 (0/15)	No data
Kantele[349] b, d	46 (28/61)	32 (37/116)	67 (2/3)	12 (23/193)	0 (0/40)	0 (0/2)	0 (0/15)	No data
Weisenberg[350] b	29 (2/7)	25 (1/4)	33 (1/3)	13 (1/8)	33 (2/6)	No data	No data	No data
Angelin[351]	63 (25/40)	67 (6/9)	No data	10 (4/40)	0 (0/5)	0 (0/4)	No data	No data
von Wintersdorff[352] c	58 (18/31)	20 (6/29)	31 (5/16)	29 (5/17)	0 (0/10)	No data	17 (1/6)	No data
Paltansing[353] b, e	72 (18/25)	41 (60/146)	40 (4/10)	24 (20/82)	15 (9/60)	No data	No data	No data
Ruppé[354] f	88 (53/60)	66 (61/93)	No data	49 (89/182)	31 (48/155)	No data	No data	0 (0/2)
Kuenzli [355] b	69	No data	No data	No data	No data	No data	No data	No data
Lübbert [356] a, b	72 (13/18)g	33 (24/73)g	No data	24 (19/78)	8 (6/78)	0 (0/2)	20 (2/10)	No data

a: Travelers visiting more than one region are categorized in all the visited geographical regions. b: Study reports data on MRE acquisition in travellers. c: Study reports data on MRE prevalence in travellers. d: Travelers visiting more than one region are categorized in the geographical region with the longest stay for this study. e: One traveller who visited Iran is categorized in Asia instead of Southern Asia. f: 42 travellers visited more than one country in Asia and may be represented in more than one column in the Table; 28 of them acquired MRE. g: Exact numbers unpublished.

Southern Asia: Afghanistan, Bangladesh, Bhutan, India, Iran, Maldives, Nepal, Pakistan, Sri Lanka. Asia (without southern Asia): Armenia, Azerbaijan, Bahrain, Brunei, Cambodia, China, Cyprus, Georgia, Hong Kong, Indonesia, Iraq, Israel, Jordan, Japan, Kazakhstan, Kuwait, Kyrgyzstan, Laos, Lebanon, Mongolia, Malaysia, Myanmar, North Korea, Oman, Philippines, Qatar, Saudi Arabia, South Korea, Singapore, Palestine, Syria, Tajikistan, Thailand, Timor-Leste, Turkey, Turkmenistan, United Arab Emirates, Uzbekistan, Viet Nam, Yemen. Northern Africa: Algeria, Egypt, Libya, Morocco, Sudan, Tunisia, Western Sahara. Sub-Saharan Africa: Angola, Benin, Botswana, Burkina Faso, Burundi, Cameroon, Cape Verde, Central African Republic, Chad, Comoros, Congo (Brazzaville), Côte d'Ivoire, Democratic Republic of the Congo, Djibouti, Equatorial Guinea, Eritrea, Ethiopia, Gabon, Ghana, Guinea, Guinea-Bissau, Kenya, Lesotho, Liberia, Madagascar, Malawi, Mali, Mauritania, Mauritius, Mozambique, Namibia, Niger, Nigeria, Réunion, Rwanda, São Tomé and Príncipe, Senegal, Seychelles, Sierra Leone, Somalia, South Africa, Sudan, Swaziland, Tanzania, The Gambia, Togo, Uganda, Zambia, Zimbabwe. South and Central America: Anguilla, Antigua and Barbuda, Argentina, Aruba, Bahamas, Barbados, Belize, Bolivia, Bonaire, Sint Eustatius and Saba, Brazil, British Virgin Islands, Cayman Islands, Chile, Colombia, Costa Rica, Cuba, Curaçao, Dominica, Dominican Republic, Ecuador, El Salvador, Falkland Islands, French Guiana, Grenada, Guadeloupe, Guatemala, Guyana, Haiti, Honduras, Jamaica, Martinique, Mexico, Montserrat, Nicaragua, Panama, Paraguay, Peru, Puerto Rico, Saint Kitts and Nevis, Saint Lucia, Saint Martin, Saint Vincent and the Grenadines, Saint-Barthélemy, Sint Maarten, Suriname, Trinidad and Tobago, Turks and Caicos Islands, US Virgin Islands, Uruguay, Venezuela. North America: Bermuda, Canada, Greenland, Saint Pierre and Miquelon, United States. Europe: Åland Islands, Albania, Andorra, Austria, Belarus, Belgium, Bosnia and Herzegovina, Bulgaria, Channel Islands, Croatia, Czech Republic, Denmark, Estonia, Faeroe Islands, Finland, the former Yugoslav Republic of Macedonia, France, Germany, Gibraltar, Greece, the Holy See, Hungary, Iceland, Ireland, Isle of Man, Italy, Latvia, Liechtenstein, Lithuania, Luxembourg, Malta, Monaco, Montenegro, Netherlands, Norway, Poland, Portugal, Moldova, Romania, Russia, San Marino, Serbia, Slovakia, Slovenia, Spain, Svalbard and Jan Mayen, Sweden, Switzerland, Ukraine, United Kingdom. Oceania: American Samoa, Australia, Cook Islands, Fiji, French Polynesia, Guam, Kiribati, Marshall Islands, Micronesia, Nauru, New Caledonia, New Zealand, Niue, Norfolk Island, Northern Mariana Islands, Palau, Papua New Guinea, Pitcairn Islands, Samoa, Solomon Islands, Tokelau, Tonga, Tuvalu, Vanuatu, Wallis and Futuna.

Table 4: Antibiotic drug resistance of newly acquired multidrug-resistant Enterobacteriaceae in travellers (n = 11 studies)

Study	Ciprofloxacin % (ratio)	Cotrimoxazole % (ratio)	Gentamicin % (ratio)	Amikacin % (ratio)	Tobramycin % (ratio)	Carbapenem % (ratio)	Nitrofurantoin % (ratio)	Colistin % (ratio)	Fosfomycin % (ratio)
Tängdén[346] a	50[b]	79 (19/24)	45[b]	No data	38[b]	0[b]	0[b]	No data	8.0[b]
Kennedy[347] c	55 (12/22)	No data	50 (11/22)	No data	59 (13/22)	No data	No data	No data	No data
Östholm-Balkhed[348] a	31 (36/116)	70 (81/116)	41 (48/116)	2 (2/116)	46 (53/116)	0 (0/116)	7 (8/116)	No data	3 (3/116)
Kantele[349]	No data	No data	No data	No data	No data	No data	No data	No data	No data
Weisenberg[350] a	43 (3/7)[d]	86 (6/7)	43 (3/7)	No data	No data	0 (0/7)	No data	No data	No data
Angelin[351]	57 (28/49)	75[b]	30[b]	No data	No data	0 (0/49)	2[b]	No data	No data
von Wintersdorff [352] e	37 (45/122) *qnrB;* 56 (68/122) *qnrS*	No data	71 (86/122) *aac(6')-aph(2")*	71 (86/122) *aac(6')-aph(2")*	71 (86/122) *aac(6')-aph(2")*	0 (0/122) *bla*NDM	No data	No data	No data
Paltansing [353] f	36	67	35	No data	37	0	29	0	No data
Ruppé[354]	No data	No data	No data	No data	No data	0.6 (3/526)[g]	No data	No data	No data
Kuenzli[355] a	41 (64/157)	49 (77/157)	No data	5 (7/157)	18 (28/157)	0 (0/157)	2 (3/157)	0 (0/157)	0.6 (1/157)
Lübbert[356] a	43 (25/58)	83 (48/58)	17 (10/58)	2[b]	22[b]	0[b]	No data	0[b]	16[b]

bla: beta-lactamase; CPE: carbapenemase-producing Enterobacteriaceae; ESBL: extended-spectrum beta-lactamase. a: Resistance among acquired ESBL-positive isolates detected in post-travel samples. b: Data extracted from bar chart, exact numbers unpublished. c: Resistance among prevalent ESBL-positive isolates detected in post-travel samples. d: Percentage of susceptibility to levofloxacin. e: Prevalent resistance genes in faecal samples post-travel. f: Resistance among prevalent ESBL-positive isolates detected in pre- and post-travel samples. g: Three acquired CPE detected in post-travel samples.

Duration of multidrug-resistant

Enterobacteriaceae carriage after return, risk factors for a long duration and rate of infection after travel. Five studies analysed MRE carriage six months after travel, and the persistence rate of acquired MRE after six months was 6–24% of travellers (*Table 2*).[346,347,353,354,356] Ruppé *et al.* analysed MRE carriage one, two, three, six and twelve months after travel, showing persistence of carriage of an acquired MRE in 34, 19, 10, 5 and 2%, respectively.[354] Travelers to Asia showed longer carriage of MRE compared with other travel destinations. Carriage of multidrug-resistant *E. coli* had a lower risk for prolonged carriage than other multidrug-resistant species. No other risk factors were found for prolonged carriage of MRE. Eight travellers in this study reported an episode of urinary tract infection after their return, but no microbiological data were available.[354] In the study by Tängdén *et al.*, five of 21 travellers remained carriers of MRE after six months. However, none of these participants reported clinical infections.[346] In the study of Kennedy *et al.*, one person developed a urinary tract infection with a travel-related

organism.[347] Kantele *et al*. performed a one-year laboratory-based follow-up and did not find any clinical samples with MRE.[349]

Rate of transmission to household members

Only one study screened household contacts for MRE after return of the index traveller. Household contacts were defined as persons who shared the same household with a participant on a regular basis. Two of 11 contacts were found MRE-positive.[353] Both carried a different ESBL-producing *E. coli* based on multilocus sequence typing (MLST) than the associated traveller.

Limitations of the studies

The quality of the studies and the susceptibility of bias between the studies were assessed. In all but one study, participants constituted a non-random sample of the general travelling population.[346-350,352-356] However, Angelin *et al*. studied healthcare students working or studying abroad.[351] Studies were performed on three different continents. Travel destinations and travel behaviour may differ considerably between different nationalities and age groups. Including co-travellers, as done in all studies except Paltansing *et al*. and Ruppé *et al*., can result in similar travel behaviour and therefore, similar risk factors. Overall, the main outcome was not influenced by recall or interviewer bias. For other outcomes such as risk factors, the risk of recall bias or interviewer bias was low because of the use of self-administered questionnaires.

Every study had participants lost to follow-up for post-travel stool samples and follow-up stool samples. Asymptomatic faecal carriage of MRE is probably not related to loss to follow-up, therefore, the risk of information bias is small. Ruppé *et al*. calculated posttravel MRE carriage as those travellers with persisting MRE carriage divided by all travellers with MRE acquisition plus all travellers without MRE post-travel.[354] However, travellers without MRE were not included in the follow-up. As a result, local MRE acquisition was not included in the calculated post-travel MRE carriage prevalence. Therefore the true prevalence can be assumed to be higher.

In five studies, travellers visited multiple regions or even continents during their trip.[346-349,356] In these travellers, it was not possible to attribute MRE prevalence or MRE acquisition to a certain geographical region. However, travellers in these studies were included in the MRE prevalence or MRE acquisition rates of more than one geographical region, which may have introduced information bias.

Seven studies used stool samples for detection of MRE[346,348-350,352,354,356] and three studies used rectal or perianal swabs for detection of MRE.[347,353,355] This might have influenced detection of MRE carriage.

Discussion

In this systematic review we found a high prevalence of faecal carriage of MRE after international travel. The highest prevalence of MRE was observed in isolates from travellers returning from southern Asia, with up to 88% acquisition of MRE. In addition to the antibiotics not effective against MRE, an alarmingly high prevalence of resistance to other commonly used antibiotics such as cotrimoxazole (49–86%), ciprofloxacin (31–57%) and aminoglycosides (gentamicin 17–71%) was observed in ESBL-positive isolates in travellers in all studies.[346-356]

Returning international travellers with MRE may introduce these microorganisms in their home countries. This may cause community-onset infections with MRE in patients without obvious risk factors transmitted by healthy carriers through food or person-to-person contact.[338] Infections caused by MRE are associated with poorer outcome and a higher overall mortality rate than infections caused by susceptible bacteria.[357] In this review, all studies showed an increased prevalence of faecal carriage of ESBL after international travel. It is not possible to evaluate the proportion of travellers who will develop infection with these resistant bacteria. However, studies have demonstrated that international travel is a risk factor associated with developing an infection with an MRE.[340,341,358]

Many countries have infection prevention and control guidelines to detect and treat multidrug-resistant organisms (MDROs) including MRE.[359] In countries with low prevalence of MRE, infection prevention and control guidelines mainly include strategies for early identification and isolation of patients recently hospitalized in foreign hospitals.[359,360] Patients with a recent history of travel to MRE-endemic areas but not admitted to healthcare facilities abroad are not normally considered at risk for carriage of MDROs. However, in hospitalized patients with a recent history of travel, increased rates of carriage of MRE have been observed.[339,358,359] Physicians should be aware of the risk that patients with recent travel to areas with high faecal carriage of MRE, as presented in this review, may introduce MRE to the hospital. Routine screening for MRE seems indicated in such patients. Furthermore, empiric antibiotic therapy may fail when an infection by MRE is not taken into account. Therefore, careful recording of travel history needs to be incorporated in each patient evaluation. As shown in this review, there is also an increased risk of resistance against other antibiotics in travellers with MRE carriage. It is likely that this is caused by multiple genes, each encoding resistance to different classes of antibiotics, which are often found on the same bacterial mobile genetic element (e.g. a plasmid).[361] As a result, other antibiotics, such as aminoglycosides, will also fail in many MRE-positive patients.

Of all MDROs, emergence of CPE is most worrisome because of the limited treatment options for these infections. NDM-1-producing Enterobacteriaceae have been found in environmental samples in endemic regions.[362] CPE (NDM-1) in patients from the United Kingdom with a recent history of travelling or medical tourism to India are already an important public health problem.[337] Case reports have also demonstrated acquisition of

CPE in travellers without contact with medical healthcare facilities.[363,364]In this review, four travellers from India were carrying a carbapenemase-producing *E. coli*.[354,355] Preliminary results of the Carriage Of Multiresistant Bacteria After Travel (COMBAT) study, a large-scale multicentre longitudinal cohort study conducted in the Netherlands among 2001 travellers, show acquisition of CPE in four travellers.[365]

There are, besides the destination of travel, additional risk factors for acquiring MRE during travel. Antibiotic therapy was found to increase the risk.[349,351] In five studies, traveller's diarrhoea or gastroenteritis were associated with an increased risk of MRE acquisition during.[346-349,354] Also, in one study, meticulous hand hygiene or strict consumption of bottled water did not lower the risk of acquiring MRE.[351] Therefore, it is not clear whether hygiene-related travel advice will decrease faecal carriage of MRE. Surprisingly, healthcare-related activities did not pose an increased risk of acquiring MRE in one study.[351]

MRE and CPE could also be carried by food. International spread of these bacteria by food supply has been reported.[366] In this review, only one study showed that food consumption (ice cream and pastry) was associated with MRE carriage in travellers to southern Asia, whereas most of the studies did not focus on dietary patterns during travel.

One limitation of this review is the recruitment of travellers from travel clinics only, resulting in inclusion of very few travellers with European destinations. Some European countries such as Greece and Cyprus are also endemic for MRE and popular travel destinations.[363] In addition, travellers visiting their country of origin, especially Morocco and Turkey usually do not ask for a pre-travel consultation, although these countries are endemic for MRE and CPE.[363] It is not clear whether not including these patients may have led to an under- or overestimation of MRE acquisition.

Another limitation is the lack of sufficient data regarding the duration of carriage and the transmission among non-travelling household members. The study by Ruppé *et al*. suggests that three months after return, MRE carriage is comparable with the baseline prevalence before travelling. However, the study did not include baseline prevalence in the follow-up. The COMBAT study will address some of these questions.[367]

Conclusion

International travel is a major risk factor for acquisition of MRE. This risk is particularly high after travelling to (southern) Asia and in persons with travel-related diarrhoea and antibiotic use. Carriage of MRE-positive isolates is also associated with a high risk of resistance to ciprofloxacin, cotrimoxazole and aminoglycosides. Further research is needed to assess duration of carriage, spread to household contacts and whether introduction of MRE results in an increase of MRE infections. Our results, combined with the worldwide emergence of CPE, further stress the importance of infection prevention and control guidelines.

Chapter 12

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Urinary Tract Infections in a University Hospital: Pathogens and Antibiotic Susceptibility

Abstract

Background

A substantial group of patients visit the emergency department (ED) with complaints of urinary tract infections (UTI). Treatment advice is based on national and local public health surveillance data. It is unclear whether this advice is adequate for hospitals with selected patient populations, such as university hospitals.

Methods

We performed a retrospective study on patients visiting the ED of the Erasmus University Medical Center (Erasmus MC) in the Netherlands from January 1st, 2013 until December 31st, 2014 with a suspected complicated UTI (cUTI) and positive urinary cultures. Patient data, data concerning the ED visit and microbiological data were analysed.

Results

439 patients visited the ED, of whom 429 had a cUTI. Our results were compared with NethMap data. Distribution of uropathogens was comparable with the overall distribution in the Netherlands. Antibiotic susceptibility was comparable for intravenous antibiotics, but was lower for oral antibiotics. Susceptibility for empiric antibiotic therapy (i.e. cefuroxime and gentamicin) was 96.2%. Pathogens differed from the index culture in 56.2% (104/185) of the urinary cultures available from the previous year. Using logistic regression, we found that a shorter time between last admission to the initiated antibiotic regimen was associated with lower susceptibility of cultured uropathogens.

Conclusion

The distribution and antibiotic susceptibility of uropathogens for intravenous antibiotics in a Dutch university hospital is comparable with overall distribution in the Netherlands. Empiric antibiotic therapy in our local guideline appears to be an adequate antibiotic regimen for cUTI and we therefore recommend treating patients accordingly. Extension of the chosen regimen based on earlier cultured pathogens is advised, and narrowing of the antibiotic regimen strongly discouraged.

Introduction

Background and rationale

Urinary tract infection (UTI) is suspected in a substantial group of patients visiting the emergency department (ED). In the United States, UTIs accounted for approximately 2% of ED visits in 2014 for a total of 2.3 million people.[368] This percentage is similar in the Netherlands.[369] There is continuous debate about the appropriate antibiotic treatment for patients with UTI, despite guidelines on the subject. The Dutch guidelines for antibiotic therapy are based on national resistance data on pathogens causing UTI.[370] It is questionable if, and to what extent, these data are applicable to the patient population encountered in specialized hospitals, such as university hospitals.

Patients in university hospitals often have a complex medical history and in particular, patients from nephrology and urology departments are more frequently treated for UTIs with antibiotics. These patients are at risk for colonization with antibiotic-resistant uropathogens. When UTI occurs, it is likely that the uropathogens are less susceptible to routinely prescribed antibiotics.[371-373] Data comparing the distribution and antibiotic susceptibility of uropathogens in Dutch university hospitals with the overall distribution in the Netherlands are currently lacking.

Dutch national guidelines advise to treat complicated UTIs (cUTI) with amoxicillin or a second-generation cephalosporin combined with an aminoglycoside, or with a third-generation cephalosporin.[370] A cUTI is defined by the 'The Dutch Working Party on Antibiotic Policy' (SWAB) as all UTIs with the exception of cystitis in non-immunocompromised, non-pregnant women with no anatomical and functional abnormalities of the urogenital tract and no signs of tissue invasion, and in men younger than 40 years without a medical history, no previous lower urinary tract symptoms and no findings at physical examination.[370] In the Erasmus University Medical Center Rotterdam, the Netherlands (Erasmus MC), cefuroxime combined with gentamicin is the antibiotic regimen of choice for cUTI based on local resistance data. This regimen can only be administrated intravenously, which requires hospitalization, regardless of the patient's clinical condition. Furthermore, side effects of gentamicin include nephrotoxicity and ototoxicity.[374] Although this risk is particularly applicable after multiple doses in patients with renal insufficiency, aminoglycosides are frequently left out, resulting in inappropriate treatment.[375-377] The duration of hospital stay or even prevention of admission may be achieved if hospitals can identify patients who can be safely treated with other specific antibiotic-regimens, based on their medical history and available data from previously obtained cultures.

When initiating adequate antibiotic therapy, physicians should take the increase of antibiotic resistance into account. However, there are currently not enough data to enable a more tailor-made decision for the first choice of the antibiotic regimen. Recently, a study in a university hospital in Israel showed that patients who had a culture with a resistant uropathogen had high rates of a repeat resistant uropathogen in a subsequent

culture.[378] This chance of a repeat resistant uropathogen was reduced with time, or with an intervening culture without resistant uropathogens. Data that enables extension or narrowing of the empiric regimen in a university hospital ED population are not available. However, these data would substantially contribute to more efficient antibiotic treatment and prevention of antibiotic resistance.[379]

Objectives

The primary goal of this research was to study the distribution of uropathogens and their antibiotic resistance patterns in a university hospital population. Second, we investigated susceptibility to the empiric regimen consisting of cefuroxime and gentamicin in this population, and studied the probability of extending or narrowing of this regimen, based on previously cultured pathogens.

Materials and Methods

Study design, setting, and patients

We conducted an observational retrospective study in the Erasmus MC. This is the largest university hospital of the Netherlands with approximately 30,000 adult ED visits per year. All urinary cultures with at least one pathogen and an available antibiogram taken from patients visiting the ED from January 1st, 2013 until December 31st, 2014 were obtained from the Department of Medical Microbiology and Infectious Disease.

Urine samples were cultured by standard microbiological culture techniques. Bacterial species were identified by Matrix Assisted Laser Desorption/Ionization Time-of-Flight Analyser Mass Spectrometry (MALDI-TOF MS) analysis (Microflex, Bruker Daltonics, Bremen, Germany). Susceptibility testing was performed with VITEK®2 (bioMérieux, Marcy l'Etoile, France). Antibiotic resistance was determined according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoints.[380] Only samples from patients 18 years or older having a UTI were included (i.e. index culture). Patients were only included once, and the first obtained sample of each patient in the abovementioned period was used. Uropathogens were considered to be identical (i.e. the same uropathogen), if the index culture and previously cultured uropathogens as well as its antibiotic susceptibility were identical.

Variables

For each patient, demographic data (e.g. age, sex, previous medical history) and data concerning their ED visit, such as history, vital parameters (e.g. blood pressure, heart rate, respiratory rate, oxygen saturation, temperature), laboratory results (e.g. C-reactive protein (CRP), leukocyte count, and presence of pyuria, defined as leukocytes in urine dipstick), results of blood cultures, previous urinary cultures acquired within 12 months prior to the ED-visit with antibiogram available, data on initiated antibiotics,

and disposition were obtained from electronic patient records. In patients who were previously hospitalized in the Erasmus MC, the dates of the last admission and discharge were obtained, and time since last admission and duration of the last admission were calculated. The number of admissions in the last year was also obtained. Comorbidities considered relevant were renal transplantation, urological anomalies (e.g. recent urological interventions, neo-bladder reconstruction, urological tract anomalies), and immunocompromised status (defined as patients with congenital or acquired immunodeficiency, patients undergoing active treatment for malignancies, patients using immunosuppressive medication). Patients were grouped in 'never hospitalized within the Erasmus MC' (Erasmus MC-naïve), and 'previously hospitalized in the Erasmus MC'. Previously hospitalized patients were categorized based on the time between the last admission, either > 12 months or ≥ 12 months ago. We made a subset of patients recently hospitalized (defined as < 3 months). Data on hospitalization in other hospitals or residing in a nursing home were not available.

We combined the SWAB definition[370] and the Centres for Disease Control and Prevention (CDC) definition[381] to define a cUTI: an urinary culture with no more than two species of organisms identified, at least one of which is a bacterium of ≥ 10^3 colony forming units (in contrast to the ≥ 10^5 colony forming units, as defined in the CDC definition) and one of the following criteria: 1) a positive blood culture from the same moment with the same micro-organism as in the urinary culture; 2) a body temperature > 38.0 °C; 3) symptomatology of a UTI (e.g. dysuria, urinary frequency or urgency, suprapubic or costovertebral tenderness); or 4) according to the treating physician (i.e. UTI reported as (most likely) diagnosis in discharge letter). A UTI was considered to be complicated when there were signs of systemic illness. Patients met our definition of cUTI when they were fulfilled at least one of the following: being male and older than 39 years,[370] having a body temperature > 38.0 °C, meeting two or more systemic inflammatory response syndrome (SIRS) criteria (of note, missing SIRS criteria were coded as negative),[34] having costovertebral tenderness, being ill according to the treating physician, having a CRP > 60 mg/l,[382] having a blood culture with the same pathogen as in the urine culture, having a renal transplantation in medical history, being immunocompromised, or the decision for hospitalization by the treating physician. Cefuroxime combined with gentamicin was considered empiric therapy in the ED, and we therefore described the proportion of patients having a UTI in whom empiric therapy would have been an adequate antibiotic regimen without resistance of the causing pathogen against these agents. We also described the population of pathogens cultured with their susceptibility to different, frequently prescribed antibiotic regimens, including susceptibility to cefuroxime and gentamicin, in Erasmus MC-naïve versus previously hospitalized patients (< 12 versus ≥ 12 months ago). We compared the index culture and its susceptibility for the prescribed antibiotic regimen with previously cultured pathogens. Lastly, we compared prevalence susceptibility of uropathogens for frequently prescribed antibiotics in our population with national antibiotic susceptibility.[383]

Statistical analyses

We presented patient characteristics as mean and interquartile range (IQR), or as an absolute number (proportion) with percentage (%) and 95% confidence interval (95% CI). Categorical variables were compared using the Pearson chi-squared test. We performed one sample t-tests for the comparison of proportions and 95% CIs of susceptibility in our population with Dutch national susceptibility data (NethMap).[383] We performed univariate and multivariate logistic regression analysis on susceptibility of the found bacteria for initiated therapy, empiric therapy and cefuroxime monotherapy over days since last admission. Other factors included in the models were sex and age. Results are presented as odds ratios (ORs) and 95% CIs. All analyses were conducted with IBM SPPS Statistics for Windows version 21 (IBM Corp., Armonk, N.Y., USA). A P value < 0.05 was considered significant.

Results

Inclusion of patients

A total of 2,481 urinary cultures were obtained in the ED between January 1st, 2013 and December 31st, 2014, of which 806 (32.5%) contained at least one pathogen. After selecting first isolates, 722 (89.6%) cultures of unique patients remained. Of these patients, 439 (60.8%) had a UTI according to the predefined criteria and 427 had a cUTI. A total of 355 (83.1%) patients were admitted to the hospital, and in 348 (98.0%), antibiotics were initiated. The flowchart of these results and medical decisions with respect to hospital admission and initiation of antibiotics is shown in *Figure 1.*

Patient characteristics

Of the 427 patients with cUTI, a majority were male (223 patients, 52.2%), with a median age of 59 years. The vast majority of patients had relevant comorbidities (72.8%) and 63.2% were hospitalized the prior year. Only 12.2% of the patients were not previously admitted to Erasmus MC. Most frequently cultured pathogen was E. coli (51.3%). Other frequently cultured micro-organisms were *K. pneumoniae, E. faecalis, P. mirabilis, P. aeruginosa,* and *S. agalactiae* (*Group B Streptococcus*) (9.5%, 9.7%, 6.7%, 5.6% and 2.6%, respectively). Patient characteristics are shown in *Table 1.*

Antibiotic susceptibility

In all patients who were hospitalized after their ED visit with a cUTI, we found susceptibility to cefuroxime and/ or gentamicin in 96.2% (228/237) for *E. coli*, 90.9% (40/44) for *K. pneumoniae*, and of 100% (31/31) for *P. mirabilis*. These rates are comparable to NethMap-data.[383] Susceptibility to meropenem was 100%, except for *P. aeruginosa* (susceptibility rate 92.3% (24/26)). Compared to the general resistances rates in the Netherlands, we found more resistance of *E. coli* and *K. pneumoniae* for trimethoprim-

sulfamethoxazole and more resistance of *E. coli* and *P. mirabilis* for ciprofloxacin. All susceptibility patterns can be found in *Table 2A*.

Using multivariate logistic regression, we found that a shorter time between the last admission to Erasmus MC was associated with lower susceptibility rates for initiated antibiotic therapy (OR 1.22; 95% CI 1.04, 1.43; p = 0.015). We also found that a shorter the time since the last admission was associated with lower susceptibility for cefuroxime (OR 1.31; 95% CI 1.14, 1.49; p < 0.001). We found no association between age and sex and

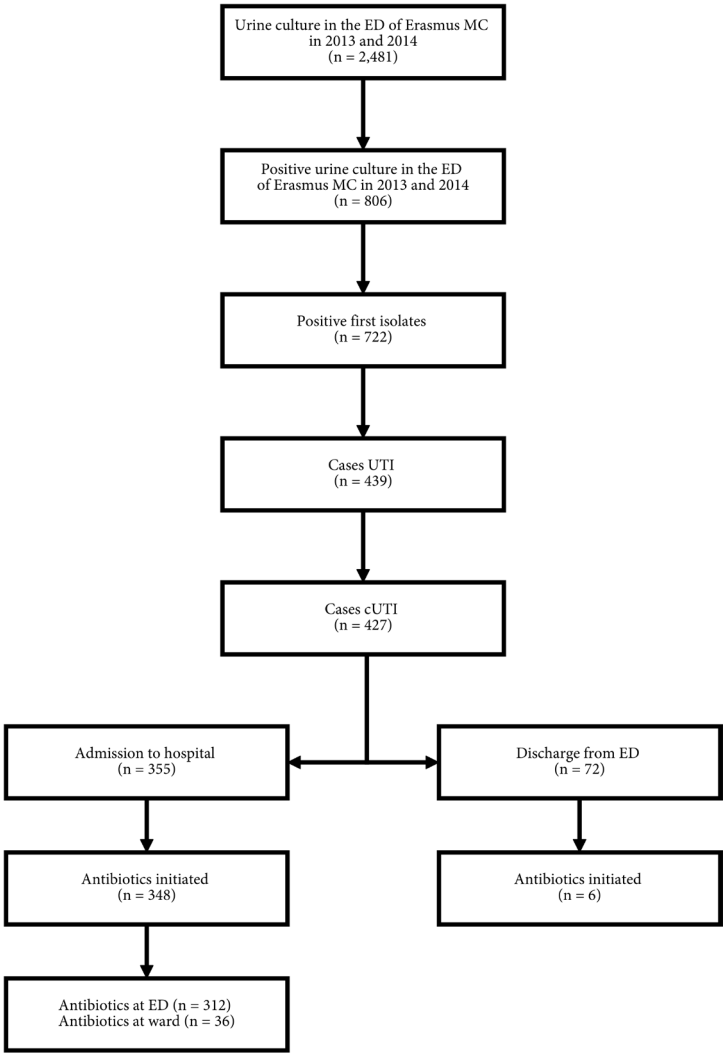

Figure 1: Flow diagram on selection of patients.

ED: eemergency department; UTI: urinary tract infection; cUTI = complicated urinary tract infection.

Table 1: Patient characteristics	
	Patients with cUTI (n = 427)
Sex, male [n (%)]	223 (52.2)
Age [mean (SD)]	59 (17)
First responsible specialism at ED [n (%)]	
Internal medicine	221 (51.8)
Surgery	97 (22.7)
Urology	48 (11.2)
Emergency medicine	6 (1.4)
Other	55 (12.9)
Comorbidities [n (%)]	
Yes	311 (72.8)
Status after renal transplantation	106 (24.8)
Urological problem	193 (45.2)
Immunocompromised status	185 (43.3)
No	115 (26.9)
Time since last admission	
< 3 months [n (%)]	172 (40.3)
3- 6 months [n (%)]	33 (7.7)
7-9 months [n (%)]	21 (4.9)
10-12 months [n (%)]	25 (5.9)
≥ 12 months [n (%)]	106 (24.8)
Never admitted [n (%)]	70 (16.4)
Length of last hospitalization, days*[median (IQR, Range)]	3 (IQR 15, Range 123)
Duration of last hospitalization, days*[median (IQR, Range)]	5 (IQR 7, Range 125)
Number of hospitalizations in the last year*[median (IQR, Range)]	1 (IQR 3, Range 13)
Clinical presentation at ED	
Ill according to physician's discretion [n (%)]	130 (30.4)
Pulse rate, b/min [median (IQR)]	99 (85-112)
SBP, mmHg [median (IQR)]	130 (114-146)
DBP, mmHg [median (IQR)]	75 (65-85)
Breathing frequency, n/min [median (IQR)]	20 (16-25)
Body temperature, °C [median (IQR)]	38.2 (37.2-38.8)
C-reactive protein, mg/l [median (IQR)]	60.0 (23.8-122.2)
Leukocyte count, 109/l [median (IQR)]	11.5 (8.1-15.8)
Pyuria [n (%)]	354 (82.9)

Number of micro-organisms in urinary culture [n (%)]	
1	392 (91.8)
2	35 (8.2)
Micro-organism in urinary culture [n (%)]	n = 462
Escherichia coli	237 (51.3)
Klebsiella pneumoniae	44 (9.5)
Enterococcus faecalis	45 (9.7)
Proteus mirabilis	31 (6.7)
Pseudomonas aeruginosa	26 (5.6)
Group B Streptococcus	12 (2.6)
Other	67 (14.5)

*cUTI: complicated urinary tract infection; n: number; SD: standard deviation; ED: emergency department; SBP: systolic blood pressure; DBP: diastolic blood pressure; IQR: inter quartile range.*Data available for n =357.*

susceptibility (OR 1.30; 95% CI 0.73, 2.31; p = 0.364, and OR 0.98; 95% CI 0.97, 1.01; p = 0.19, respectively). We also found no association between the time in days between the last admission to Erasmus MC and susceptibility for empirical therapy (i.e. cefuroxime and gentamicin) (OR 1.17; 95% CI 0.95, 1.45; p = 0.14).

We tested non-linearity by adding a quadratic term to the natural logarithm of days since the last admission to Erasmus MC. We detected no non-linearity, which implies there is no specific cut-off period for losing non-susceptible uropathogens. Susceptibility for amoxicillin-clavulanic acid, cefuroxime, gentamicin, trimethoprim-sulfamethoxazole, and cefuroxime/gentamicin was lowest if last admission < 3 months ago, and highest for never admitted patients (*Tables 2B-2E*).

In 427 patients with a cUTI, 462 pathogens were cultured (427 single isolates, 35 double isolates). Of 185 index cultures, previous cultures were available. Of all urine cultures obtained within the last year, 56.2% (104/185) contained pathogens different from the index culture. In 71.2%, the current pathogen was susceptible for the initiated antibiotic therapy, compared to 91.4% if the pathogen matched previous cultures (p < 0.001, see *Table 3*).

Of the 427 patients with cUTI, 61 were Erasmus MC-naïve, 251 were admitted < 12 months, and 106 were admitted ≥ 12 months ago. In patients admitted < 12 months ago, uropathogens carried higher resistance rates for the initiated treatment than those of patients who were last hospitalized ≥ 12 months ago, or were never hospitalized (24.3% vs 12.3% vs 12.9%, respectively; p = 0.002, see *Table 4*). Majority of the patients admitted < 12 months ago were admitted in the last three months (68.9%).

Table 2 A: Susceptibility rates of cultured pathogens for frequently prescribed antibiotics in patients hospitalised in Erasmus MC and in the Netherlands, as reported by NethMap

Cultured pathogens (n = 462)	*E. coli* (n = 237)	NethMap *E. coli*	*K. pneumoniae* (n = 44)	NethMap *K. pneumoniae*	*P. mirabilis* (n = 31)	NethMap *P. mirabilis*	*P. aeruginosa* (n = 26)	NethMap *P. aeruginosa*	*E. Faecalis* (n = 45)	Other (n = 67)
Amoxicillin-clavulanic acid										
n	194		36		28		-	-	45(100)	*
%	81.9%	64%	81.8%	81%	90.3%	92%				
95% CI	(76.9-86.8)		(70.0-93.7)		(79.3-100)					
Cefuroxime										
n	199		36		31		-	-	-	*
%	84.0%	87%	81.8%	84%	100%	99%				
95% CI	(79.3-88,7)		(70.0-93.7)							
Meropenem										
n	237		44		31		24		-	*
%	100%	100%	100%	100%	100%	100%	92.3%	99%		
95% CI							(81.3-100)			
Ciprofloxacin										
n	180		36		19		21		-	*
%	75.9%	86%	81.8%	87%	61.3%	88%	80.8%	89%		
95% CI	(70.5-81.4)		(70.0-93.7)		(43.1-79.4)		(64.5-97.0)			
Gentamicin										
n	222		40		27		24	97%	-	*
%	93.7%	95%	90.9%	95%	87.1%	94%	92.3%			
95% CI	(93.2-98.3)		(82.1-99.8)		(74.6-99.6)		(81.3-100)			

Trimethoprim-sulfamethoxazole										
N	139		31		19		-	-	-	*
%	58.6%	77%	70.5%	85%	61.3%	73%				
95% CI	(52.3-65.0)		(56.4-84.5)		(43.1-79.4)					
Nitrofurantoin										
N	226		-	-	-	-	-	-	45 (100)	*
%	95.4%	98%								
95% CI	(92.7-98.1)									
Cefuroxime/ gentamicin										
N	228		40		31	100%	-	-	-	*
%	96.2	98%	90.9	96%	100%					
95% CI	(93.7-98.6)		(82.1-99.7)							

*n: number; %: percentage; 95% CI: 95% confidence intervals.*Due to the large variation in 'other' uropathogens, overall susceptibility in this group was not representative and therefore not mentioned.*

Table 2 B: Susceptibility rates of cultured pathogens for frequently prescribed antibiotics of patients who were admitted < 3 months to Erasmus MC

Cultured pathogens (n = 189)	*E. coli* (n = 84)	*K. pneumoniae* (n = 18)	*P. mirabilis* (n = 12)	*P. aeruginosa* (n = 15)	*E. faecalis* (n = 23)	Other (n = 45)
Amoxicillin-clavulanic acid	62 (73.8)	13 (72.2)	11 (91.7)	-	23 (100)	*
Cefuroxime	66 (78.6)	12 (66.7)	12 (100)	-	-	*
Meropenem	84 (100)	18 (100)	12 (100)	13 (86.7)	-	*
Ciprofloxacin	58 (69.0)	14 (77.8)	7 (58.3)	12 (80.0)	-	*
Gentamicin	76 (90.5)	15 (83.3)	11 (91.7)	14 (93.3)	-	*
Trimethoprim-sulfamethoxazole	41 (48.8)	13 (72.2)	6 (50.0)	-	-	*
Nitrofurantoin	81 (96.4)	3 (17.6)	-	-	23 (100)	*
Cefuroxime/ gentamicin	79 (84.0)	15 (83.3)	12 (100)	14 (93.3)	-	*

*Data presented in number and percentage. *Due to the large variation in 'other' uropathogens, overall susceptibility in this group was not representative and therefore not mentioned.*

Table 2 C: Susceptibility rates of cultured pathogens for frequently prescribed antibiotics of patients who were admitted < 12 months to Erasmus MC

Cultured pathogens (n = 270)	*E. coli* (n = 130)	*K. pneumoniae* (n = 25)	*P. mirabilis* (n = 23)	*P. aeruginosa* (n = 16)	*E. faecalis* (n = 30)	Other (n = 45)
Amoxicillin-clavulanic acid	101 (77.7)	18 (72.0)	21 (91.3)	-	34 (100)	*
Cefuroxime	103 (79.2)	18 (73.0)	23 (100)	-	-	*
Meropenem	130 (100)	25 (100)	23 (100)	14 (87.5)	-	*
Ciprofloxacin	94 (72.3)	20 (80.0)	13 (56.5)	13 (81.3)	-	*
Gentamicin	118 (90.8)	22 (88.0)	20 (87.0)	15 (93.8)	-	*
Trimethoprim-sulfamethoxazole	61 (46.9)	18 (72.0)	13 (56.5)	-	-	*
Nitrofurantoin	125 (96.2)	7 (29.2)	-	-	34 (100)	*
Cefuroxime/ gentamicin	121(93.1)	22 (88.0)	23 (100)	15 (93.8)	-	*

*Data presented in number and percentage. *Due to the large variation in 'other' uropathogens, overall susceptibility in this group was not representative and therefore not mentioned.*

Table 2 D: Susceptibility rates of cultured pathogens for frequently prescribed antibiotics of patients who were admitted ≥ 12 months to Erasmus MC

Cultured pathogens (n = 117)	*E. coli* (n = 65)	*K. pneumoniae* (n = 15)	*P. mirabilis* (n = 6)	*P. aeruginosa* (n = 6)	*E. faecalis* (n = 7)	Other (n = 17)
Amoxicillin-clavulanic acid	53 (81.5)	14 (93.3)	5 (83.3)	-	7 (100)	*
Cefuroxime	58 (89.2)	14 (93.3)	6 (100)	-	-	*
Meropenem	65 (100)	15 (100)	6 (100)	6 (100)	-	*
Ciprofloxacin	50 (76.9)	12 (80.0)	4 (66.7)	5 (83.3)	-	*
Gentamicin	62 (95.4)	14 (93.3)	5 (83.3)	5 (83.3)	-	*
Trimethoprim-sulfamethoxazole	41 (63.1)	9 (60.0)	4 (66.7)	-	-	*
Nitrofurantoin	61 (95.3)	4 (26.7)	-	-	7 (100)	*
Cefuroxime/ gentamicin	65 (100)	12 (92.3)	6 (100)	5 (83.3)	-	*

*Data presented in number and percentage. *Due to the large variation in 'other' uropathogens, overall susceptibility in this group was not representative and therefore not mentioned.*

Table 2 E: Susceptibility rates of cultured pathogens for frequently prescribed antibiotics of patients who were never admitted to Erasmus MC

Cultured pathogens (n = 74)	*E. coli* (n = 42)	*K. pneumoniae* (n = 4)	*P. mirabilis* (n = 2)	*P. aeruginosa* (n = 4)	*E. faecalis* (n = 8)	Other (n = 14)
Amoxicillin-clavulanic acid	40 (95.2)	4 (100)	2 (100)	-	8 (100)	*
Cefuroxime	38 (90.5)	4 (100)	2 (100)	-	-	*
Meropenem	42 (100)	4 (100)	2 (100)	4 (100)	-	*
Ciprofloxacin	36 (85.7)	4 (100)	2 (100)	3 (75)	-	*
Gentamicin	42 (100)	4 (100)	2 (100)	4 (100)	-	*
Trimethoprim-sulfamethoxazole	29 (69.0)	4 (100)	2 (100)	-	-	*
Nitrofurantoin	40 (95.2)	1 (25)	-	-	8 (100)	*
Cefuroxime/ gentamicin	42 (100)	4 (100)	2 (100)	4 (100)	-	*

Data presented in number and percentage. Due to the large variation in 'other' uropathogens, overall susceptibility in this group was not representative and therefore not mentioned.

Discussion

Our study shows that susceptibility rates to empirical intravenous antibiotic therapy in our cohort of patients visiting the ED of a Dutch university hospital are comparable to national epidemiological data. However, resistance to orally available antibiotics is higher for the most frequently cultured pathogens. A shorter time between presentation in the ED and the last admission was associated with lower susceptibility of uropathogens for initiated antibiotic therapy.

As in most studies, we found higher susceptibility rates for meropenem than for cefuroxime and/or gentamicin, which is aligned with NethMap 2018,[383] and are most likely the result of restricted use of carbapenems, since they are considered last-resort antibiotics. In line with the principles of antimicrobial stewardship, carbapenems should continuously be prescribed with caution.[384]

We also found that susceptibility of prevalent uropathogens to frequently prescribed oral antibiotics was lower than nationwide susceptibility rates, especially for ciprofloxacin and trimethoprim-sulfamethoxazole. This difference is most explicit within the subgroup of patients who were admitted within one year before presentation at the ED. It is likely that this discrepancy is due to the specific patient population encountered in university hospitals. Patients who are using immunosuppressive medication or who have anatomical anomalies frequently require treatment with antibiotics and are more often admitted. These patients are not only at risk for UTIs in general, but also for UTIs with more uncommon and more resistant uropathogens.[385,386] Notably, the NethMap report calculates resistance percentages for all hospitals combined and not for university hospitals separately, which probably resulted in higher susceptibility rates.

More than half of the cultured uropathogens differed from previously cultured uropathogens. This finding suggests a high prevalent heterogeneity of uropathogens in single individuals. There was significantly higher resistance for initiated antibiotics in patients who were admitted < 12 months ago, compared to patients admitted ≥ 12 months ago. This confirms the evidence that patients who are frequently admitted to the hospital carry more resistant uropathogens than patients who are less frequently or never admitted.[378,387] We were not able to define a safe cut-off point, since we found a linear association over time, and the longer the time since last hospitalization, the smaller the risk. A cross-sectional study of Teunis *et al.* on duration of carriership of multi drug resistant *E. coli* in a subset of a general adult population showed that the estimated time to lose carriership was approximately 400 days.[388] In the prospective COMBAT (Carriage Of Multiresistant Bacteria After Travel) study, 633 individuals acquired multi drug resistant *E. coli* during travel, in whom median duration of colonization after travel was 30 days, and of whom 11.3% remained colonized 12 months after return; however, this was performed predominantly with individuals without comorbidity and infections.[389] In clinical practice, the results of previously obtained cultures contribute to the decision to initiate an antibiotic regimen, but information from earlier obtained cultures should be applied with caution. Based on our data, we suggest treatment with empiric therapy,

including gentamicin, in all patients – also those who were admitted recently. Antibiotic regimen should be extended and not narrowed, based on cultures obtained in the year before presentation at the ED.

In kidney transplant recipients or patients with severe pre-existent renal insufficiency (eGFR < 30 ml/min) there is continuous discussion on the safety of gentamicin. Evidence for significant nephrotoxicity after a single dose of aminoglycosides is controversial, [374,390] but most physicians are cautious with prescribing aminoglycosides in patients with kidney transplants or severe renal insufficiency.[387,391]

However, these patients accounted for a substantial part of our study population, and for this group, monotherapy with cefuroxime or ciprofloxacin is not advisable, since susceptibility rates were below the threshold of 90%. In these selected groups another empiric regimen, like meropenem, may be justified. Especially in tertiary hospitals, where decision-making regarding the choice for antibiotic treatment in an aging, multimorbid patient population is often complex, antimicrobial stewardship is recommended. However, we also show that guidelines on empiric therapy based on local resistance data are effective, as long as they are followed.

Due to the retrospective nature of our study we encountered several limitations. We selected patients based on positive urinary cultures and subsequently selected patients with cUTIs. In a small but substantial group, this led to misclassification of cUTI: antibiotics were initiated in only six of the 72 patients who met our criteria for cUTI and who were discharged from the ED. Patients with cUTI without positive urinary cultures, for example, due to pre-treatment with antibiotics or due to a negative urinalysis and no subsequent culture, were not selected. This might have led to a selection bias. However, our data (i.e. the cultured uropathogens and their antibiotic susceptibility) were selected are used in the national NethMap data. We also have no information on antibiotic treatment of patients in general practice or in other hospitals, and if antibiotics would have been used, this could potentially have caused an increase in resistance in our population.

Also, important differences between our data and NethMap 2018 results are seen in the susceptibility rates of *E. coli* and *K. pneumoniae* for amoxicillin-clavulanic acid. This is a result of a new test panel for Gram-negative bacteria, resulting in higher minimal inhibitory concentrations for amoxicillin-clavulanic acid and higher resistance levels from 2016 onwards. For our data, susceptibility rates from the period 2013-2014 are applicable. Therefore, we compared our data with NethMap reports for this period and our resistance percentages for amoxicillin-clavulanic acid are comparable.[383]

In conclusion, the distribution and antibiotic susceptibility for intravenous antibiotics of uropathogens in a Dutch university hospital is comparable with overall distribution in the Netherlands. Cefuroxime in combination with gentamicin is therefore an adequate antibiotic regimen for cUTI, and we recommend treating patients accordingly. Extension of the chosen regimen based on earlier cultured pathogens is advised, and narrowing of the antibiotic regimen strongly discouraged, especially the omission of gentamicin.

In a strictly selected population (e.g. recently admitted renal transplant recipients, pre-existing severe kidney insufficiency), prescription of meropenem as an alternative empiric therapy could be considered.

Chapter 13

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Appropriate Empirical Antibiotic Therapy and Mortality: Conflicting Data Explained by Residual Confounding

Abstract

Objective

Clinical practice universally assumes that appropriate empirical antibiotic therapy improves survival in patients with bloodstream infection. However, this is not generally supported by previous studies. We examined the association between appropriate therapy and 30-day mortality, while minimizing bias due to confounding by indication.

Methods

We conducted a retrospective cohort study between 2012 and 2017 at a tertiary university hospital in the Netherlands. Adult patients with bloodstream infection attending the emergency department were included. Based on *in vitro* susceptibility, antibiotic therapy was scored as appropriate or inappropriate. Primary outcome was 30-day mortality. To control for confounding, we performed conventional multivariable logistic regression and propensity score methods. Additionally, we performed an analysis in a more homogeneous subgroup (i.e. antibiotic monotherapy).

Results

We included 1,039 patients, 729 (70.2%) received appropriate therapy. Overall 30-day mortality was 10.4%. Appropriately treated patients had more unfavourable characteristics, indicating more severe illness. Despite adjustments, we found no association between appropriate therapy and mortality. For the antibiotic monotherapy subgroup (n = 449), patient characteristics were more homogeneous. Within this subgroup, appropriate therapy was associated with lower mortality (Odds Ratios [95% Confidence Intervals] ranging from: 0.31 [0.14; 0.67] to 0.40 [0.19; 0.85]).

Conclusions

Comparing heterogeneous treatment groups distorts associations despite use of common methods to prevent bias. Consequently, conclusions of such observational studies should be interpreted with care. If possible, future investigators should use our method of attempting to identify and analyse the most homogeneous treatment groups nested within their study objective, because this minimizes residual confounding.

Introduction

Bacterial infections can result in considerable mortality and have a profound global burden.[392-394]. Patients with a severe infection (e.g. sepsis) often present in an acute care setting, such as the emergency department (ED). Initiation of targeted antibiotic therapy in the ED is important in patients with a suspected bacterial infection and is possible when the causative pathogen is proven by cultures with determination of the antibiogram.[395] However, this process usually takes over 24 hours and therefore empirical therapy is initiated in the ED. Appropriate empirical antibiotic therapy (i.e. appropriate therapy) is defined as applying the antibiotic agent which matches *in vitro* susceptibility of the isolated bacteria, but was initially provided without evidence on the causative pathogen or its antibiogram.[396] Clinical practice universally assumes that appropriate therapy improves survival in patients with bloodstream infection (BSI).

Although an overall beneficial outcome of appropriate antibiotic therapy in patients with BSI was demonstrated by meta-analyses,[397,398] studies that did not find lower mortality continued to be published.[48,396,399-404] An explanation for these conflicting data is confounding by indication,[405] yet this was not investigated in these studies.[48,396,399-404] Confounding by indication arises because patients at risk of dying of BSI are more likely to receive broad spectrum antibiotic therapy – thus more often appropriate – as physicians want to ensure appropriateness most in severely ill patients.[394] This results in an imbalance in – measured and unmeasured – patient characteristics (i.e. underlying risk profile) between appropriately and inappropriately treated patients, thereby biasing the genuine relation between appropriate therapy and mortality.[406]

The main objective of this study was to examine whether administration of appropriate empirical antibiotic therapy affects 30-day mortality in adult patients with BSI attending the ED, while minimizing bias due to confounding by indication. Subsequently, we focused on methodologically explaining why prior investigators suggested no impact of appropriate therapy on survival.

Materials and methods

Study design and setting

We conducted a retrospective cohort study at the Erasmus University Medical Center Rotterdam (Erasmus MC), which is a tertiary university hospital in the Netherlands. We used data from all patients attending the ED with BSI from July 2012 through December 2017. Blood cultures are taken in patients suspected for BSI, and subsequently empiric antibiotic therapy is started. Antibiotic advice is protocolized in guidelines based on local and national prevalence and resistance data.[407,408] These guidelines provide an advice depending on the suspected source of infection and clinical judgement of severity of disease, e.g. working diagnosis. The Medical Ethics Committee of the Erasmus MC concluded that our study did not fall under the scope of the Medical Research Involving

Human Subjects Act and therefore no informed consent needed to be obtained. Our study is registered under MEC-2018-1450.

Selection of participants

Patients were eligible for inclusion if they were at least 18 years of age and had a laboratory proven bacterial BSI at the ED. BSI was defined as presence of a known pathogen in one blood culture or a common commensal (e.g. *S. epidermidis*)[409] in at least two blood cultures collected on separate occasions within two days from ED admission.[409,410] Only the first episode of BSI was included to prevent domination of results by individuals that frequently visited the ED.

Data collection and processing

We combined electronic databases with data from the ED and the department of Medical Microbiology and Infectious Diseases. The ED database included empiric antibiotic therapy administered during the ED visit, potentially relevant and retrospectively available patient characteristics (serving as proxies for severity of disease), and mortality. Treatment strategy was either no antibiotic therapy, antibiotic monotherapy (if only one drug was administered), or antibiotic combination therapy (if more than one drug was administered). Also, patient charts were reviewed to assess dosage errors. General and demographic patients characteristics collected were: sex, age, arrival (by ambulance or other mode of transportation), triage category (according to the Manchester Triage System), [411] disposition (direct intensive care unit admittance or other), chills ,[412] vomiting, [412] need for vasopressors, suspected site of infection (unknown, respiratory, abdominal, urogenital, skin or soft tissue, intravascular or thorax, central nervous system, other), and origin of infection (nosocomial or community-acquired).[413] To account for severity of disease we used the first recorded vital signs (i.e. body temperature, heart rate, respiratory rate, systolic blood pressure, oxygen saturation, and consciousness), whether there was need for any supplemental oxygen, and calculated the National early warning score (NEWS)(Methods S1). [414,415] Additionally, to account for comorbidity we collected all components of the age-adjusted Charlson comorbidity index (CCI) (Methods S1).[416] The primary outcome was 30-day mortality, because we expected 30 days to be a biologically plausible window to represent the effect of appropriate therapy on mortality.[405] For mortality data we used municipal death registration records.

The Medical Microbiology and Infectious Diseases database contained data about type of pathogen and their susceptibility (antibiogram) for all positive blood cultures collected at the ED. Type of pathogen was identified directly in one millilitre of blood by MALDI-TOF MS analysis (Microflex, Bruker Daltonics, Bremen, Germany). The *in vitro* susceptibility to antibiotic agents testing was performed with VITEK 2 (bioMérieux, Marcy l'Etoile, France). Based on earlier applied antibiotic therapy at the ED and established susceptibility of the isolated pathogen, appropriateness of empirical therapy administered at the ED was scored. In accordance with previous studies, no empiric antibiotic therapy, ineffective antibiotic therapy (based on antibiogram or if a

dosage error was reported), or not intravenously administered antibiotic therapy (except for antibiotics with high bioavailability, i.e. metronidazole and ciprofloxacin) were all considered inappropriate.[396-405]

Data analysis and control for confounding bias

For descriptive statistics we examined all patient characteristics among appropriately versus (vs.) inappropriately treated patients. Based on distribution data were tested with an unpaired t-test, chi-squared test, or Fisher's exact test.

We considered patient characteristics as confounders during further analyses if, based on expert knowledge, controlling for the variable would reduce bias when studying the relation between appropriate therapy and 30-day mortality.[406] To improve our propensity score methods, we only included potential confounding variables in our models that were statistically related to outcome, as this decreases variance without increasing bias (*Methods S2*).[417]

We conducted inferential statistics to investigate the association between appropriate therapy and 30-day mortality while attempting to control for confounding by indication. Results were presented as odds ratios (OR) with 95% confidence intervals (CI). We handled missing data using multiple imputations. For efficiency purposes we imputed 20 datasets using the chained equations method.[418]

To limit confounding by indication, we controlled for measured proxies of disease severity (e.g. arrival mode, triage category, direct intensive care unit admittance, components of NEWS, components of CCI) with multiple statistical techniques. First, we performed a conventional multivariable logistic regression analysis. However, this method is known to fall short in case of confounding by indication.[419] Therefore, secondly, we used propensity score methods. Propensity score methods directly focus on indication for treatment under study and potentially provide more precise estimates in studies in which confounding by indication may occur.[419] We applied three analytical procedures with the obtained propensity scores, namely 1) adjustment by logistic regression, 2) stratification, and 3) inverse probability of treatment weighting (Methods S2).[420-422] To assess the impact of potential contaminated BSI (i.e. those with a common commensal on multiple blood cultures), we subsequently performed a sensitivity analysis after exclusion of these patients.

Finally, we attempted to limit confounding bias by selecting patients treated with – appropriate or inappropriate – antibiotic monotherapy. When comparing the total appropriately to inappropriately treated group, we expected various degrees of confounding bias for different treatment strategies (i.e. no antibiotic therapy, antibiotic combination therapy, antibiotic monotherapy). We expected that patients with the lowest acuity and the lowest risk of dying would more often receive no – thus inappropriate – antibiotic therapy. We also expected that severely ill patients with high chance of dying are more likely to receive antibiotic combination therapy to broaden the spectrum,

Table 1: Patient characteristics in appropriately versus inappropriately treated patients (total population)

	Appropriate n = 729 (70.2)	Inappropriate n = 310 (29.8)	P-value
Characteristic			
Sex, male	425 (58.3)	201 (64.8)	.06
Age, mean (SD), years*	60.9 (15.5)	60.1 (15.9)	.44
Arrival by ambulance*	202 (27.7)	47 (15.2)	<.001
Triage category, acute/highly urgent*,†	205 (29.6)	33 (11.1)	<.001
Direct intensive care unit admittance*	66 (9.1)	8 (2.6)	<.001
Chills*	311 (42.7)	134 (43.2)	.92
Vomiting	178 (24.4)	68 (21.9)	.43
Need for vasopressors*	36 (4.9)	5 (1.6)	.02
Suspected site of infection, unknown	169 (23.2)	70 (22.6)	.90
Origin, nosocomial	384 (52.7)	175 (56.5)	.29
Comorbidities, any‡‡	673 (92.3)	277 (89.4)	.15
Antibiotic treatment strategy			
Combination therapy	382 (52.4)	22 (7.1)	<.001
Monotherapy	347 (47.6)	102 (32.9)	<.001
No antibiotic therapy	0 (0.0)	186 (60.0)	<.001
Vital signs			
Body temperature, mean (SD), °C*,‡	38.4 (1.2)	38.0 (1.1)	<.001
Heart rate, mean (SD), /min§	108 (23.8)	100 (19.6)	<.001
Respiratory rate, mean (SD), /min*,‖	24 (8.5)	21 (7.1)	<.001
Systolic blood pressure, mean (SD), mmHg*,¶	125 (28.5)	125 (24.5)	.77
Oxygen saturation, mean (SD), %**	95 (5.8)	96 (2.4)	<.001
Any supplemental oxygen*	339 (46.5)	62 (20.0)	<.001
Consciousness, not alert*,††	96 (15.5)	16 (6.5)	<.001
NEWS, mean (SD)	6.0 (3.8)	3.8 (3.1)	<.001

*Data are presented as No. (%) unless otherwise indicated. Data in this table is not imputed yet. NEWS, national early warning score. *Confounding variables. †Data on triage category were missing for 50 (4.6%) patients. ‡Data on body temperature were missing for 9 (0.9%) patients. §Data on heart rate were missing for 24 (2.3%) patients. ‖Data on respiratory rate were missing for 370 (35.5%) patients. ¶Data on systolic blood pressure were missing for 20 (1.9%) patients. **Data on oxygen saturation were missing for 43 (4.3%) patients. ††Data on consciousness were missing for 175 (16.8%) patients. ‡‡Table S1.*

resulting in more often appropriate therapy. Therefore, when studying the relation between appropriate therapy and mortality in the total population, including these treatment strategies potentially contributes to large heterogeneity between appropriately and inappropriately treated patients, which increases risk of confounding bias. We expected that the subset of patients who received antibiotic monotherapy was the least

confounded group with more homogeneous measured and unmeasured confounders. All hypothesis tests were 2-sided, with a significance level of P <.05. Statistical analyses were performed using R version 3.4.4.

Results

Patient characteristics

We identified 1.286 adult patients with a positive laboratory proven blood culture taken at the ED. We excluded 247 patients with recurrent BSI, resulting in 1.039 unique patients of whom 729 (70.2%) received appropriate therapy and 310 (29.8%) received inappropriate therapy. Mortality was 10.4%. Patient characteristics are shown in *Table 1*.

Patients receiving appropriate therapy had less favourable measured characteristics than patients receiving inappropriate antibiotic therapy: they more frequently arrived by ambulance (27.7% vs. 15.2%), had higher triage categories (29.6 % vs. 11.1%), were more often admitted directly to the intensive care unit (9.1% vs. 2.6%), needed vasopressors more frequently (4.9% vs. 1.6%), and received more antibiotic combination therapy (52.4% vs. 7.1%). In addition, appropriately treated patients had more abnormal vital signs and on average a higher NEWS of 6.0 (± 3.8) vs. 3.8 (± 3.1).

Appropriate empirical antibiotic therapy and 30-day mortality

Crude 30-day mortality for appropriately treated patients was 11.1% (81 patients) vs. 8.7% (27 patients) for inappropriately treated patients (OR [95%CI]: 1.31 [0.84; 2.10]). There was no association between appropriate therapy and 30-day mortality after conventional adjustment for confounders, adjustment for propensity score, propensity score stratification and inverse probability of treatment weighting (OR[95%CI] ranging from: 0.71 [0.43; 1.19] to 1.03 [0.76; 1.40], Fig 1).

For sensitivity analysis, we examined the impact of excluding patients with common commensal bacteria on multiple blood cultures collected on separate occasions within two days from ED admission. In our study, 24 patients had at least two subsequent blood cultures with a common commensal (17 *Staphylococcus epidermidis*, 3 *Staphylococcus hominis*, 1 *Bacillus licheniformis*, 1 *Rhodococcus equi*, 1 *Staphylococcus capitis*, and 1 *Staphylococcus lugdunensis*). Appropriate therapy was administered in 9 (37.5%) patients. Excluding these patients did not affect our results.

Subgroup analysis antibiotic monotherapy

There were 449 patients treated with antibiotic monotherapy of whom 347 (77.3%) received appropriate therapy. Mortality was 7.1%. Patient characteristics were comparable for appropriately and inappropriately treated patients, indicating more homogeneity in the monotherapy subgroup compared to the total population (*Table 2*).

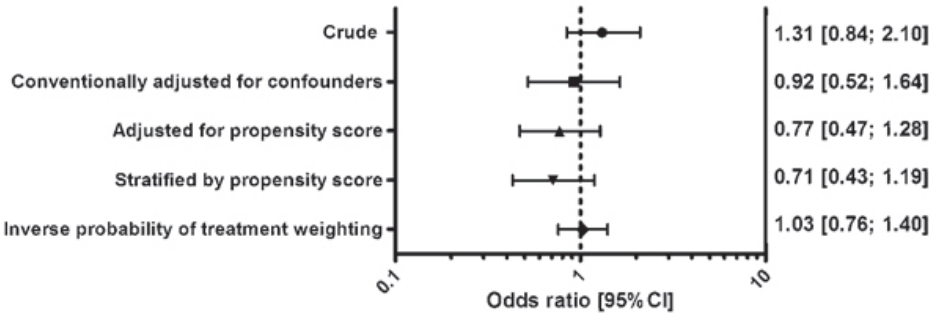


Figure 1. Estimates of appropriate empirical antibiotic therapy on 30-day mortality (total population).

CI: confidence interval. Confounding variables: age, arrival, triage category, direct intensive care unit admittance, chills, need for vasopressors, body temperature, respiratory rate, systolic blood pressure, supplemental oxygen, consciousness, diabetes mellitus with end-organ damage, mild liver disease, malignancy, chronic kidney disease, chronic obstructive pulmonary disease, cerebrovascular accident or transient ischemic attack, and dementia. For a detailed description of statistical adjustment techniques, see Methods S2. This figure shows attenuation of estimates after adjustment for confounders.

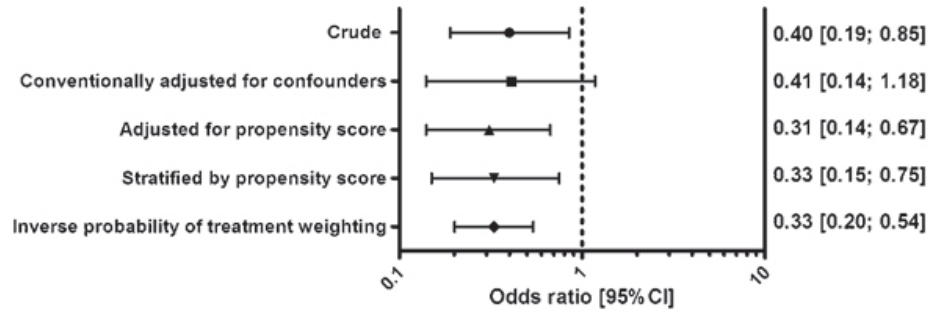


Figure 2. Estimates of appropriate empirical antibiotic therapy on 30-day mortality (antibiotic monotherapy).

CI: confidence interval. Confounding variables: age, arrival, triage category, direct intensive care unit admittance, chills, need for vasopressors, body temperature, respiratory rate, systolic blood pressure, supplemental oxygen, consciousness, diabetes mellitus with end-organ damage, mild liver disease, malignancy, chronic kidney disease, chronic obstructive pulmonary disease, cerebrovascular accident or transient ischemic attack, and dementia. For a detailed description of statistical adjustment techniques, see Methods S2. This figure shows attenuation of estimates after adjustment for confounders.

Table 2: Patient characteristics in appropriately versus inappropriately treated patients (antibiotic monotherapy)

	Appropriate n = 347 (77.3)	Inappropriate n = 102 (22.7)	P-value
Characteristic			
Sex, male	200 (57.6)	67 (65.7)	.18
Age, mean (SD), years*	60.1 (15.4)	63.0 (15.1)	.09
Arrival by ambulance*	55 (15.9)	14 (13.7)	.71
Triage category, acute/highly urgent*	52 (15.7)	12 (12.2)	.49
Direct intensive care unit admittance*	10 (2.9)	2 (1.9)	>.99
Chills*	164 (47.3)	47 (46.1)	.92
Vomiting	86 (24.8)	21 (20.6)	.46
Need for vasopressors*	3 (0.9)	2 (2.0)	.70
Suspected site of infection, unknown	86 (24.8)	20 (19.6)	.34
Origin, nosocomial	207 (59.7)	63 (61.8)	.79
Comorbidities, any†	322 (92.8)	95 (93.1)	>.99
Vital signs			
Body temperature, mean (SD), °C*	38.3 (1.1)	38.1 (1.2)	.05
Heart rate, mean (SD), beats/min	103 (20.6)	100 (21.6)	.21
Respiratory rate, mean (SD), breaths/min*	21 (7.0)	20 (6.4)	.21
Systolic blood pressure, mean (SD), mmHg*	128 (25.7)	123 (21.1)	.05
Oxygen saturation, mean (SD), %	96 (5.5)	96 (2.3)	.67
Any supplemental oxygen*	106 (30.5)	33 (32.4)	.82
Consciousness, not alert*	18 (6.3)	7 (8.5)	.65
NEWS, mean (SD)	4.5 (3.0)	4.3 (3.4)	.48

*Data are presented as No. (%) unless otherwise indicated. Data in this table is not imputed yet. NEWS: national early warning score. *Confounding variables. †Table S2.*

In the monotherapy subgroup, crude 30-day mortality for appropriately treated patients was 5.5% (19 patients) vs. 12.7% (13 patients) for inappropriately treated patients. Appropriate therapy was associated with lower 30-day mortality after crude estimation, adjustment for propensity score, propensity score stratification, and inverse probability of treatment weighting (OR [95%CI] ranging from: 0.31 [0.14; 0.67] to 0.40 [0.19; 0.85], *Figure 2*). Conventional adjustment for confounders had an OR with 95%CI of 0.41 [0.14; 1.18].

Discussion

This study aimed to address the confounding that exists in establishing the effects of antibiotic appropriateness in patients with BSI. Despite extensive adjustment for confounding, we found no association between appropriate empirical antibiotic therapy and mortality when assessing all patients. This finding – in line with previous studies [396,399-404] – remains counterintuitive and is in contrast to fundamentals of current clinical practice. [394]

We hypothesized that confounding by indication was the explanation for finding no association between appropriate therapy and mortality in previous studies. Patients at risk of dying of BSI are more likely to receive broad spectrum antibiotic – thus more often appropriate – therapy as physicians want to ensure appropriateness most in severely ill patients. As a result, the association between appropriate therapy and mortality is biased. In our study, the first clue for confounding by indication was more unfavourable patient characteristics in the appropriately treated group. We noticed this heterogeneity as well in the study of Anderson *et al*., which also found no association between appropriate therapy and mortality. [404] However, the authors did not consider confounding by indication as a potential explanation for their findings. [404] A second clue for confounding was attenuation of estimates when controlling for bias – with both conventional multivariable logistic regression and propensity score methods. We noticed that in prior studies, that also found no association, there was attenuation of estimates after adjustment for confounders. [401,402] Since we only adjusted for observed confounders, unmeasured – residual – confounders could still be of potential bias.

Chance of residual confounding is absent in totally homogenous groups (e.g. as in an ideal randomized controlled trial). [406] Our total population was heterogeneous in measured patient characteristics and we expected various degrees of confounding bias for different treatment strategies. We expected that patients receiving antibiotic combination – thus more often appropriate – therapy were the most ill and patients receiving no antibiotic therapy – thus inappropriate therapy – were the lower acuity patients. The remainder of patients received antibiotic monotherapy. Therefore, to obtain more homogeneous patient groups we performed a subgroup analysis for patients treated with antibiotic monotherapy. Physicians chose to treat these patients with antibiotic monotherapy, presumably based on a more comparable judgment of illness. In addition, the severely confounded treatment strategies – i.e. antibiotic combination therapy and no antibiotic therapy – are per definition excluded during this subgroup analysis. We found that for antibiotic monotherapy measured patient characteristics of appropriately and inappropriately treated patients were more homogeneous, lowering the chance of residual confounding. In this subgroup appropriate therapy was associated with lower 30-day mortality. This finding is in line with our expectations and current practice, and supports our hypothesis that residual confounding distorts associations when comparing heterogeneous treatment groups.

Reducing confounding by indication through analysing homogeneous subgroups – in

our study antibiotic monotherapy – is not often done. Previous studies on appropriate therapy and mortality disregarded severely confounded treatment strategies (i.e. antibiotic combination therapy, no antibiotic therapy), which resulted in comparison of heterogeneous groups. [396,399-404] Therefore, the conclusions of these studies are potentially not trustworthy.

To prevent confounding, we adjusted for validated risk scores (e.g. NEWS, CCI) and applied several adjustment techniques (i.e. conventional multivariable logistic regression and propensity score methods). However, for the total population, these techniques fell short and we were unable to prevent bias. Apparently, a physicians' decision to initiate a certain therapy is not only based on findings that are represented by such risk score systems, hence statistical adjustment techniques fall short. Thus, conclusions of observational studies comparing heterogeneous groups should be interpreted with care. If possible, future investigators should use our method of attempting to identify and analyse the most homogeneous treatment groups nested within their study objective, as we demonstrated that this minimizes residual confounding.

Limitations

Our study has limitations. First, we used retrospectively collected data making our study prone to bias. However, the quality of available data was assumed to be high as all data used was essential for daily clinical practice. For only 13 patients (1.3%) documentation was unclear on whether antibiotic therapy was administered at the ED or after discharge, therefore we scored them as inappropriate therapy.

Also, we want to emphasize that we considered the association between empiric antibiotic treatment at the ED and 30-day mortality, as this was our main study objective. Depending on disease course and culture results, antibiotic treatment could have been modified later on resulting in a different definitive antibiotic treatment. Aside from empiric antibiotic treatment at the ED, this may have altered survival as well.

Conclusions

We initially found that appropriate empirical antibiotic therapy was not beneficial in patients with BSI. We showed that this counterintuitive finding was presumably the result of residual confounding. Analysing heterogeneous treatment groups results in confounding, which distorts associations and subsequent conclusions despite the use of common methods to prevent bias. With a subgroup analysis in a more homogeneous population (i.e. antibiotic monotherapy), we found the expected benefit of appropriate therapy. Our study underlines the complexities of performing clinical observational research. In case of heterogeneous groups results should always be interpreted with care. If possible, future investigators should attempt to identify and analyse the most homogeneous treatment groups nested within their study objective, because this minimizes residual confounding.

Supporting information files

Methods S1. Detailed description variables

National early warning score

We collected all vital signs of the National early warning score (NEWS):[414] body temperature, heart rate, respiratory rate, systolic blood pressure, oxygen saturation, any supplemental oxygen, and consciousness (AVPU score: alert, voice, pain, unresponsive).[414]

Each vital sign was graded 0-3.[414] Scores for vital signs were added to obtain a total score. A NEWS over 7 triggers urgent clinical review. See supplementary methods S1 Table 1 for more information about grading of vital signs.[414]

Methods S1 Table 1: National early warning score grading

Grading of vital signs	3	2	1	0	1	2	3
Body temperature, °C	< 35.0		35.1–36.0	36.1–38.0	38.1–39.0	> 39.0	
Heart rate, beats/min	< 41		41–50	51–90	91–110	111–130	> 130
Respiratory rate, breaths/min	< 91	91–100	101–110	111–219			> 219
Systolic blood pressure	< 9		9–11	12–20		21–24	> 25
Oxygen saturation	< 92	92–93	94–95	> 96			
Any supplemental oxygen		Yes		No			
Consciousness AVPU (Alert, Verbal, Pain, Unresponsive)				Alert			Not alert

Charlson comorbidity index

We collected all comorbidities of the Charlson comorbidity index (CCI):[416] diabetes mellitus (uncomplicated or end-organ damage), liver disease (mild or moderate to severe), malignancy (leukaemia, lymphoma, localized solid tumour, or metastatic solid tumour), acquired immunodeficiency syndrome, chronic kidney disease, congestive heart failure, myocardial infarction, chronic obstructive pulmonary disease, peripheral vascular disease, cerebrovascular accident or transient ischemic attack, dementia, hemiplegia, connective tissue disease, and peptic ulcer disease.

Table S1: Comorbidities of Charlson comorbidity index (total population)

Comorbidities	Appropriate n = 729 (70.2)	Inappropriate n = 310 (29.8)	P value
Diabetes mellitus, uncomplicated	147 (20.2)	53 (17.1)	.29
Diabetes mellitus, end-organ damage*	10 (1.4)	3 (1.0)	.77
Liver disease, mild*	93 (12.8)	47 (15.2)	. 35
Liver disease, moderate to severe	6 (0.8)	3 (1.0)	>.99
Malignancy, leukaemia, lymphoma, localized solid tumour*	120 (16.5)	61 (19.7)	.25
Malignancy, metastatic solid tumour*	93 (12.8)	40 (12.9)	>.99
Acquired immunodeficiency syndrome	2 (0.3)	1 (0.3)	>.99
Chronic kidney disease*	124 (17.0)	45 (14.5)	.37
Congestive heart failure	96 (13.2)	37 (11.9)	.66
Myocardial infarction	103 (14.1)	36 (11.6)	.32
Chronic obstructive pulmonary disease*	95 (13.0)	39 (12.6)	.92
Perivascular disease	77 (10.6)	44 (14.2)	.12
Cerebrovascular accident or transient ischemic attack*	115 (15.8)	26 (8.4)	.002
Dementia*	30 (4.1)	6 (1.9)	.12
Hemiplegia	3 (0.4)	0 (0.0)	.62
Connective tissue disease	57 (7.8)	20 (6.5)	.52
Peptic ulcer disease	17 (2.3)	8 (2.6)	>.99

*Data are presented as No. (%) unless otherwise indicated. *Confounding variables.*

Methods S2. Statistical appendix

Propensity score methods

We obtained the propensity score by multivariable logistic regression, with appropriate empirical antibiotic therapy (AEAT) as dependent variable and all confounders as independent variables. The propensity score is a balancing score, ranging from 0 to 1, representing probability of AEAT assignment conditional on observed confounders.[420]

We applied three analytical procedures with the obtained propensity score. First, we used the propensity score as single independent covariate representing all confounders during logistic regression. Then we stratified on propensity score by bins of 0.1. For patients within the same bin, distribution of observed confounders is conditionally similar for appropriately and inappropriately treated patients if there is overlap in propensity score. This concept mimics process of randomization. After trimming all patients with non-overlapping propensity scores we obtained odds ratios with standard comparison and performed Mantel-Haenszel pooling.[420] Finally, we used inverse probability of treatment weighting as adjustment technique, which uses the propensity score as a weight during subsequent standard comparison.[417]

Based on previous simulation studies, we only included potential confounding variables in our statistical models that were statistically related to outcome (relative risk > 1.3) as this decreases variance without increasing bias]. [417] This is mainly important for our propensity score model. Including variables not associated with outcome (30-day mortality), but with exposure (AEAT) can lead to overseparation.

Propensity scores were estimated in our total population and subsequently used in subgroup analyses (i.e. antibiotic monotherapy). Recent simulation studies showed this is a feasible approach.[422]

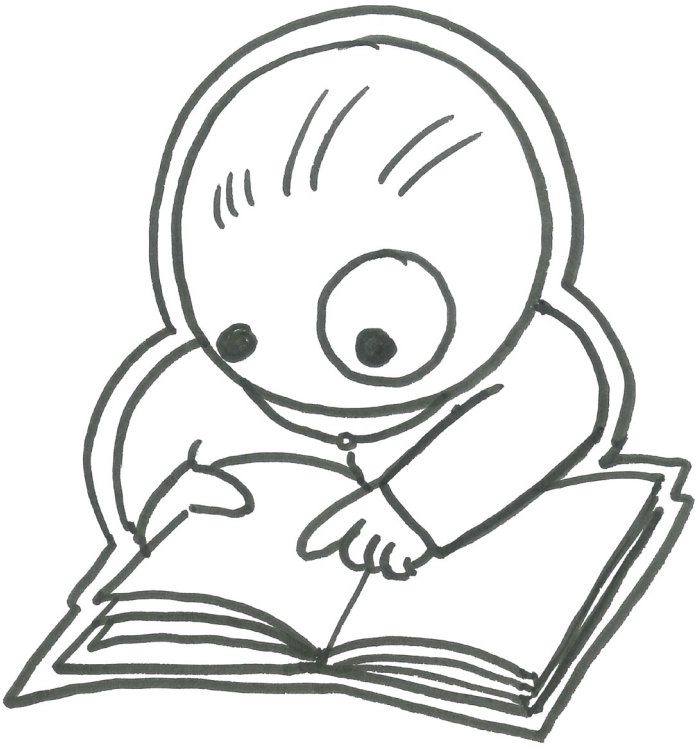
Table S2: Comorbidities of Charlson comorbidity index (antibiotic monotherapy)

Comorbidities	Appropriate n = 347 (77.3)	Inappropriate n = 102 (22.7)	P value
Diabetes mellitus, uncomplicated	64 (18.4)	17 (16.7)	.79
Diabetes mellitus, end-organ damage*	5 (1.4)	0 (0.0)	.59
Liver disease, mild*	53 (15.3)	15 (14.7)	>.99
Liver disease, moderate to severe	2 (0.6)	2 (2.0)	.22
Malignancy, leukaemia, lymphoma, localized solid tumour*	64 (18.4)	20 (19.6)	.90
Malignancy, metastatic solid tumour*	45 (13.0)	19 (18.6)	.20
Acquired immunodeficiency syndrome	2 (0.6)	1 (1.0)	.54
Chronic kidney disease*	85 (24.5)	21 (20.6)	.49
Congestive heart failure	52 (15.0)	11 (10.8)	.36
Myocardial infarction	48 (13.8)	16 (15.7)	.76
Chronic obstructive pulmonary disease*	39 (11.2)	19 (18.6)	.07
Perivascular disease	31 (8.9)	13 (12.7)	.34
Cerebrovascular accident or transient ischemic attack*	57 (16.4)	11 (10.8)	.21
Dementia*	11 (3.2)	1 (1.0)	.39
Hemiplegia	1 (0.3)	0 (0.0)	>.99
Connective tissue disease	27 (7.8)	6 (5.9)	.67
Peptic ulcer disease	9 (2.6)	3 (2.9)	.88

*Data are presented as No. (%) unless otherwise indicated. *Confounding variables.*

General Discussion, Conclusions and Further Research Directives

Summary



Chapter 14

General Discussion, Conclusions and Further Research Directives

In 2012, acute medicine was recognized as a subspecialty of internal medicine in the Netherlands. Acute medicine has evolved since then and is nowadays a fully-fledged specialisation of internal medicine. However, compared to most other subspecialties in internal medicine, research in acute medicine is still in its infancy. The research described in this thesis addresses the diversity of pathology encountered in the Emergency Department (ED) in order to improve quality of patient care in the acute care chain. This thesis aims to add to this area by studying: 1) the value of history, physical examination, and additional testing in the early identification of severity of illness in individual patients; 2) prediction models for risk of admission, mortality or catastrophic deterioration and early warning systems to identify the most severely ill; 3) factors that influence the choice of antibiotic therapy in patients with suspected infection and predictors of antibiotic susceptibility, in order to achieve appropriate antibiotic treatment in the severely ill.

In this chapter we summarize the main findings of this thesis, discuss these findings and place them under a unifying perspective. Last, we give suggestions for further research.

The value of history taking, clinical examination and additional testing in the early identification of illness in individual patients

Despite an ongoing increase in readily available technology in medicine, evidence still supports the importance of history taking and physical examination in diagnosis in the ED, in order to ensure appropriate treatment.[423] The timing and sequence of history taking and physical examination as part of the overall assessment differ between acutely and non-acutely ill patients. Ideally, in acutely ill patients the ABCDE approach is used to assess the patient and initiate treatment, while in non-acutely ill patients a complete history and physical examination is performed. In the ABCDE approach each step life-threatening problems should be treated before continuing to the next, following the principles "Treat first what kills first" and "Do no further harm". This approach was first used in the Advanced Trauma Life Support, which was developed by James Styner in 1976,[22] and are incorporated in many courses for management of acutely ill patients, such as the ALS course.[424] Despite its more than 30 years history, there remains insufficient evidence that use of the ABCDE approach in acutely ill patients reduces death rates and disability, being supported primarily by expert consensus.[383] There is a positive effect of training the ABCDE approach on cognitive knowledge, critical decision making and practical skills.[425]

In this **first part of this thesis** we studied the value of history, physical examination and additional testing in the early identification of severity of illness in individual patients.

In the ABCDE approach, 'Circulation' is assessed in order to identify a patient in shock. Physicians use clinical examination, vital signs and laboratory testing and other diagnostic findings, in order to predict the type and severity of shock.[426-428] A low systolic blood pressure is commonly associated with shock, and hypotension (i.e. systolic blood pressure ≤ 90 mmHg) is widely accepted as a potential sign of circulatory failure. However,

hypotensive patients can have normal tissue perfusion, and, as we show in **Chapter 6**, hypotension can have a benign aetiology, as in patients with postural orthostatic tachycardia syndrome (POTS), where a change to supine position leads to hypotension and tachycardia. Also, normotension does not rule out shock since in some patients with shock the blood pressure can be normal, as the result of habitual hypertension, or when compensation mechanisms are still intact (i.e. compensated shock).[24,429] In compensated shock heart rate increases, but this increase can be influenced by patient factors (e.g. anxiety, resting heart rate) as well as medications.[429] In patients with shock, respiratory rate increases first, even before an increase in heart rate or a drop in blood pressure. This makes respiratory rate a clinically strong and early indicator of (worsening of) illness and shock.[430] However, the reliability of measurements of respiratory rate is mostly poor. In the ED, respiratory rates are often estimated instead of actually counted, [431] resulting in inaccurate measurements. When it is counted for an abbreviated period rather than a full minute (e.g. 15 or 30 seconds), measurements are less accurate.[432,433] Individuals who are aware that their respiratory rate is being assessed tend to breathe more slowly.[432] A study in six large tertiary-care centres in the United States showed that 72% of the respiratory rates recorded in patient charts were 18 or 20 per minute. When they counted respiratory rates for 60 seconds, these rates were found in only 13% of the patients and they concluded that respiratory rates of 18 and 20 are overrepresented in patient charts.[68] Thus, in order to be of use in the early detection of severe illness respiratory rate should be properly measured, preferably by both nurses and physicians, and it should be counted for a longer period of time, or appropriate adjuncts should be used (e.g. stopwatch, mobile applications) .

Physicians do not only rely on vital signs; they also make use of clinical parameters such as altered mentation, cold, clammy, mottled skin and oliguria. These clinical parameters are the consequences of microvascular alterations. In the early phases of shock compensatory mechanisms lead to reduced blood flow in skin and muscle, resulting in a cold and mottled skin. Sweating stops in order to maintain sufficient fluid for the circulation. These parameters can be non-invasively assessed using the capillary refill time, mottling scores (e.g. the knee mottling score) and temperature assessment of the extremities or an increased peripheral temperature gradient – all of these reflect an impaired circulation.[27,426,434] Most of these parameters have been validated in studies within intensive care units (ICUs) [27] but validation studies in the ED are lacking, despite also being frequently used in this setting. Unfortunately, even when using these clinical parameters the accuracy of physicians for recognizing a compromised circulation hovers around 50%.[27]

To improve diagnostic accuracy, physicians also employ laboratory testing (clinical chemistry) for biochemical parameters. The most used marker for hypoperfusion is lactate,[426] and hyperlactatemia (i.e. lactate > 2mEq/L) is part of the latest definition of septic shock.[16] In the ICU, hyperlactatemia is associated with worse outcomes.[435] This association was initially confirmed in the ED.[436,437] However, a study of Lee *et al.* on septic patients showed that lactic acidosis was better than hyperlactatemia in predicting in hospital mortality[438] and a study of van den Nouland *et al.* showed that

outcome of patients with an elevated lactate was related to the underlying cause of the hyperlactatemia (i.e. type A (tissue hypoxia) or type B (non-hypoxia)).[439] Hohenstein *et al.* showed that the use of lactate in an unselected population is limited, as an elevated lactate was only associated with hospitalization.[440] Thus, there is little value derived from a single elevated lactate measurement in an unselected population – especially in the ED, except potentially among patients in whom shock is suspected.

In order to assess the usability of capillary refill time (CRT) as part of initial assessment of the circulation, we studied in **Chapter 2** the interobserver agreement on CRT, which was moderate at best. We confirmed that CRT should be corrected for age and sex, as it increases with age and differs between sexes. Although already published in 1988,[50] these corrections are not generally used, as most assessments still use a dichotomized cut-off value of 2 seconds.[424] The low interobserver agreement, the variability between different sexes and age groups and the low discriminative power all make CRT an unsuitable screening test in the assessment of circulation. However, repeated measurements of CRT can be used as a parameter for the monitoring of circulation. In a study among patients with septic shock admitted at the ICU a resuscitation strategy that targeted normalization of capillary refill time was shown to be as good as a strategy targeting serum lactate levels. Despite the fact that all patients were admitted to the ICU, in 25% of them the CRT was not prolonged, also illustrating that CRT is not appropriate as a screening test to predict severity of illness in the ED.[441]

Another parameter that is used to assess the circulation is an increased peripheral temperature gradient: an underarm to fingertip difference of more than 4 degrees Celsius is associated with both increased mortality and morbidity in ICU patients,[442] but this temperature gradient should not be used without other hemodynamic parameters.[434] In **Chapter 3** we were unable to validate the association between an increased temperature gradient and potential shock in an ED population. We also studied the perfusion index (PI) and the pleth variability index (PVI), which are both derived from the pulse oximeter, and are therefore easy to obtain. Changes in the PI reflect changes in peripheral temperature and can potentially be used to more objectively assess peripheral perfusion in critically ill patients.[443] PVI is an automatic measurement of the respiratory variation of the plethysmographic waveform, and is therefore potentially useful in predicting fluid deficit and fluid responsiveness.[444] Unfortunately both PI and PVI were unable to distinguish patients with a decreased cardiac output.

There are several explanations for the conflicting results between our findings and existing literature. First, patients in the ED are more influenced by ambient factors in comparison to hospitalized patients. Assessment takes place shortly after admission in the ED and patients come from their homes or in less controlled environments (e.g. ambulance, car, open air). This is in contrast with the ICU and operating rooms, which often have strictly controlled environments. Ambient temperature has an effect both on skin temperature and peripheral circulation and it also affects the usefulness of measurements CRT, temperature gradients, PI and PVI. Another explanation is that patients presenting in the ED more likely to be in the earlier phases of illness, and shock

is still being compensated, making diagnosis more difficult. Lastly, patients are more mobile in the ED than in the ICU or during surgery. In the ED they are most often not sedated, whereas patients who are acutely ill often have impaired consciousness (as a consequence of illness or medication) and they are harder to instruct, resulting in artefacts and interference with measurements. This shows that not all the results of studies performed in the ICU can be directly applied in the ED, and that studies that proved beneficial in the ICU should be first be validated outside the ICU, for example, in the ED or the wards.

Of the potential indices we evaluated in the ED, only axillary humidity – measured by a hygrometer - showed an association with fluid deficit. Measurement with a hygrometer is an improvement compared to the older studies on axillary humidity, where it was subjectively measured by assessing the moistness of a patient's armpits, or by weighing tissues which absorbed sweat.[26] We see the potential of hygrometer-derived axillary humidity for use within the in-hospital and prehospital settings and for both screening and monitoring. This is particularly useful for monitoring patient groups that have a greater risk for dehydration, such as elderly and children. Measuring axillary humidity can potentially yield more useful insights on fluid deficit compared to using physical signs, such as blood pressure, heart rate, CRT, skin turgor and dry mucous membranes. However, its current form prevents it from being directly put in to practice, and improved and validated sensors are needed.

Patients suspected of fluid deficit (i.e. dehydration and volume depletion) are treated with fluid therapy. The use of fluid therapy is already changing from liberal to restrictive. Still, the surviving sepsis campaign guidelines advise rapid administration of crystalloids (30mL/kg body weight).[44] This is a strong recommendation; however, evidence from the literature is sparse and in the management of patients with septic shock this early goal-directed therapy failed to reduce mortality compared to usual care.[445,446] Aggressive fluid therapy is not without risks. There is an association between a positive fluid balance and an increased risk of acute kidney injury.[445] In many patients in the ED fluids are initiated, and, as we show in **Chapter 7**, this affects further course of hospitalization. Patients who received intravenous fluids urinated more frequently in the hospital than at home. This is a sign that their fluid status did not require that much additional fluids and that the amount of intravenous fluids potentially could have been lowered or even stopped. It might be better to do more fluid resuscitation more aggressively for patients in the ED, but more judiciously when they go to the wards in order to prevent iatrogenic damage. It will also contribute to a better quality of sleep.

In **Chapter 4**, we studied patients with severely elevated blood pressure in the ED. We found that hypertensive urgency and emergency could not be ruled out based on history and physical examination alone. The Dutch clinical practice guideline on hypertensive urgency and emergency which advises additional tests was inconsistently followed. Although guidelines are developed to improve the quality of care received by patients, not all recommendations in guidelines seem appropriate and valid, and there are more guidelines that are not strictly followed.[447,448] Physicians can – and should - deviate from

guidelines, based on proper arguments. However, when deviating from the guidelines based on history and physical examination, physicians should know the probability of disease and the sensitivity, specificity and diagnostic accuracy of history, physical examination and additional testing and, ideally, guidelines should be based on studies containing such information. Benabbas *et al.* systematically reviewed paediatric acute appendicitis and found that no single finding during history and physical examination could eliminate the need for imaging. A negative ultrasound should be followed by a CT or MRI,[449] and this is implemented in Dutch guidelines, for both children and adults.[50,451] In a review on ED patients with suspected acute coronary syndromes (ACS), Dezman *et al.* concluded that findings in history and physical examination can be used to identify high and low risk groups for acute coronary syndrome, but further investigation with laboratory measurements and electrocardiogram is required to safely rule it out,[452] and this is also implemented in primary and secondary healthcare guidelines.[453,454] We recommend not to deviate from the guideline on severe hypertension solely based on history taking and physical examination.

In **Chapter 5** we describe patients in the ED with medically unexplained physical symptoms (MUPS). In this study, the patient characteristics of in-patients with MUPS were similar to those of outpatients with MUPS. On the other hand, characteristics of patients referred by a GP differed from those who self-presented at the ED. Referred patients had more cardiorespiratory complaints, while self-presenting patients presented more with (abdominal) pain and fatigue. These differences might be the result of guidelines. GP guidelines state that patients with suspected ACS or pulmonary embolism should be (immediately) referred to a hospital, whereas watchful waiting can be done in patients with abdominal pain that is unlikely to be an acute abdomen. It is possible that GPs followed these guidelines, but it could also be a result of a physician's judgement that patients presenting with (abdominal) pain and fatigue are "not sick" or are "low acuity" patients, which is in line with studies on GPs and MUPS. This is supported by the finding that self-referred patients with MUPS received less medication and follow up appointments compared to other patients. If it was a result of judgment, the question is whether this is based on intuitive or informed decisions.

In the ED, physicians often need to make decisions within a limited time and using limited information. They are focused on swiftly distinguishing patients who are "sick" from those who are "not sick".[455] This process, also known as 'system 1', or 'gut feeling', is a fast, automatic and unconscious process which requires minimal effort, and is in contrast to 'system 2', which is a slow, controlled and conscious process.[456] In a study on 'system 1' thinking, Wiswell *et al.* found that emergency physicians are able to accurately predict patient disposition based on short observation of patients in combination with demographics and vital signs, but the prognostic accuracy and the assessment of acuity were limited.[455] System 1 frequently makes use of heuristics – a term for an "aid to problem solving which is learned from experience".[456] The speediness in diagnostics might result in lower accuracy, and heuristics are often linked to cognitive bias.[456] Cognitive bias is a risk for the quality of care, especially in situations with limited time.[457] Kline *et al.* showed in a study on patients suspect for pulmonary embolism that

if physicians recalled that patients were smiling, they overestimated the probability of an alternative diagnosis, which was associated with a less accurate Wells' criteria.[458] Cognitive bias might also partially explain deviation of the guidelines in **Chapter 4**, as it occurred in patients in the ED with severe hypertension but without complaints, making them "not sick" or "at risk".

To prevent errors as a result of cognitive bias, physicians should be trained in recognising bias and in measures to prevent (or mitigate) bias, so that they can optimally use both subconscious and deliberate decisions in their final diagnoses.

To conclude the findings in **first part of the thesis**, physicians rely on history and physical examination in the management of both low and high acuity patients, and they should continue to do so. They are aided in this process by diagnostic tests. Additional tests that have proven to be valuable in non-ED setting (e.g. ICU, operating rooms) should be validated first in the ED before use, as studies on diagnostic testing in the ED were not always able to replicate findings. Physicians should, as much as possible, be informed or educated on sensitivity, specificity and diagnostic accuracy of the tools they use, and on factors that may bias their decision making. This knowledge, will provide better insight on which negative findings rule out certain diagnosis and can result in omitting further testing, as well as which positive findings are true positive and can result in ruling out other diagnoses.

Early identification of illness using triage, early warning scores and prediction models

In 2017, there were approximately 2 million ED visits in the Netherlands. Approximately 45% of these patients were classified as surgical, followed by 13 % classified for internal medicine.[459,460] In the ED, patients with the highest acuity should be seen before low acuity patients. Emergency departments rely on triage systems that determine the priority in which patients must be seen, based on a combination of vital signs and presenting symptoms. Many triage models exist, which are used prehospital by GPs, and in EDs.[461] Ideally, the outcome of triage is close to the "true" acuity of a patient.[7] Unfortunately, in the ED under- and over-triage often occurs with most systems (e.g. Manchester Triage System, Emergency Severity Index).[462]

To improve the quality of triage or to aid decision making by physicians and nurses, prediction models can be used as a complement, or an alternative, to triage systems. Prediction models can improve patient care and increase efficient use of resources.[463] Treatment sequence or treatment decisions (e.g. admission, level of care, choice of medication) could be based on the outcome of such models for the whole population or specific patient groups (e.g. medical patients, elderly).

In the **second part of this thesis**, we studied how triage, early warning scores and prediction models aid in the early identification of illness and further clinical decision making. In **Chapter 8**, we reviewed 22 models that predict short-term mortality in a

non-trauma population in a European setting for quality, usability and risk of bias. Most of these models had a good to excellent discriminatory performance. However, not all the models we reviewed are suitable for direct use on arrival at the ED and are not appropriate for use in triage. These models frequently employ additional parameters, such as laboratory results, or relied on subjective assessments requiring history taking and physical examination. Laboratory results can improve performance of both triage and prediction models, and some laboratory test can be performed as point-of-care testing (POCT). Using POCT results are available within minutes. This can be beneficial for both individuals and for patient flow. Singer *et al*. showed that early POCT at triage reduced ED care time by approximately one hour,[464] which reduces the chance of ED crowding. In a study by Abualeanain *et al*., POCT at triage changed triage level in more than 10% of the cases, thus improving the quality of triage and optimizing use of resources.[465] Laboratory testing can also improve performance of models even when it is not performed as POCT, however, the outcome of such models are available after a certain period of time, and can result in retriage or other treatment decisions. However, not all patients routinely require laboratory testing.

These patients could benefit from models that use vital signs - with or without easily acquired additional parameters. The performance of these models is lower than the performance of models that use more (complex) parameters, but these simpler models have the advantage that they can be directly used on arrival, and most can be automatically calculated using data from electronic healthcare records. In **Chapter 10,** we compared the predictive performance of such a simple prediction model, namely the NEWS, with qSOFA and SIRS in patients with sepsis. The NEWS had already proven its value in the wards in both predicting deterioration and outcome, and similar results were observed later in studies in the ED.[466] The NEWS can potentially be used for continuously monitoring patients for deterioration during their stay in the ED, as was shown by Alam *et al*.[381] In specific populations, such as patients with pneumonia, as a higher NEWS is associated with poorer outcome, and it could be used to replace the CURB-65.[380] SIRS was part of the sepsis definition until 2015, and was used as a screening tool for sepsis. With the introduction of Sepsis 3, the use of SIRS was abandoned and qSOFA was introduced.[16] qSOFA is derived from hospital data, and data for the use in the ED was lacking. There has been a debate on whether and how qSOFA should be used in screening for sepsis, as it is just a bedside prompt to quickly assess the risk for mortality.[467] It was suggested to use a NEWS ≥ 7 combined with a (suspected) infection the ED as a screening tool for sepsis, replacing SIRS and qSOFA.[468] With our finding that NEWS had the highest performance in predicting mortality in patients with suspected sepsis, we support this suggestion. Unfortunately, studies on NEWS as a general triage tool – as a replacement of, or supplement to an existing triage system - are lacking. It is of great interest to perform such studies, as it can improve the quality of triage, can be used for retriage and to continuously monitor patients for deterioration, while reducing the number of prediction models used in the ED.

Prediction models are continuously developed and existing models are continuously improved. Validation of these models is required before they can be introduced in the

ED. Models derived from data of hospitalized patients – such as the NEWS – should be validated and when needed, cut-off values should be changed. Models that are derived from single centre ED data should be externally validated before implementing, and preferably in different countries, as the organization of healthcare varies even within Europe. In **Chapter 9** we developed and validated the CLEARED tool, which predicts the chance that an elderly patient will get admitted using readily available parameters. With an aging population and crowding of EDs, models predicting admission can improve patient care, as longer stay in the ED potentially increases chances of delirium and other negative outcome. A patient with a high chance of admission could await full evaluation in an acute medical unit. There are continuously new models developed, and existing models improved, resulting in better performing models. These developments benefit from machine learning. Hong *et al*. used machine learning models in combination with big data to develop model that could predict hospital admission with an AUC of 0.91 and 0.92, which is higher than the AUC of 0.8 we found in **Chapter 9**.[463] However it was only internally validated and it requires 972 variables. Therefore, it can only be implemented in an electronic patient record, and its implementation relies on automation. Raita *et al*. used machine learning models to predict critical care and hospitalisation outcome, and found that machine learning models outperformed the reference model based on the ESI triage categories, making it a potential alternative for ESI triage and improving patient care.[469] When a prediction model is properly validated and is ready to be implemented, a 'before and after' study for effects on outcome would be feasible, to study whether such a model has effect on mortality or on other secondary outcomes, such as duration of stay.

To conclude the findings in the **second part of this thesis**, physicians use prediction models and early warning scores to aid them in patient care, and with more complex and elderly patients encountered in the ED, such models are becoming increasingly important. While simple models are easier to use, for example as a bedside prompt, use of machine learning and big data can result in more accurate models. Before large-scale implementation of any model, however, studies that assess the effects on outcome are warranted.

Adequate treatment of patient with infections and sepsis

A large number of patients that visit the ED for the internal medicine have infections. These infections range from mild and self-limiting to severe and fatal, i.e. sepsis. Mortality of sepsis is high, and some studies say it is the leading cause of in-hospital mortality in the United States. The cornerstone of treatment of sepsis remains early initiation of antibiotic therapy. As in most cases the causative bacteria is not known, antibiotic therapy in sepsis should be empirical, based on national and local surveillance data, and are described in antibiotic guidelines.[470,471]

In the **third part of this thesis** we studied factors that influence antibiotic susceptibility. With an increase in antibiotic resistance and a dearth of newly developed antibiotics, physicians in the ED should be restrictive in their use with antibiotics, whilst ensuring

their initiated empirical therapy in the ED is appropriate.

If physicians prescribe according to the guidelines, empirical therapy aims to reach appropriateness in more than 90% of the patients. Antibiotic guidelines are based on surveillance data from the whole of the Netherlands, and it is unclear whether these data are applicable for specific patients groups found in hospitals with a selected population, such as a university hospitals. In **Chapter 12** we studied patients with complicated urinary tract infections consulting at Erasmus MC. We found that even in our selected population empiric therapy reached the threshold of 90% susceptibility. Susceptibility for oral antibiotics was lower, but oral antibiotics were mainly prescribed to patients who were discharged from the ED. In **Chapter 13** we studied if appropriate antibiotic therapy was associated with lower mortality. Physicians are more likely to prescribe broad spectrum antibiotics in accordance with the guidelines to patients who they think are at risk of dying of infections, as they want to ensure appropriateness in these patients. Patients who were sent home, or received inappropriate therapy – often as a result of non-adherence to the guidelines – presumably appeared less ill and had a lower risk of dying. We were unable to demonstrate the association between appropriate therapy and lower mortality, but showed this was a result of residual confounding. Residual confounding is of importance in retrospective studies, as it biases the genuine relationship between two factors, such as appropriate therapy and mortality. For example, in **Chapter 12** we also found that gentamicin was often omitted, often because of the potential toxicity, and this was mostly done in low acuity patients, where the risk of dying was assessed as low. However, in **Chapter 13** we showed that in a patient group with more balanced patient characteristics, appropriate treatment was associated with reduced mortality. Therefore, deviating from the guidelines is – even in low acuity patients – is associated with a higher risk of mortality.

Not only non-adherence to the guidelines can result in inappropriate therapy, this can also be the result of multidrug resistant (MDR) bacteria. The Netherlands has low resistance rates compared to other European countries. One of the best known risks for MDR bacteria is frequent treatment with antibiotics. Antibiotic prescription by Dutch GPs is the lowest of Europe.[472] There is a correlation between outpatient antibiotic use and antibiotic resistance. Patients frequently using antibiotics are more at risk for colonisation with MDR bacteria, and these mostly are patients with chronic illnesses, or immunocompromised patients, e.g. as a result of chemotherapy in patients with hematologic and oncologic illness, patients with organ transplants and patients with autoimmune diseases. The number of patients with chronic illnesses is increasing, and so is the number of chronic illnesses per patient.[473] Patients with chronic illnesses and recurrent or long-standing use of antibiotics (e.g. patients with renal transplants, or urologic anomalies) are encountered more frequently in university hospitals than non-university hospitals, which can explain the higher resistance for oral antibiotics we found in **Chapter 12**. Physicians relying on previous urinary cultures should realize that other microorganisms are found in newly obtained cultures of more than half of the patients, and broadening – not narrowing – of the antibiotic regimen based on earlier cultured pathogens is advised.

In international studies, recent hospitalization and residency in a nursing home are also risk factors for carriage of MDR bacteria.[474,475] These results cannot directly be extrapolated to the Netherlands, as the prevalence of MDR in the community is much lower as a result of the restrictive antibiotic use and of 'search and destroy' policies for certain MDR bacteria, including Methicillin-resistant *Staphylococcus aureus* (MRSA). High-risk groups (e.g. patients recently hospitalized in a foreign hospital, seamen, pig farmers) are actively screened and pre-emptively isolated. Patients who are infected or colonized with MDR bacteria are also isolated during hospitalisation until decolonisation is established successfully.[476] Although the risk for infections with MDR bacteria after recent hospitalization is low, there is a higher risk for infection with certain other microorganisms (e.g. *Pseudomonas* in hospital acquired pneumonia), and our guidelines distinguish community acquired infections from hospital acquired infections.

Individuals carrying MDR bacteria can pass on this antibiotic resistance to household contacts, or further spread this resistance into the community via the faeco-oral transmission.[472,477] This risk for transmission is higher in countries with poor sanitation.[478] Some of the countries with poor sanitation, are considered to be excellent travel destinations.[479] In **Chapter 11**, we studied post-travel faecal carriage of MDR Enterobacteriaceae. We found that after travelling to countries with high MDR in the community, the risk of carriage of MDR is also very high. These findings were confirmed in the 'Carriage Of Multiresistant Bacteria After Travel' (COMBAT) Study. This study also showed that after one year 11.3% of the individuals were still carriers of MDR bacteria.[389] With an increase of outbound international travel, both of healthy young individuals and elderly individuals with chronic illnesses, and an increase in inbound international travel from rapidly developing countries such as China, the number of tourists is expected to double in 2030. It is likely that physicians in the ED will encounter patients colonized with MDR bacteria.[480,481] Currently, Dutch hospitals only screen for certain MDR bacteria (e.g. MRSA). The Dutch antibiotic guidelines do consider patients with known colonisation with MDR bacteria at risk, resulting in isolation of these patients. However, international travel or residency in a country with high resistance is not considered as such.[471] There have been cases that show sepsis with MDR bacteria after travel related colonization; however, the exact risk has not been properly studied. In patients with known healthcare related colonisation with MDR bacteria, Rottier *et al*. found that blood cultures were positive in 18% of the cases in patients receiving empiric therapy for suspected gram negative sepsis. In these blood cultures, in 46% positive *Enterobacteriaceae* were found, and MDR bacteria as a result of colonisation only contributed to 8.3% of these blood cultures (i.e. 3.8% of the total number of positive blood cultures).[482] The authors conclude that prior colonisation with MDR bacteria and prior antibiotic use have low positive predictive value for the presence of MDR bacteria. Unfortunately, no patient characteristics are provided in this study, and sepsis was defined by initiation of antibiotics and obtaining blood cultures. However, with the low number of positive cultures and no data on mortality, these results are harder to interpret for clinical practice. The findings of **Chapters 12 and 13** suggest that in case of high acuity patients with know or presumed colonisation with MDR bacteria it is better to achieve appropriate therapy by broadening the antibiotic spectrum, despite the

findings of Rottier *et al.*, however, more studies are required.

To conclude the findings in the **third part of this thesis,** patients with bacterial infections who are appropriately treated have lower chance of mortality. Physicians appear be less likely to conform to antibiotic use guidelines when managing low acuity patients or when drug toxicity is a huge concern. As a result, there is a lower likelihood of appropriate therapy and higher risk for mortality. Appropriate therapy is also affected by emerging antimicrobial resistance, which can be the result of recurrent use of antibiotics, increase in international travel, and prolonged colonization (can last for more than one year). More studies are needed to examine the relationship between colonization with MDR and subsequent risk of infection.

Future research directions

Acute physicians are trained for the immediate and early management of adult patients who present in hospital as emergencies, and for the coordination of care of multiple patients. Patients are getting older and pathology is increasingly becoming more complex. They encounter demanding patients - who want certainty – and insurers, who want to keep costs as low as possible. Research should further focus on distinguishing those who are acutely ill from those who are not so that appropriate intervention can be initiated early for those who will benefit most, whilst limiting overtreatment for those who are unlikely to benefit. This requires evidence-based assessment of patients, safe discharge when possible, and swift admission when needed. The supportive value of diagnostic aides, such as prediction models, should be explored further.

Assessment of illness in individual patients

Research on assessment of illness in individual patients in the ED should focus recognising illness as early as possible, using readily available parameters and point-of-care testing. Currently, the parameters we use (e.g. vital signs, laboratory testing) have reasonable sensitivity and specificity, however, there is room for improvement. In 2019, point-of-care ultrasound (POCUS) was implemented in the Dutch internal medicine residency training program and it is expected that POCUS will improve the quality of physical examination in both acutely ill patients as well as in patients with other illnesses. It is important to study not only the value of ultrasound in clinical decision-making, but also whether it has an effect on outcome. Furthermore, since there is no standard ultrasound curriculum, research on methods of training and implementation is also feasible.

Another factor that should be used in assessment of patients is loss of mobility. Loss of mobility contributes to worse outcomes after hospitalization, and some suggest that mobility is a vital parameter.[483] Unfortunately, most patients are assessed while lying on hospital beds and impaired mobility is not always tested or noted in patient records. There are several ways of measuring mobility, varying from simple to complex. Currently, there is no consensus which of the available methods to use. The method should be easy

to perform, be applicable for most patients, including the sickest, and the results should be reproducible. When these criteria are met, and the results on outcome are confirmed, then it can be used as a new vital parameter.

Axillary humidity, as we showed in this thesis, is associated with hydration state of patients. It has potential to become a novel index for hydration, as was already shown in previous studies, as well as for fluid deficit. Research is needed to find the optimal sensors, and for new sensors the diagnostic accuracy for specific groups of patients and individuals should be studied. The sensors we used were – despite the fact they worked – not designed for this purpose, and more appropriate sensors are required. With improvement in sensor building, it is likely that better and smaller sensors will become available. Collaboration between university hospitals and technical universities will aid such improvements. Also, the type of sensors that is used to measure skin moisture – as a proxy for hydration – can vary. We used a sensor using hygrometry, but potentially bio-electrical impedance analysis, spectroscopy, or other methods could be used. If possible, such techniques should not only be used in hospital, but they should also be integrated in wearables. Wearables with heart rate monitoring, ECG, and pulse oximetry are already available. This allows measurement in a non-hospital setting, making this technique available for a broader public with interest in humidity state, such as athletes, which can use it to optimize their fluid balance. A positive effect of such developments is that the price of such techniques lowers, making it available for other care settings (e.g. elderly homes, third world countries).

Assessment of patient disposition – admission or safe discharge

Patients should not only be assessed for illness, but also for the probability of admission or discharge. The chance of admittance can be predicted with models that use readily available parameters, such as the CLEARED tool. However, prediction models that use POCT laboratory in combination with triage results might even perform better, and this is worth investigating. If a model identifies patients who are likely to get admitted – especially elderly – these patients might benefit from early admission to acute medical units or wards, where there are less disturbing factors, they can have proper beds, and basic physiological needs are met (e.g. food and drinks, assistance with toileting). Such interventions might also reduce crowding, especially in EDs with an AMU or short stay departments.

Most patients who visit the ED get directly discharged, and these are mostly the low acuity patients. In Erasmus MC, the one-week mortality rate of patients who were discharged with near normal vital signs is approximately 0.4%. Despite the fact that this percentage is low, it accounted for 362 deaths in a five-year period. Physicians that assess patients based on available data (e.g. vital signs, triage category, additional testing) cannot fully identify those without risk of dying.[484] Several studies have been performed to identify low risk of mortality. There are models for specific patients groups (e.g. patients with pulmonary embolism, acute heart failure, pneumonia), or for all ED patients. A prospective study of Lyngholm *et al*. showed that ED patients with a normal

d-dimer had a 30-day mortality of 0.4%, which was significantly lower than patients with abnormal d-dimers. A retrospective study in Erasmus MC had similar findings, but also showed that a severely elevated d-dimer (i.e. upper decile) is associated with increased mortality.[485,486] Despite these results, it seems impractical to perform a d-dimer test in all patients to distinguish patients with low and high risk of mortality; what then should be done with an elevated d-dimer in a patient without complaints? Therefore, there remains a need for studies that attempt to identify patients – especially those with near normal vital signs - and an increased chance of dying, as they might benefit from additional intervention, while patients with near normal vital sign and low risk of dying can be safely discharged from the ED.

Prediction models and early warning scores

Computer learning and big data will help identify that patients that are – or are not - at risk. Complex models containing many variables will greatly improve the diagnostic accuracy of these models. However, these models are based on information found in in the electronic patient charts, and not all observations that influence a physician's decision making are not noted in the charts. These unmeasured and unmeasurable factors may impact decision making, which can result in residual confounding in retrospective analysis. In patients suspect for pulmonary embolism, a recollection of a smiling patient was associated with a higher chance of a probable alternative diagnosis.[458] In patients with stroke, crossed legs seems to be associated with outcome. Remi *et al*. found a more favourable outcome, while Bazan *et al*. found an association with unilateral neglect.[487,488] Patients with crossed legs might seem more at ease, resulting in an assessment of lower acuity. Even in the famous book The House of God, Samuel Shem describes signs associated with outcome: "These are classic signs: the O sign on the left and the Q sign on the right. The O sign is reversible, but once they get to the Q sign, they never come back." These signs have never been confirmed in studies, and while most clinicians know the signs, they are hardly ever noted in charts. Future research should also target decision making, and should try to identify factors that physicians (unconsciously or unwittingly) use in their decision making, such as the crossed legs sign, or distractions such as the use of mobile phone while in the ED. Documenting these signs in health records makes them usable for machine learning and provide opportunities for improvement of prediction models.

Adequate treatment of patient with infections and sepsis

Even in a country with low antibiotic resistance as the Netherlands, it is likely that acute physicians will encounter more and more patients with MDR bacteria, as most patients with infections are admitted via the ED. Physicians in the ED should remain rational in use of antibiotics, whilst ensuring appropriate empirical therapy in the ED, as adequate antibiotic treatment remains the cornerstone of treatment of patients with bacterial sepsis. This requires collaboration of acute physicians and infectious disease specialists in patient care, research and in implementing guidelines. The guidelines used in the ED are based on national and local surveillance data. However, as we have shown, guidelines are

not always followed. It is important to study if, and to what extent, antibiotic guidelines are followed. If physicians deviate from these guidelines, the factors involved in such decision should be identified. Interventions to improve following guidelines should be based on these findings.

Currently, the antibiotic guidelines do not take into account travel to, or residence in, countries with high percentages of community dwelling MDR bacteria. However, with the continuous increase in inbound and outbound international travel, further studies should also focus on the risk that community acquired MDR bacteria form as potential pathogens, as this field remains partly unexplored.

Research methods

Research in acute medicine will benefit from local, national and international collaboration, as research fields overlap with other fields of internal medicine, as well as with other specialties. We have started a research collaboration with our first Flash Mob Research study, and we demonstrated that it is possible to obtain much data in short periods of time when working together. Using Flash Mob Research we were able to involve many hospitals, with both acute and emergency physicians acting as ambassadors, and it formed the foundation of formalizing a study consortium. We have further collaborated with the participants of this network in subsequent studies, and the first international study using the Flash Mob method has already been performed. This research network is a solid base for future research and should not only be used for cross sectional studies in a short amount of time, but also for prospective studies. Not all the hospitals need to participate for each study and still high numbers of inclusion can be reached. Participants of this consortium can find other interested parties performing similar studies, facilitating collaboration. The different hospital settings (e.g. university hospitals, large teaching hospitals) also allow for better internal and external validation of results. International collaboration can help identify practice differences between-countries and within-country, and will make outcome of studies more generalizable. Therefore, we expect that this research networks will prove very powerful.

In conclusion, the time is now for research in acute medicine!

Chapter 15

Summary

In **Chapter 1** we provide a general introduction to the different topics that we studied in this thesis. We give a brief history of acute medicine. We discuss the history, development and usability of triage, various prediction models and early warning systems and last, we discuss the assessment and treatment of patients with potentially critical illnesses. We conclude this chapter with the outline of the thesis.

In the **first part of this thesis**, consisting of chapters 2 to 7 contains studies on the value of history, clinical examination and additional testing in the early identification of illness.

In **Chapter 2** we used novel method of research, called Flash Mob Research to study interobserver agreement of various methods to measure capillary refill time (CRT). CRT is a clinical test used to assess the circulatory status of patients by measuring the time it takes for the colour of the skin to change back to normal after applying a pressure on a capillary bed. Different methods and normal values are in place in daily clinical practice. Physicians in the Netherlands were recruited by using word-of-mouth referrals, conventional media, and social media to participate in this nationwide, single-day, "nine-to-five," multicentre, cross-sectional, observational study to evaluate CRT.

We found that interobserver agreement on CRT is, at best, moderate. The results of CRT measured at the sternum and phalanx cannot be used interchangeable, and different duration of applying pressure results in different CRTs. Age and sex influence CRT, and a single cut-of value cannot be used. The Flash Mob Research study method we used was a success, as we were able to investigate a relatively simple research question in 38 hospitals, using an inexpensive, quick and reliable method and also generate positive reactions of patients, laymen and press. We concluded that the use of CRT in the initial assessment of patients can be omitted.

In **Chapter 3** we studied four indices that can potentially be used for assessment of the circulation, namely the pulse oximetry derived perfusion index (PI) and pleth variability index (PVI), the iButton® derived axillary humidity, and peripheral temperature gradients. In studies in settings others than the ED, such as the intensive care unit (ICU) and during surgery, these indices have been used in diagnosing dehydration and volume depletion. We performed a study using a convenience sample of patients visiting the ED of the Erasmus University Medical Center. Patients were dichotomized in having volume depletion or not based on physicians judgement who used all available parameters. Only axillary humidity differed significantly between these patients and can potentially be of additional value in diagnosing volume depletion. However, further development of the sensor, as well as further research are needed before axillary humidity measurements can be used in daily practice.

In **Chapter 4** we present the results of both a prospective and a retrospective study on hypertensive urgency and emergency in the emergency department (ED). Hypertension is common in the ED, and there is always debate if patients with asymptomatic severe hypertension should be evaluated for the presence of hypertensive urgency and emergency. Hypertensive emergency is distinguished from urgency by the presence of

acute hypertensive end-organ damage and therefore is an indication for prompt and aggressive treatment, while in hypertensive urgency there is no acute organ-damage. First, we retrospectively analysed patients with severe hypertension in the ED, and found that 22% met criteria for hypertensive urgency (i.e. end-organ damage present or pending) and 31% met the criteria for hypertensive emergency (i.e. no end-organ damage present or pending, and no pain or stress induced hypertension). Anamnestic non-adherence for antihypertensive drugs was recorded in only 6% of the patients as an attributing factor. Second, we prospectively studied adherence for antihypertensive drugs in 53 patients with a hypertensive urgency or emergency by measuring drug plasma levels. Approximately 5% of the patients who visited the ED with severe hypertension were asymptomatic, but were diagnosed as hypertensive urgency or emergency after extensive testing, showing the lack of symptoms cannot be used to rule out urgency or emergency. Whilst patients who admitted to nonadherence were excluded from this sample, still 22.6% were non-adherent for at least one of the prescribed antihypertensive drugs. This illustrates that in patients with hypertensive urgency and emergency drug nonadherence is common, but often overlooked and drug-adherence should be assessed in the ED.

In **Chapter 5** we performed an international multicentre study on patients who visit the ED with medically unexplained physicals symptoms (MUPS). MUPS form a high burden for both general practice and outpatients clinics. Diagnostic and treatment strategies between patients with and without MUPS should differ, and in patients with MUPS focus should lie on validating symptoms and provide explanations. Not much is known about patients with MUPS in the ED. We therefore retrospectively studied the incidence of MUPS and characteristics of patients presenting with MUPS. In a significant number of patients, physical symptoms remain unexplained after assessment in the ED, although follow up studies are needed to see how these symptoms evolve over time. We found a resemblance in patient characteristics of patients with unexplained symptoms presenting in the ED compared to patients at the general physician and outpatient clinics.

In **Chapter 6** we provide a review on the postural orthostatic tachycardia syndrome (POTS), based on two patients who present with different complaints. In POTS a change from a supine to an upright position causes an abnormally large increase in heart rate and orthostatic hypertension, resulting in or accompanied by various physical and psychological complaints. Although POTS is relatively common, it is relatively unfamiliar. The first step in treatment are lifestyle measures, which can be followed by pharmacotherapy.

In **Chapter 7** we performed a second Flash Mob Research on the quality and quantity of sleep in hospitalized patients. In one day we included more than 2,000 patients from 39 hospitals. Overall, sleep quality was lower and 70% of patients reported to have been awakened by external causes, which in half of the cases concerned hospital staff. Sleep disturbing factors that were mostly reported were noises of other patients and staff, medical devices, pain and toilet visits. With this study we aimed to raise awareness for the importance of adequate sleep. It also shows how decisions made in the ED influence the course of hospitalization and provides targets for interventions to minimize disturbing

factors, in order to improve quality of sleep.

In the **second part of this thesis**, consisting of chapters 8 to 10, contains studies on prediction models and early warning scores.

In **Chapter 8** we provide a systematic review of prediction models for mortality that can be used to identify patients that visit the ED at risk for deterioration and mortality, in order to timely treat these patients. We identified 15 articles, of which the majority investigated in-hospital mortality. These models had discriminative abilities ranging from Area Under the Curve between 0.63 and 0.93. However, our quality analysis revealed that most studies had a moderate risk of bias in one or more domains. Two models performed best; the PARIS model and the full model. However, these models are not yet implemented and generalizability to non-European EDs is limited. We concluded that there is a need for large validation studies comparing models on both discriminative abilities and if it has effect on mortality. In subsequent model development, methodological quality should be improved.

In **Chapter 9** we describe the development and validation of a clinical prediction tool for admission for elderly in the ED. As length of stay in the ED is correlated to an extended in-hospital length of stay, prediction of admission and subsequent early admission might be beneficial for both individual patients as well as patient flow. We developed and validated the CLEARED-tool, which uses parameters that are easily obtainable at presentation in the ED, including vital signs, referral status, Manchester Triage Score category and the need for laboratory testing and radiology. We validated this tool both internally and externally, with Areas Under the Curve of 0.73 – 0.80. However, before implementation prospective evaluation of the effect on length of stay and outcome is necessary.

In **Chapter 10** we retrospectively studied three scores in patients with suspected infection presenting to the ED using a database containing all ED visits with demographics, vital parameters, results of laboratory testing, disposition and mortality data. The scores we studied were the quick Sepsis Related Organ Failure Assessment (qSOFA), Systemic Inflammatory Response Syndrome (SIRS) criteria and National Early Warning Score (NEWS). We found that qSOFA had highest sensitivity but lacked specificity, while SIRS had highest specificity but lacked sensitivity. Overall NEWS performed best, followed by qSOFA and SIRS. Our findings suggest that the NEWS – with a suggested cut-off of 7 - might be eligible for use in the ED, despite the fact it was not designed for this use, however, this requires conformation by prospective studies.

In the **third part of this thesis**, consisting of chapters 11 to 13 contains studies on antibiotic susceptibility.

In **Chapter 11** we provide a systematic review on international travel and the risk of post-travel faecal carriage of multidrug-resistant *Enterobacteriaceae* (MRE). International travel is major risk factor for acquisition of MRE, and individuals travelling to (southern)

Asia had the highest risk (up to 88% acquisition of MRE). Travelers with travel-related diarrhoea and travelers who used antibiotics also had an increased risk. Further studies to assess the duration of carriage of MRE and to assess the chance of contaminating household contacts. It also remains unclear if carriage of MRE results in an increase in infections, but we do suggest to adapt the choice of antibiotic drugs to these findings when treating recent travellers with infections which might be caused by *Enterobacteriaceae*, such as urinary tract infections. Our results also show the importance of infection prevention and control guidelines.

In **Chapter 12** we studied patients visiting the ED with a suspected complicated urinary tract infection. We analysed our results and compared these data with national data from the NethMap report. We found that antibiotic susceptibility for intravenous antibiotics was comparable to NethMap data, however, susceptibility was lower for oral antibiotics. This last finding is probably the result of a population at risk for recurrent complicated urinary tract infections and subsequent antibiotic use, e.g. patients with anatomic anomalies and renal transplant. We also found a linear relation between the time of the last hospitalization and the susceptibility of antibiotics given in the ED – the shorter the time, the lower the susceptibility. However, despite this finding empirical therapy (i.e. cefuroxime and gentamicin) reached susceptibility over 90%, and to achieve acceptable susceptibility the guidelines on empirical therapy should be followed. We also found that urinary cultures differed from previous cultures in more than 56% of the patients. We therefore advice broadening, but not narrowing, of the antibiotic regimen based on earlier cultured pathogens.

In **Chapter 13** we studied whether administration of appropriate antibiotic therapy is associated with reduced mortality in patients with a blood stream infection in the ED. We also wanted to explain why prior investigators were unable to confirm this association. We were unable to demonstrate lower mortality in patients receiving appropriate therapy in the entire study population, despite multiple adjustments for confounding. We assumed this was the result of residual confounding. We then studied a subset of our population, namely patients only receiving one antibiotic drug. In this monotherapy-only group, characteristics of patients who did or did not receive appropriate therapy were more homogeneous, and within these groups we showed that appropriate therapy reduced mortality. With this study we also show that it is not always possible to correct unbalanced groups, and that residual confounding is a serious risk for retrospective studies when comparing unbalanced groups. We therefore advise when comparing retrospective data, the most homogeneous groups should be used.

In **Chapter 14** we discussed these findings, provided conclusions per part of this thesis and provided further research directives. In **Chapter 15** we summarize the findings of this thesis.

Chapter 15

Samenvatting

Hoofdstuk 1 geeft een algemene introductie over de verschillende onderwerpen die in dit proefschrift aan de orde komen. Er wordt een kort overzicht gegeven van de geschiedenis van de acute geneeskunde. Daarna volgt een beschrijving van de geschiedenis, de ontwikkeling en de bruikbaarheid van triage, van diverse voorspelmodellen en van *Early Warning Systems*. Hierna volgt een beschrijving van de beoordeling en behandeling van patiënten die potentieel ernstig ziek zijn. Dit hoofdstuk eindigt met de indeling van dit proefschrift.

Het **eerste deel van dit proefschrift,** bestaand uit de hoofdstukken 2 tot en met 7, bevat studies die gaan over de waarde van anamnese, lichamelijk onderzoek en aanvullend onderzoek bij het vroegtijdig herkennen van ziekte.

In **Hoofdstuk 2** wordt met behulp van een nieuwe onderzoeksmethode, genaamd *Flash Mob Research*, de overeenstemming tussen waarnemers bij de verschillende methoden om capillaire vullingstijd te meten bestudeerd. De capillaire vullingstijd is een klinisch onderzoek wat wordt gebruikt om de bloedsomloop te beoordelen. Bij de test wordt de tijd gemeten die de huid nodig heeft om weer de normale kleur te krijgen na een periode van druk op het capillaire bed. In de dagelijkse praktijk worden verschillende methoden met verschillende normaalwaardes gebruikt. Artsen in Nederland werden mondeling, via reguliere kanalen en via sociale media uitgenodigd om mee te doen aan dit ééndaagse, landelijke, 'negen-tot-vijf', multicenter, cross-sectionele, observationele onderzoek naar capillaire vullingstijd.

De overeenstemming tussen waarnemers bij het beoordelen van capillaire vullingstijd is op zijn best redelijk. De uitkomsten van de capillaire vullingstijd gemeten op het borstbeen en de vinger zijn niet onderling uitwisselbaar. Een verschillende duur van het uitoefenen van druk geeft een verschil in capillaire vullingstijd. De *Flash Mob Research* methode die gebruikt is was een succes; het stelde ons in staat om op een goedkope, snelle en betrouwbare manier een relatief eenvoudige onderzoeksvraag te onderzoeken in 38 ziekenhuizen. Patiënten, leken en de media reageerden positief. De conclusie van dit hoofdstuk is dat het gebruik van de capillaire vullingstijd bij de initiële beoordeling van patiënten achterwege gelaten kan worden.

In **Hoofdstuk 3** zijn vier parameters bestudeerd die mogelijk van toegevoegde waarde zijn bij de beoordeling van de circulatie, namelijk de *perfusion index* en de *pleth variability index* – beide parameters kunnen worden bepaald met behulp van een pulseoximeter, de vochtigheid van de oksel – gemeten met een iButton® en de temperatuurgradiënt tussen de elleboog en de vinger. In studies buiten de spoedeisende hulp, zoals op de intensive care of rondom operaties zijn deze parameters gebruikt in de beoordeling van ondervulling en dehydratie. Dit werd onderzocht met behulp van een steekproef op de spoedeisende hulp van het Erasmus MC. Patiënten werden aan de hand van het klinische oordeel van de arts – die gebruik kon maken van alle beschikbare gegevens – verdeeld in twee groepen: wel of geen vochttekort. Alleen de vochtigheid van de oksel was significant verschillend tussen beide patiëntengroepen en is mogelijk van toegevoegde waarde bij het diagnosticeren van vochttekort. Echter, zowel doorontwikkeling van de sensor, als

verder onderzoek zijn nodig voordat het meten van de vochtigheid van de oksel gebruikt kan worden in de dagelijks praktijk.

Hoofdstuk 4 beschrijft de resultaten van zowel een prospectieve als een retrospectieve studie naar hypertensieve noodgevallen en urgenties op de spoedeisende hulp. Hypertensie komt veel voor op de spoedeisende hulp, en er is blijvende discussie of patiënten met een asymptomatische ernstige hypertensie beoordeeld moeten worden op de aanwezigheid van een hypertensief noodgeval of urgentie. Bij een hypertensief noodgeval is er sprake van eindorgaanschade op basis van de verhoogde bloeddruk, en is er een indicatie voor snelle en agressieve behandeling, terwijl er bij een hypertensieve urgentie geen acute eindorgaanschade is.

Als eerste werden patiënten met een ernstige hypertensie op de SEH retrospectief geanalyseerd, waarbij er in 22% van de gevallen werd voldaan aan de criteria van een hypertensief spoedgeval, waarbij er sprake was van (dreigende) eindorgaanschade. In 31% van de gevallen was er sprake van een hypertensieve urgentie, waarbij er geen sprake was van (dreigende) orgaanschade, en waarbij de bloeddrukverhoging niet door pijn en stress werd veroorzaakt. In slechts 6% van de gevallen werd in de anamnese therapieontrouw voor de antihypertensieve medicijnen als deel van de oorzaak beschreven.

In het tweede deel werd de therapietrouw voor antihypertensieve medicatie in 53 patiënten met een hypertensief noodgeval of hypertensieve urgentie bestudeerd door het meten van plasmaspiegels van de medicijnen. Ondanks dat patiënten die toegaven therapieontrouw te zijn waren geexcludeerd, was 22.6% van de patiënten therapieontrouw voor tenminste een van de antihypertensieve medicijnen. Dit toont aan dat therapieontrouw bij patiënten met een hypertensief noodgeval of hypertensieve urgentie veelvoorkomend is, maar dat er te weinig aan gedacht wordt op de spoedeisende hulp, en dat therapieontrouw moet worden nagevraagd op de spoedeisende hulp.

Hoofdstuk 5 beschrijft een internationale multicenter studie naar patiënten die de spoedeisende hulp bezochten met somatisch onvoldoende verklaarde lichamelijke klachten (SOLK). SOLK is een veelvoorkomend probleem in zowel de huisartsenpraktijk als op poliklinieken. Bij patiënten met SOLK dient zowel het diagnostisch traject als de behandelstrategie te verschillen van patiënten zonder SOLK, waarbij bij patiënten met SOLK de aandacht moet liggen op het valideren van de klachten en het geven van adequate uitleg. Er is weinig bekend over patiënten met SOLK op de spoedeisende hulp. Met behulp van een retrospectief onderzoek werden de incidentie van SOLK, alsmede de patiënt karakteristieken bestudeerd. Bij een groot aantal patiënten bleef de klachten na beoordeling op de spoedeisende hulp onverklaard, alhoewel vervolgstudies nodig zijn naar het beloop van deze klachten in de tijd.

Hoofdstuk 6 geeft aan de hand van twee patiënten die zich presenteerden met verschillende klachten een review naar het posturaal orthostatisch tachycardie syndroom (POTS). Bij POTS geeft een verandering van een liggende naar staande houding een abnormale verhoging van de hartslag en orthostatische hypotensie, wat resulteert in

of gepaard gaat met verschillende lichamelijke en geestelijke klachten. Alhoewel POTS relatief veelvoorkomend is, is het nog vrij onbekend. De eerste stap in behandeling is leefstijladvies, gevolgd door farmacologische interventies.

Hoofdstuk 7 beschrijft een tweede *Flash Mob Research* naar de kwaliteit en kwantiteit van slaap bij in het ziekenhuis opgenomen patiënten. In één dag werden in 39 ziekenhuizen meer dan 2,000 patiënten geïncludeerd. In de gehele populatie was de kwaliteit van slaap lager en 70% van de patiënten rapporteerden te zijn wakker geworden door externe oorzaken – in de helft van de gevallen betrof dit ziekenhuispersoneel. Factoren die van invloed waren op de slaap werden geluiden van medepatiënten, ziekenhuispersoneel, medische apparaten, pijn en toiletbezoek. Het doel van deze studie is om bewustwording te creëren voor het belang van voldoende, goede slaap. Het geeft ook aan hoe beslissingen gemaakt op de spoedeisende hulp het verdere beloop van een ziekenhuisopname beïnvloeden. Het biedt mogelijkheden voor interventies om factoren die slaap verstoren te minimaliseren, om zo de kwaliteit van slaap te verbeteren.

Het **tweede deel van dit proefschrift,** bestaand uit de hoofdstukken 8 tot en met 10, bevat studies over voorspelmodellen en *Early Warning Scores*.

Hoofdstuk 8 geeft met een systematische review een overzicht van modellen die mortaliteit voorspellen van patiënten die opgenomen worden via de spoedeisende hulp. Deze modellen kunnen worden gebruikt om patiënten te identificeren die een risico lopen op achteruitgang en mortaliteit, om idealiter deze patiënten zo snel mogelijk te kunnen behandelen. Er werden 15 artikelen gevonden, waarvan de meerderheid van de studies mortaliteit in het ziekenhuis bestudeerde. Het discriminerende vermogen van deze modellen - uitgedrukt met de *Area under the Curve* - varieerde tussen 0.63 en 0.93. Bij analyse van de kwaliteit van deze studies bleek dat de meeste studies het risico op bias gemiddeld was. De twee beste modellen waren het '*Paris model*' en het '*full model*'. Echter, deze modellen zijn nog nergens ingevoerd en de generaliseerbaarheid naar andere niet-Europese spoedeisende hulp afdelingen is beperkt. De conclusie van dit hoofdstuk is dat het noodzakelijk is om zowel de discriminerende vermogens als het effect op mortaliteit van dezer deze modellen in grote studies te vergelijken. Bij het ontwikkelen van nieuwe modellen moet de methodologische kwaliteit worden verbeterd.

Hoofdstuk 9 beschrijft de ontwikkeling en validatie van een instrument om opname van ouderen vanaf de spoedeisende hulp te voorspellen. Langer verblijf op de spoedeisende hulp is gecorreleerd met een verlengde opname, en het voorspellen van een opname gevolgd door een directe opname heeft mogelijk een gunstig effect voor zowel de individuele patiënt als voor de patiëntenstroom. Dit resulteerde in de *CLEARED-tool*. Dit instrument maakt gebruik van parameters die gemakkelijk te verkrijgen zijn bij aankomst op de spoedeisende hulp, zoals vitale parameters, manier van verwijzing, triage categorie en de noodzaak tot het verrichten van laboratorium onderzoek en radiologisch onderzoek. Dit instrument is zowel intern als extern gevalideerd, met daarbij *Areas under the Curve* tussen 0.73 en 0.80. Echter, voor invoering is een prospectieve evaluatie van het effect op de opnameduur en op de uitkomst noodzakelijk.

In **Hoofdstuk 10** worden drie scores bestudeerd in patiënten die de spoedeisende hulp bezochten en waarbij er het vermoeden op een infectie bestond. Er werd gebruik gemaakt van een database met alle spoedeisende hulp bezoeken met demografische gegevens, vitale parameters, uitslagen van laboratorium diagnostiek, opname- en ontslag gegevens en mortaliteitsdata. De bestudeerdescores waren de *quick Sepsis Related Organ Failure Assessment (*qSOFA*)*, het *Systemic Inflammatory Response Syndrome* (SIRS) en de *National Early Warning Score* (NEWS). qSOFA had de hoogste sensitiviteit, waarbij het ontbrak aan specificiteit, terwijl SIRS de hoogste specificiteit had, maar waarbij het ontbrak aan sensitiviteit. De NEWS presteerde globaal het beste, gevolgd door qSOFA en SIRS. De bevindingen suggereren dat de NEWS, met een aangeraden afkapwaarde van 7, geschikt kan zijn voor gebruik op de spoedeisende hulp, ondanks dat deze score hiervoor initieel niet ontwikkeld is. Echter, dit vereist bevestiging met behulp van prospectieve studies.

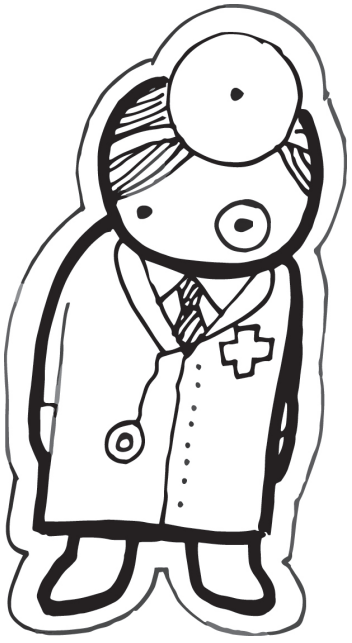
Het **derde deel van dit proefschrift,** bestaand uit de hoofdstukken 11 tot en met 13, bevat studies over gevoeligheid voor antibiotica.

Hoofdstuk 11 geeft middels een systematische review overzicht van het risico op fecaal dragerschap van multiresistente *Enterobacteriaceae* na internationale reizen. Internationale reizen zijn een zeer groot risico voor het oplopen resistentie, en het risico was het grootst voor reizigers naar (zuidelijk) Azia, waarbij tot 88% een multiresistente *Enterobacteriaceae* opliep. Reizigers met reizigersdiarree of reizigers die antibiotica gebruikten hadden ook een verhoogd risico op dragerschap. Er zijn meer studies nodig naar de duur van dragerschap van multiresistente *Enterobacteriaceae*, en naar de kans op besmetting van huisgenoten. Het is er ook geen duidelijkheid of dragerschap van multiresistente *Enterobacteriaceae* meer infecties veroorzaakt, maar bij patiënten die recent op reis zijn geweest die zich presenteren met een infectie die mogelijk veroorzaakt wordt door *Enterobacteriaceae*, zoals urineweginfecties, is het advies het antibiotisch regime aan te passen. Onze resultaten bevestigen ook het belang van richtlijnen voor infectie preventie en controle.

In **Hoofdstuk 12** worden patiënten die de spoedeisende hulp bezoeken met een mogelijke gecompliceerde urineweginfectie bestudeerd. De gegevens van deze studie werden vergeleken met landelijke gegevens, verkregen uit het NethMap rapport. De gevoeligheid voor intraveneuze antibiotica is vergelijkbaar met de landelijke gevoeligheid, zoals beschreven in het NethMap rapport. De gevoeligheid voor orale antibiotica was echter lager, wat waarschijnlijk het gevolg is van de populatie die het risico loopt op gecompliceerde urineweginfecties, zoals patiënten die een niertransplantatie ondergingen of met anatomische afwijkingen. Er was een lineaire relatie tussen de laatste opname en de gevoeligheid voor antibiotica, waarbij een recentere opname meer kans op resistentie werd gevonden. Ondanks deze bevinding gaf de empirische therapie (cefuroxim en gentamicine) voldoende antibiotische dekking om meer dan 90% gevoeligheid te bereiken, wat pleit voor het volgen van de richtlijnen. Positieve urinekweken verschilden in meer dan 56% van de gevallen van eerdere kweken, en daarom is het advies om het antibiotisch beleid niet te versmallen, maar wel te verbreden op basis van de oude kweken.

Hoofdstuk 13 bestudeert of het toedienen van adequate antibiotica is geassocieerd met verlaging van sterfte in patiënten met een bloedbaaninfectie op de spoedeisende hulp. Daarnaast was het doel om te verklaren waarom deze associatie in eerdere studies niet altijd gevonden werd. In de gehele populatie was het niet mogelijk om lagere sterfte aan te tonen in patiënten die adequaat antibiotisch werden behandeld, ondanks meerdere correcties voor verstorende factoren. Er werd verondersteld dat dit het gevolg was van *residual confounding*. Vervolgens werd een subgroep van de populatie gekozen, te weten patiënten die slechts één antibioticum kregen. In deze antibiotica monotherapie groep waren de karakteristieken van patiënten die adequaat en inadequaat werden behandeld meer homogeen, en binnen deze groepen werd aangetoond dat adequate therapie mortaliteit verlaagd. Deze studie toont ook aan dat het niet altijd mogelijk is om te corrigeren voor ongebalanceerde groepen. Het advies is daarom om bij het vergelijken van retrospectieve data de meest homogene groepen te gebruiken.

In **Hoofdstuk 14** worden deze bevindingen per deel van dit proefschrift bediscussieerd, en worden richtingen voor toekomstig onderzoek aangestipt. In **Hoofdstuk 15** worden de bevindingen van dit proefschrift samengevat.



References

References

1. Kellermann AL, Martinez R. The ER, 50 years on. *N Engl J Med 2011;364:2278-9.*
2. KNMG: Vaststelling CCMS-besluit Spoedeisende geneeskunde. *Medisch Contact 26 november 2008*
3. Scott I, Vaughan L, Bell D. Effectiveness of acute medical units in hospitals: a systematic review. *Int J Qual Health Care 2009;21:397-407.*
4. Daly S, Campbell DA, Cameron PA. Short-stay units and observation medicine: a systematic review. *Med J Aust 2003;178:559-63.*
5. Kremers M. Rollen en verantwoordelijkheden van internisten en SEH-artsen op de Nederlandse Spoedeisende Hulp: een exploratieve studie.*(unpublished)*
6. Storm-Versloot MN, Ubbink DT, Kappelhof J, Luitse JS. Comparison of an informally structured triage system, the emergency severity index, and the manchester triage system to distinguish patient priority in the emergency department. *Acad Emerg Med 2011;18:822-9.*
7. Lentz BA, Jenson A, Hinson JS, et al. Validity of ED: Addressing heterogeneous definitions of over-triage and under-triage. *Am J Emerg Med 2017;35:1023-5.*
8. Grossmann FF, Zumbrunn T, Ciprian S, et al. Undertriage in older emergency department patients--tilting against windmills? *PLoS One 2014;9:e106203.*
9. Seiger N, van Veen M, Steyerberg EW, van der Lei J, Moll HA. Accuracy of triage for children with chronic illness and infectious symptoms. *Pediatrics 2013;132:e1602-8.*
10. Gasperini B, Cherubini A, Fazi A, Maracchini G, Prospero E. Older adults in Emergency Departments: the challenge of undertriage. *Intern Emerg Med 2016;11:1145-7.*
11. McGinn TG, Guyatt GH, Wyer PC, Naylor CD, Stiell IG, Richardson WS. Users' guides to the medical literature: XXII: how to use articles about clinical decision rules. Evidence-Based Medicine Working Group. *JAMA 2000;284:79-84.*
12. Steyerberg EW, Vergouwe Y. Towards better clinical prediction models: seven steps for development and an ABCD for validation. *Eur Heart J 2014;35:1925-31.*
13. Hargett CW, Tapson VF. Clinical probability and D-dimer testing: how should we use them in clinical practice? *Semin Respir Crit Care Med 2008;29:15-24.*
14. van der Hulle T, Cheung WY, Kooij S, et al. Simplified diagnostic management of suspected pulmonary embolism (the YEARS study): a prospective, multicentre, cohort study. *Lancet 2017;390:289-97.*
15. de Gelder J, Lucke JA, Blomaard LC, et al. Optimization of the APOP screener to predict functional decline or mortality in older emergency department patients: Cross-validation in four prospective cohorts. *Exp Gerontol 2018;110:253-9.*
16. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA 2016;315:801-10.*
17. Ahn S, Rice TW, Yeung SJ, Cooksley T. Comparison of the MASCC and CISNE scores for identifying low-risk neutropenic fever patients: analysis of data from three emergency departments of cancer centers in three continents. *Support Care Cancer 2018;26:1465-70.*
18. Subbe CP, Kruger M, Rutherford P, Gemmel L. Validation of a modified Early Warning Score in medical admissions. *QJM 2001;94:521-6.*
19. Friedman AM, Campbell ML, Kline CR, Wiesner S, D'Alton ME, Shields LE. Implementing Obstetric Early Warning Systems. *AJP Rep 2018;8:e79-e84.*

20. Dean NP, Fenix JB, Spaeder M, Levin A. Evaluation of a Pediatric Early Warning Score Across Different Subspecialty Patients. *Pediatr Crit Care Med 2017;18:655-60.*
21. Brink A, Alsma J, Fortuin AW, et al. Prediction models for mortality in adult patients visiting the Emergency Department: a systematic review. *Acute Med. 2019;18(3):171-183.*
22. Carmont MR. The Advanced Trauma Life Support course: a history of its development and review of related literature. *Postgrad Med J 2005;81:87-91.*
23. Levy MM, Evans LE, Rhodes A. The Surviving Sepsis Campaign Bundle: 2018 Update. *Crit Care Med 2018;46:997-1000.*
24. Holler JG, Bech CN, Henriksen DP, Mikkelsen S, Pedersen C, Lassen AT. Nontraumatic hypotension and shock in the emergency department and the prehospital setting, prevalence, etiology, and mortality: a systematic review. *PLoS One 2015;10:e0119331.*
25. McKenzie K, Puskarich MA, Jones AE. What Is the Prognosis of Nontraumatic Hypotension and Shock in the Out-of-Hospital and Emergency Department Setting? *Ann Emerg Med 2016;67:114-6.*
26. McGee S, Abernethy WB, 3rd, Simel DL. The rational clinical examination. Is this patient hypovolemic? *JAMA 1999;281:1022-9.*
27. Hiemstra B, Eck RJ, Keus F, van der Horst ICC. Clinical examination for diagnosing circulatory shock. *Curr Opin Crit Care 2017;23:293-301.*
28. Elder A, Japp A, Verghese A. How valuable is physical examination of the cardiovascular system? *BMJ 2016;354:i3309.*
29. Martin GS. Sepsis, severe sepsis and septic shock: changes in incidence, pathogens and outcomes. *Expert Rev Anti Infect Ther 2012;10:701-6.*
30. Wiersinga WJ, van Zanten ARH, Kaasjager KA, van der Poll T. [Sepsis: new insights, new definition]. *Ned Tijdschr Geneeskd 2017;161:D1551.*
31. Cutuli SL, De Pascale G, Antonelli M. 'sigmaetapsiiotavarsigma' yesterday, sepsis nowadays: what's changing? *J Thorac Dis 2017;9:E166-E7.*
32. Vincent JL, Abraham E. The last 100 years of sepsis. *Am J Respir Crit Care Med 2006;173:256-63.*
33. Angus DC, van der Poll T. Severe sepsis and septic shock. *N Engl J Med 2013;369:840-51.*
34. Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest 1992;101:1644-55.*
35. Netea MG, van der Meer JW, van Deuren M, Kullberg BJ. Proinflammatory cytokines and sepsis syndrome: not enough, or too much of a good thing? *Trends Immunol 2003;24:254-8.*
36. Levy MM, Fink MP, Marshall JC, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med 2003;31:1250-6.*
37. Dellinger RP, Carlet JM, Masur H, et al. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. *Crit Care Med 2004;32:858-73.*
38. Gao F, Melody T, Daniels DF, Giles S, Fox S. The impact of compliance with 6-hour and 24-hour sepsis bundles on hospital mortality in patients with severe sepsis: a prospective observational study. *Crit Care 2005;9:R764-70.*
39. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med 2001;345:1368-77.*
40. Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med 2006;34:1589-96.*
41. Jozwiak M, Monnet X, Teboul JL. Implementing sepsis bundles. *Ann Transl Med 2016;4:332.*

42. Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med 2013;39:165-228.*
43. Nguyen HB, Jaehne AK, Jayaprakash N, et al. Early goal-directed therapy in severe sepsis and septic shock: insights and comparisons to ProCESS, ProMISe, and ARISE. *Crit Care 2016;20:160.*
44. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Intensive Care Med 2017;43:304-77.*
45. Briegel J, Mohnle P. [Surviving Sepsis Campaign update 2018: the 1 h bundle : Background to the new recommendations]. *Anaesthesist 2019.*
46. Geller AI, Lovegrove MC, Shehab N, Hicks LA, Sapiano MRP, Budnitz DS. National Estimates of Emergency Department Visits for Antibiotic Adverse Events Among Adults-United States, 2011-2015. *J Gen Intern Med 2018;33:1060-8.*
47. Shehab N, Patel PR, Srinivasan A, Budnitz DS. Emergency department visits for antibiotic-associated adverse events. *Clin Infect Dis 2008;47:735-43.*
48. Alam N, Oskam E, Stassen PM, et al. Prehospital antibiotics in the ambulance for sepsis: a multicentre, open label, randomised trial. *Lancet Respir Med 2018;6:40-50.*
49. Simpson SQ. New Sepsis Criteria: A Change We Should Not Make. *Chest 2016;149:1117-8.*
50. Schriger DL, Baraff L. Defining normal capillary refill: variation with age, sex, and temperature. *Ann Emerg Med 1988;17:932-5.*
51. Pickard A, Karlen W, Ansermino JM. Capillary refill time: is it still a useful clinical sign? *Anesth Analg 2011;113:120-3.*
52. Cooksley T, Kitlowski E, Haji-Michael P. Effectiveness of Modified Early Warning Score in predicting outcomes in oncology patients. *QJM 2012;105:1083-8.*
53. Mrgan M, Rytter D, Brabrand M. Capillary refill time is a predictor of short-term mortality for adult patients admitted to a medical department: an observational cohort study. *Emerg Med J 2014;31:954-8.*
54. Lima A, Jansen TC, van Bommel J, Ince C, Bakker J. The prognostic value of the subjective assessment of peripheral perfusion in critically ill patients. *Crit Care Med 2009;37:934-8.*
55. Lockey A, Pitcher D. *Advanced Life Support ERC 2010 Edition.*
56. Beecher HK, Simeone FA, et al. The internal state of the severely wounded man on entry to the most forward hospital. *Surgery 1947;22:672-711.*
57. Champion HR, Sacco WJ, Carnazzo AJ, Copes W, Fouty WJ. Trauma score. *Crit Care Med 1981;9:672-6.*
58. Lobos AT, Menon K. A multidisciplinary survey on capillary refill time: Inconsistent performance and interpretation of a common clinical test. *Pediatr Crit Care Med 2008;9:386-91.*
59. Crook J, Taylor RM. The agreement of fingertip and sternum capillary refill time in children. *Arch Dis Child 2013;98:265-8.*
60. King D, Morton R, Bevan C. How to use capillary refill time. *Arch Dis Child Educ Pract Ed 2014;99:111-6.*
61. van Genderen ME, Lima A, Akkerhuis M, Bakker J, van Bommel J. Persistent peripheral and microcirculatory perfusion alterations after out-of-hospital cardiac arrest are associated with poor survival. *Crit Care Med 2012;40:2287-94.*
62. Anderson B, Kelly AM, Kerr D, Clooney M, Jolley D. Impact of patient and environmental factors on capillary refill time in adults. *Am J Emerg Med 2008;26:62-5.*
63. Schriger DL, Baraff LJ. Capillary refill--is it a useful predictor of hypovolemic states? *Ann Emerg Med 1991;20:601-5.*

64. Lewin J, Maconochie I. Capillary refill time in adults. *Emerg Med J 2008;25:325-6.*
65. Anderson B KA, Kerr D, Jolley D. Capillary refill time in adults has poor inter-observer agreement. *Hong Kong Journal of Emergency Medicine 2008;15:71-74.*
66. Brabrand M, Hosbond S, Folkestad L. Capillary refill time: a study of interobserver reliability among nurses and nurse assistants. *Eur J Emerg Med 2011;18:46-9.*
67. Espinoza ED, Welsh S, Dubin A. Lack of agreement between different observers and methods in the measurement of capillary refill time in healthy volunteers: an observational study. *Rev Bras Ter Intensiva 2014;26:269-76.*
68. Semler MW, Stover DG, Copland AP, et al. Flash mob research: a single-day, multicenter, resident-directed study of respiratory rate. *Chest 2013;143:1740-4.*
69. Longman Dictionary of Contemporary English. *http://www.ldoceonline.com/dictionary/flashmob.*
70. Viera AJ, Garrett JM. Understanding interobserver agreement: the kappa statistic. *Fam Med 2005;37:360-3.*
71. Bhave G, Neilson EG. Volume depletion versus dehydration: how understanding the difference can guide therapy. *Am J Kidney Dis 2011;58:302-9.*
72. Mange K, Matsuura D, Cizman B, et al. Language guiding therapy: the case of dehydration versus volume depletion. *Ann Intern Med 1997;127:848-53.*
73. Hooper L, Abdelhamid A, Attreed NJ, et al. Clinical symptoms, signs and tests for identification of impending and current water-loss dehydration in older people. *Cochrane Database Syst Rev 2015:CD009647.*
74. Fortes MB, Owen JA, Raymond-Barker P, et al. Is this elderly patient dehydrated? Diagnostic accuracy of hydration assessment using physical signs, urine, and saliva markers. *J Am Med Dir Assoc 2015;16:221-8.*
75. Lima A, Bakker J. Noninvasive monitoring of peripheral perfusion. *Intensive Care Med 2005;31:1316-26.*
76. Cannesson M, Desebbe O, Rosamel P, et al. Pleth variability index to monitor the respiratory variations in the pulse oximeter plethysmographic waveform amplitude and predict fluid responsiveness in the operating theatre. *Br J Anaesth 2008;101:200-6.*
77. van Genderen ME, Bartels SA, Lima A, et al. Peripheral perfusion index as an early predictor for central hypovolemia in awake healthy volunteers. *Anesth Analg 2013;116:351-6.*
78. Chu H, Wang Y, Sun Y, Wang G. Accuracy of pleth variability index to predict fluid responsiveness in mechanically ventilated patients: a systematic review and meta-analysis. *J Clin Monit Comput 2016;30:265-74.*
79. Kuwata S, Suehiro K, Juri T, et al. Pleth variability index can predict spinal anaesthesia-induced hypotension in patients undergoing caesarean delivery. *Acta Anaesthesiol Scand 2018;62:75-84.*
80. Oskay A, Eray O, Dinc SE, Aydin AG, Eken C. Prognosis of Critically ill patients in the ED and value of perfusion index measurement: a cross-sectional study. *Am J Emerg Med 2015;33:1042-4.*
81. Hasanin A, Mukhtar A, Nassar H. Perfusion indices revisited. *J Intensive Care 2017;5:24.*
82. Shimizu M, Kinoshita K, Hattori K, et al. Physical signs of dehydration in the elderly. *Intern Med 2012;51:1207-10.*
83. Hasselberg MJ, McMahon J, Parker K. The validity, reliability, and utility of the iButton(R) for measurement of body temperature circadian rhythms in sleep/wake research. *Sleep Med 2013;14:5-11.*
84. Eaton D, Bannister P, Mulley GP, Connolly MJ. Axillary sweating in clinical assessment of dehydration in ill elderly patients. *BMJ 1994;308:1271.*

85. Kinoshita K, Hattori K, Ota Y, et al. The measurement of axillary moisture for the assessment of dehydration among older patients: a pilot study. *Exp Gerontol 2013;48:255-8.*
86. Hooper L, Abdelhamid A, Ali A, et al. Diagnostic accuracy of calculated serum osmolarity to predict dehydration in older people: adding value to pathology laboratory reports. *BMJ Open 2015;5:e008846.*
87. Stookey JD. High prevalence of plasma hypertonicity among community-dwelling older adults: results from NHANES III. *J Am Diet Assoc 2005;105:1231-9.*
88. El-Sharkawy AM, Watson P, Neal KR, et al. Hydration and outcome in older patients admitted to hospital (The HOOP prospective cohort study). *Age Ageing 2015;44:943-7.*
89. Frangeskou M, Lopez-Valcarcel B, Serra-Majem L. Dehydration in the Elderly: A Review Focused on Economic Burden. *J Nutr Health Aging 2015;19:619-27.*
90. Loupec T, Nanadoumgar H, Frasca D, et al. Pleth variability index predicts fluid responsiveness in critically ill patients. *Crit Care Med 2011;39:294-9.*
91. Karras DJ, Kruus LK, Cienki JJ, et al. Evaluation and treatment of patients with severely elevated blood pressure in academic emergency departments: a multicenter study. *Ann Emerg Med 2006;47:230-6.*
92. Patel KK, Young L, Howell EH, et al. Characteristics and Outcomes of Patients Presenting With Hypertensive Urgency in the Office Setting. *JAMA Intern Med 2016;176:981-8.*
93. Vilela-Martin JF, Vaz-de-Melo RO, Kuniyoshi CH, Abdo AN, Yugar-Toledo JC. Hypertensive crisis: clinical-epidemiological profile. *Hypertens Res 2011;34:367-71.*
94. McNaughton CD, Self WH, Zhu Y, Janke AT, Storrow AB, Levy P. Incidence of Hypertension-Related Emergency Department Visits in the United States, 2006 to 2012. *Am J Cardiol 2015;116:1717-23.*
95. Zampaglione B, Pascale C, Marchisio M, Cavallo-Perin P. Hypertensive urgencies and emergencies. Prevalence and clinical presentation. *Hypertension 1996;27:144-7.*
96. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA /PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension 2018;71:1269-324.*
97. van den Born BJ, Beutler JJ, Gaillard CA, de Gooijer A, van den Meiracker AH, Kroon AA. Dutch guideline for the management of hypertensive crisis -- 2010 revision. *Neth J Med 2011;69:248-55.*
98. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens 2013;31:1281-357.*
99. Pinna G, Pascale C, Fornengo P, et al. Hospital admissions for hypertensive crisis in the emergency departments: a large multicenter Italian study. *PLoS One 2014;9:e93542.*
100. Leiba A, Cohen-Arazi O, Mendel L, Holtzman EJ, Grossman E. Incidence, aetiology and mortality secondary to hypertensive emergencies in a large-scale referral centre in Israel (1991-2010). *J Hum Hypertens 2016;30:498-502.*
101. Bender SR, Fong MW, Heitz S, Bisognano JD. Characteristics and management of patients presenting to the emergency department with hypertensive urgency. *J Clin Hypertens (Greenwich) 2006;8:12-8.*
102. Chowdhury R, Khan H, Heydon E, et al. Adherence to cardiovascular therapy: a meta-analysis of

prevalence and clinical consequences. *Eur Heart J 2013;34:2940-8.*

103. Herttua K, Tabak AG, Martikainen P, Vahtera J, Kivimaki M. Adherence to antihypertensive therapy prior to the first presentation of stroke in hypertensive adults: population-based study. *Eur Heart J 2013;34:2933-9.*

104. van der Nagel BCH, Versmissen J, Bahmany S, van Gelder T, Koch BCP. High-throughput quantification of 8 antihypertensive drugs and active metabolites in human plasma using UPLC-MS/MS. *J Chromatogr B Analyt Technol Biomed Life Sci 2017;1060:367-73.*

105. Sokolow M, Lyon TP. The ventricular complex in left ventricular hypertrophy as obtained by unipolar precordial and limb leads. *Am Heart J 1949;37:161-86.*

106. Martin JF, Higashiama E, Garcia E, Luizon MR, Cipullo JP. Hypertensive crisis profile. Prevalence and clinical presentation. *Arq Bras Cardiol 2004;83:131-6; 25-30.*

107. Al-Bannay R, Husain AA. Hypertensive crisis. Clinical presentation, comorbidities, and target organ involvement. *Saudi Med J 2010;31:916-20.*

108. Berkhemer OA, Fransen PS, Beumer D, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med 2015;372:11-20.*

109. Olsen MH, Angell SY, Asma S, et al. A call to action and a lifecourse strategy to address the global burden of raised blood pressure on current and future generations: the Lancet Commission on hypertension. *Lancet 2016;388:2665-712.*

110. Salkic S, Batic-Mujanovic O, Ljuca F, Brkic S. Clinical presentation of hypertensive crises in emergency medical services. *Mater Sociomed 2014;26:12-6.*

111. Merlo C, Bally K, Tschudi P, Martina B, Zeller A. Management and outcome of severely elevated blood pressure in primary care: a prospective observational study. *Swiss Med Wkly 2012;142:w13507.*

112. McNaughton CD, Brown NJ, Rothman RL, et al. Systolic Blood Pressure and Biochemical Assessment of Adherence: A Cross-Sectional Analysis in the Emergency Department. *Hypertension 2017;70:307-14.*

113. Dias E, Hachey B, McNaughton C, et al. An LC-MS assay for the screening of cardiovascular medications in human samples. *J Chromatogr B Analyt Technol Biomed Life Sci 2013;937:44-53.*

114. Saguner AM, Dur S, Perrig M, et al. Risk factors promoting hypertensive crises: evidence from a longitudinal study. *Am J Hypertens 2010;23:775-80.*

115. Burnier M. Drug adherence in hypertension. *Pharmacol Res 2017;125:142-9.*

116. Florczak E, Tokarczyk B, Warchol-Celinska E, et al. Assessment of adherence to treatment in patients with resistant hypertension using toxicological serum analysis. A subgroup evaluation of the RESIST-POL study. *Pol Arch Med Wewn 2015;125:65-72.*

117. De Geest S, Ruppar T, Berben L, Schonfeld S, Hill MN. Medication non-adherence as a critical factor in the management of presumed resistant hypertension: a narrative review. *EuroIntervention 2014;9:1102-9.*

118. de Souza WA, Sabha M, de Faveri Favero F, Bergsten-Mendes G, Yugar-Toledo JC, Moreno H. Intensive monitoring of adherence to treatment helps to identify "true" resistant hypertension. *J Clin Hypertens (Greenwich) 2009;11:183-91.*

119. Eskas PA, Heimark S, Eek Mariampillai J, Larstorp AC, Fadl Elmula FE, Hoieggen A. Adherence to medication and drug monitoring in apparent treatment-resistant hypertension. *Blood Press 2016;25:199-205.*

120. Jung O, Gechter JL, Wunder C, et al. Resistant hypertension? Assessment of adherence by toxicological urine analysis. *J Hypertens 2013;31:766-74.*

121. Pucci M, Martin U. Detecting non-adherence by urine analysis in patients with uncontrolled hypertension: rates, reasons and reactions. *J Hum Hypertens 2017;31:253-7.*
122. Tomaszewski M, White C, Patel P, et al. High rates of non-adherence to antihypertensive treatment revealed by high-performance liquid chromatography-tandem mass spectrometry (HP LC-MS/MS) urine analysis. *Heart 2014;100:855-61.*
123. Brinker S, Pandey A, Ayers C, et al. Therapeutic drug monitoring facilitates blood pressure control in resistant hypertension. *J Am Coll Cardiol 2014;63:834-5.*
124. Gupta P, Patel P, Strauch B, et al. Biochemical Screening for Nonadherence Is Associated With Blood Pressure Reduction and Improvement in Adherence. *Hypertension 2017;70:1042-8.*
125. Kamran A, Sadeghieh Ahari S, Biria M, Malepour A, Heydari H. Determinants of Patient's Adherence to Hypertension Medications: Application of Health Belief Model Among Rural Patients. *Ann Med Health Sci Res 2014;4:922-7.*
126. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. *Clin Ther 2001;23:1296-310.*
127. Williams B, MacDonald TM, Morant S, et al. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. *Lancet 2015;386:2059-68.*
128. Zeller A, Taegtmeyer A, Martina B, Battegay E, Tschudi P. Physicians' ability to predict patients' adherence to antihypertensive medication in primary care. *Hypertens Res 2008;31:1765-71.*
129. Kronish IM, Woodward M, Sergie Z, Ogedegbe G, Falzon L, Mann DM. Meta-analysis: impact of drug class on adherence to antihypertensives. *Circulation 2011;123:1611-21.*
130. Sharpe M. Medically unexplained symptoms and syndromes. *Clin Med (Lond) 2002;2:501-4.*
131. Hiller W, Fichter MM, Rief W. A controlled treatment study of somatoform disorders including analysis of healthcare utilization and cost-effectiveness. *J Psychosom Res 2003;54:369-80.*
132. Fink P, Rosendal M, Olesen F. Classification of somatization and functional somatic symptoms in primary care. *Aust N Z J Psychiatry 2005;39:772-81.*
133. Verhaak PF, Meijer SA, Visser AP, Wolters G. Persistent presentation of medically unexplained symptoms in general practice. *Fam Pract 2006;23:414-20.*
134. Olde Hartman TC, Woutersen-Koch H, Van der Horst HE. Medically unexplained symptoms: evidence, guidelines, and beyond. *Br J Gen Pract 2013;63:625-6.*
135. Nimnuan C, Hotopf M, Wessely S. Medically unexplained symptoms: an epidemiological study in seven specialities. *J Psychosom Res 2001;51:361-7.*
136. Kroenke K, Rosmalen JG. Symptoms, syndromes, and the value of psychiatric diagnostics in patients who have functional somatic disorders. *Med Clin North Am 2006;90:603-26.*
137. Weiland A, Blankenstein AH, Van Saase JL, et al. Training Medical Specialists to Communicate Better with Patients with Medically Unexplained Physical Symptoms (MUPS). A Randomized, Controlled Trial. *PLoS One 2015;10:e0138342.*
138. Stephenson DT, Price JR. Medically unexplained physical symptoms in emergency medicine. *Emerg Med J 2006;23:595-600.*
139. Barsky AJ, Orav EJ, Bates DW. Somatization increases medical utilization and costs independent of psychiatric and medical comorbidity. *Arch Gen Psychiatry 2005;62:903-10.*
140. Kroenke K. Patients presenting with somatic complaints: epidemiology, psychiatric comorbidity and management. *Int J Methods Psychiatr Res 2003;12:34-43.*
141. Giesen P, Franssen E, Mokkink H, van den Bosch W, van Vugt A, Grol R. Patients either contacting a general practice cooperative or accident and emergency department out of hours: a comparison.

Emerg Med J 2006;23:731-4.
142. Theadom A, Dupont S, Byron K. Functional somatic symptoms in accident and emergency--An exploratory study. *Accid Emerg Nurs 2006;14:171-7.*
143. Williams ER, Guthrie E, Mackway-Jones K, et al. Psychiatric status, somatisation, and health care utilization of frequent attenders at the emergency department: a comparison with routine attenders. *J Psychosom Res 2001;50:161-7.*
144. Reid S, Wessely S, Crayford T, Hotopf M. Medically unexplained symptoms in frequent attenders of secondary health care: retrospective cohort study. *BMJ 2001;322:767.*
145. den Boeft M, Twisk JW, Terluin B, et al. The association between medically unexplained physical symptoms and health care use over two years and the influence of depressive and anxiety disorders and personality traits: a longitudinal study. *BMC Health Serv Res 2016;16:100.*
146. Dirkzwager AJ, Verhaak PF. Patients with persistent medically unexplained symptoms in general practice: characteristics and quality of care. *BMC Fam Pract 2007;8:33.*
147. Salmon P, Humphris GM, Ring A, Davies JC, Dowrick CF. Primary care consultations about medically unexplained symptoms: patient presentations and doctor responses that influence the probability of somatic intervention. *Psychosom Med 2007;69:571-7.*
148. Salmon P, Ring A, Humphris GM, Davies JC, Dowrick CF. Primary care consultations about medically unexplained symptoms: how do patients indicate what they want? *J Gen Intern Med 2009;24:450-6.*
149. Weiland A, Blankenstein AH, Van Saase JL, et al. Training Medical Specialists in Communication about Medically Unexplained Physical Symptoms: Patient Outcomes from a Randomized Controlled Trial. *PLoS One. 2015 Sep 18;10(9):e0138342.*
150. Raj SR. Postural tachycardia syndrome (POTS). *Circulation 2013;127:2336-42.*
151. Mathias CJ, Low DA, Iodice V, Owens AP, Kirbis M, Grahame R. Postural tachycardia syndrome--current experience and concepts. *Nat Rev Neurol 2011;8:22-34.*
152. Benarroch EE. Postural tachycardia syndrome: a heterogeneous and multifactorial disorder. *Mayo Clin Proc 2012;87:1214-25.*
153. Goldstein DS, Robertson D, Esler M, Straus SE, Eisenhofer G. Dysautonomias: clinical disorders of the autonomic nervous system. *Ann Intern Med 2002;137:753-63.*
154. Schondorf R, Benoit J, Wein T, Phaneuf D. Orthostatic intolerance in the chronic fatigue syndrome. *J Auton Nerv Syst 1999;75:192-201.*
155. Low PA, Sandroni P, Joyner M, Shen WK. Postural tachycardia syndrome (POTS). *J Cardiovasc Electrophysiol 2009;20:352-8.*
156. Shannon JR, Flattem NL, Jordan J, et al. Orthostatic intolerance and tachycardia associated with norepinephrine-transporter deficiency. *N Engl J Med 2000;342:541-9.*
157. Raj V, Opie M, Arnold AC. Cognitive and psychological issues in postural tachycardia syndrome. *Auton Neurosci 2018;215:46-55.*
158. Arnold AC, Ng J, Raj SR. Postural tachycardia syndrome - Diagnosis, physiology, and prognosis. *Auton Neurosci 2018;215:3-11.*
159. Khurana RK. Visceral sensitization in postural tachycardia syndrome. *Clin Auton Res 2014;24:71-6.*
160. Gibbons CH, Bonyhay I, Benson A, Wang N, Freeman R. Structural and functional small fiber abnormalities in the neuropathic postural tachycardia syndrome. *PLoS One 2013;8:e84716.*
161. Garland EM, Celedonio JE, Raj SR. Postural Tachycardia Syndrome: Beyond Orthostatic Intolerance. *Curr Neurol Neurosci Rep 2015;15:60.*

162. Raj SR, Biaggioni I, Yamhure PC, et al. Renin-aldosterone paradox and perturbed blood volume regulation underlying postural tachycardia syndrome. *Circulation 2005;111:1574-82.*
163. Mustafa HI, Garland EM, Biaggioni I, et al. Abnormalities of angiotensin regulation in postural tachycardia syndrome. *Heart Rhythm 2011;8:422-8.*
164. Thieben MJ, Sandroni P, Sletten DM, et al. Postural orthostatic tachycardia syndrome: the Mayo clinic experience. *Mayo Clin Proc 2007;82:308-13.*
165. Sheldon RS, Grubb BP, 2nd, Olshansky B, et al. 2015 heart rhythm society expert consensus statement on the diagnosis and treatment of postural tachycardia syndrome, inappropriate sinus tachycardia, and vasovagal syncope. *Heart Rhythm 2015;12:e41-63.*
166. Rea NA, Campbell CL, Cortez MM. Quantitative assessment of autonomic symptom burden in Postural tachycardia syndrome (POTS). *J Neurol Sci 2017;377:35-41.*
167. Vernino S, Low PA, Fealey RD, Stewart JD, Farrugia G, Lennon VA. Autoantibodies to ganglionic acetylcholine receptors in autoimmune autonomic neuropathies. *N Engl J Med 2000;343:847-55.*
168. Watari M, Nakane S, Mukaino A, et al. Autoimmune postural orthostatic tachycardia syndrome. *Ann Clin Transl Neurol 2018;5:486-92.*
169. Li H, Yu X, Liles C, et al. Autoimmune basis for postural tachycardia syndrome. *J Am Heart Assoc 2014;3:e000755.*
170. Fedorowski A, Li H, Yu X, et al. Antiadrenergic autoimmunity in postural tachycardia syndrome. *Europace 2017;19:1211-9.*
171. Yu X, Li H, Murphy TA, et al. Angiotensin II Type 1 Receptor Autoantibodies in Postural Tachycardia Syndrome. *J Am Heart Assoc 2018;7.*
172. Jacob G, Costa F, Shannon JR, et al. The neuropathic postural tachycardia syndrome. *N Engl J Med 2000;343:1008-14.*
173. Sherman DG, Easton JD. Dieting and peroneal nerve palsy. *JAMA 1977;238:230-1.*
174. Landais A. Neurological complications of bariatric surgery. *Obes Surg 2014;24:1800-7.*
175. Ponnusamy V, Owens AP, Purkayastha S, Iodice V, Mathias CJ. Orthostatic intolerance and autonomic dysfunction following bariatric surgery: A retrospective study and review of the literature. *Auton Neurosci 2016;198:1-7.*
176. Grubb BP. Postural tachycardia syndrome. *Circulation 2008;117:2814-7.*
177. Staud R. Autonomic dysfunction in fibromyalgia syndrome: postural orthostatic tachycardia. *Curr Rheumatol Rep 2008;10:463-6.*
178. Lewis I, Pairman J, Spickett G, Newton JL. Clinical characteristics of a novel subgroup of chronic fatigue syndrome patients with postural orthostatic tachycardia syndrome. *J Intern Med 2013;273:501-10.*
179. Bagai K, Song Y, Ling JF, et al. Sleep disturbances and diminished quality of life in postural tachycardia syndrome. *J Clin Sleep Med 2011;7:204-10.*
180. Sharif K, Watad A, Bragazzi NL, et al. On chronic fatigue syndrome and nosological categories. *Clin Rheumatol 2018;37:1161-70.*
181. Uceyler N, Zeller D, Kahn AK, et al. Small fibre pathology in patients with fibromyalgia syndrome. *Brain 2013;136:1857-67.*
182. Levine TD, Saperstein DS. Routine use of punch biopsy to diagnose small fiber neuropathy in fibromyalgia patients. *Clin Rheumatol 2015;34:413-7.*
183. Benrud-Larson LM, Dewar MS, Sandroni P, Rummans TA, Haythornthwaite JA, Low PA. Quality of life in patients with postural tachycardia syndrome. *Mayo Clin Proc 2002;77:531-7.*
184. Benrud-Larson LM, Sandroni P, Haythornthwaite JA, Rummans TA, Low PA. Correlates of

functional disability in patients with postural tachycardia syndrome: preliminary cross-sectional findings. *Health Psychol 2003;22:643-8.*

185. Masuki S, Eisenach JH, Johnson CP, et al. Excessive heart rate response to orthostatic stress in postural tachycardia syndrome is not caused by anxiety. *J Appl Physiol (1985) 2007;102:896-903.*

186. Fleming KC, Volcheck MM. Central sensitization syndrome and the initial evaluation of a patient with fibromyalgia: a review. *Rambam Maimonides Med J 2015;6:e0020.*

187. Joyner MJ, Masuki S. POTS versus deconditioning: the same or different? *Clin Auton Res 2008;18:300-7.*

188. Z'Graggen WJ, Hess CW, Humm AM. Acute fluid ingestion in the treatment of orthostatic intolerance - important implications for daily practice. *Eur J Neurol 2010;17:1370-6.*

189. Shibata S, Fu Q, Bivens TB, Hastings JL, Wang W, Levine BD. Short-term exercise training improves the cardiovascular response to exercise in the postural orthostatic tachycardia syndrome. *J Physiol 2012;590:3495-505.*

190. Winker R, Barth A, Bidmon D, et al. Endurance exercise training in orthostatic intolerance: a randomized, controlled trial. *Hypertension 2005;45:391-8.*

191. Fu Q, Vangundy TB, Shibata S, Auchus RJ, Williams GH, Levine BD. Exercise training versus propranolol in the treatment of the postural orthostatic tachycardia syndrome. *Hypertension 2011;58:167-75.*

192. Moon J, Kim DY, Byun JI, et al. Orthostatic intolerance symptoms are associated with depression and diminished quality of life in patients with postural tachycardia syndrome. *Health Qual Life Outcomes 2016;14:144.*

193. Raj SR, Black BK, Biaggioni I, et al. Propranolol decreases tachycardia and improves symptoms in the postural tachycardia syndrome: less is more. *Circulation 2009;120:725-34.*

194. Coffin ST, Black BK, Biaggioni I, et al. Desmopressin acutely decreases tachycardia and improves symptoms in the postural tachycardia syndrome. *Heart Rhythm 2012;9:1484-90.*

195. Gee ME, Watkins AK, Brown JN, Young EJA. Ivabradine for the Treatment of Postural Orthostatic Tachycardia Syndrome: A Systematic Review. *Am J Cardiovasc Drugs 2018;18:195-204.*

196. McDonald C, Frith J, Newton JL. Single centre experience of ivabradine in postural orthostatic tachycardia syndrome. *Europace 2011;13:427-30.*

197. Kanjwal K, Karabin B, Sheikh M, et al. Pyridostigmine in the treatment of postural orthostatic tachycardia: a single-center experience. *Pacing Clin Electrophysiol 2011;34:750-5.*

198. Kpaeyeh J, Jr., Mar PL, Raj V, et al. Hemodynamic profiles and tolerability of modafinil in the treatment of postural tachycardia syndrome: a randomized, placebo-controlled trial. *J Clin Psychopharmacol 2014;34:738-41.*

199. Sandroni P, Opfer-Gehrking TL, McPhee BR, Low PA. Postural tachycardia syndrome: clinical features and follow-up study. *Mayo Clin Proc 1999;74:1106-10.*

200. Agarwal AK, Garg R, Ritch A, Sarkar P. Postural orthostatic tachycardia syndrome. *Postgrad Med J 2007;83:478-80.*

201. Gaffney FA, Lane LB, Pettinger W, Blomqvist CG. Effects of long-term clonidine administration on the hemodynamic and neuroendocrine postural responses of patients with dysautonomia. *Chest 1983;83:436-8.*

202. Raj SR, Black BK, Biaggioni I, Harris PA, Robertson D. Acetylcholinesterase inhibition improves tachycardia in postural tachycardia syndrome. *Circulation 2005;111:2734-40.*

203. Ross AJ, Ocon AJ, Medow MS, Stewart JM. A double-blind placebo-controlled cross-over study of the vascular effects of midodrine in neuropathic compared with hyperadrenergic postural

tachycardia syndrome. *Clin Sci (Lond) 2014;126:289-96.*

204. Gamaldo CE, Shaikh AK, McArthur JC. The sleep-immunity relationship. *Neurol Clin 2012;30:1313-43.*
205. Alvarez GG, Ayas NT. The impact of daily sleep duration on health: a review of the literature. *Prog Cardiovasc Nurs 2004;19:56-9.*
206. Gottlieb DJ, Punjabi NM, Newman AB, et al. Association of sleep time with diabetes mellitus and impaired glucose tolerance. *Arch Intern Med 2005;165:863-7.*
207. Hoevenaar-Blom MP, Spijkerman AM, Kromhout D, van den Berg JF, Verschuren WM. Sleep duration and sleep quality in relation to 12-year cardiovascular disease incidence: the MORGEN study. *Sleep 2011;34:1487-92.*
208. Manian FA, Manian CJ. Sleep quality in adult hospitalized patients with infection: an observational study. A*m J Med Sci 2015;349:56-60.*
209. Boonstra L, Harden K, Jarvis S, et al. Sleep disturbance in hospitalized recipients of stem cell transplantation. *Clin J Oncol Nurs 2011;15:271-6.*
210. Enomoto M, Tsutsui T, Higashino S, et al. Sleep-related problems and use of hypnotics in inpatients of acute hospital wards. *Gen Hosp Psychiatry 2010;32:276-83.*
211. De Rui M, Middleton B, Sticca A, et al. Sleep and circadian rhythms in hospitalized patients with decompensated cirrhosis: effect of light therapy. *Neurochem Res 2015;40:284-92.*
212. Yilmaz M, Sayin Y, Gurler H. Sleep quality of hospitalized patients in surgical units. *Nurs Forum 2012;47:183-92.*
213. Lieberman HR, Bathalon GP, Falco CM, Kramer FM, Morgan CA, 3rd, Niro P. Severe decrements in cognition function and mood induced by sleep loss, heat, dehydration, and undernutrition during simulated combat. *Biol Psychiatry 2005;57:422-9.*
214. Hoevenaar-Blom MP, Spijkerman AM, Kromhout D, Verschuren WM. Sufficient sleep duration contributes to lower cardiovascular disease risk in addition to four traditional lifestyle factors: the MORGEN study. *Eur J Prev Cardiol 2014;21:1367-75.*
215. Spiegel K, Leproult R, Van Cauter E. Impact of sleep debt on metabolic and endocrine function. *Lancet 1999;354:1435-9.*
216. Stang A, Moebus S, Mohlenkamp S, Erbel R, Jockel KH, Heinz Nixdorf Recall Study Investigative G. Gender-specific associations of short sleep duration with prevalent hypertension. *Hypertension 2008;51:e15-6; author reply e7.*
217. Martin JL, Fiorentino L, Jouldjian S, Mitchell M, Josephson KR, Alessi CA. Poor self-reported sleep quality predicts mortality within one year of inpatient post-acute rehabilitation among older adults. *Sleep 2011;34:1715-21.*
218. Watson PL, Ceriana P, Fanfulla F. Delirium: is sleep important? *Best Pract Res Clin Anaesthesiol 2012;26:355-66.*
219. Weinhouse GL, Schwab RJ, Watson PL, et al. Bench-to-bedside review: delirium in ICU patients - importance of sleep deprivation. *Crit Care 2009;13:234.*
220. Pilkington S. Causes and consequences of sleep deprivation in hospitalised patients. *Nurs Stand 2013;27:35-42.*
221. Dogan O, Ertekin S, Dogan S. Sleep quality in hospitalized patients. *J Clin Nurs 2005;14:107-13.*
222. Young JS, Bourgeois JA, Hilty DM, Hardin KA. Sleep in hospitalized medical patients, part 1: factors affecting sleep. *J Hosp Med 2008;3:473-82.*
223. Ghanbari Jolfaei A, Makvandi A, Pazouki A. Quality of sleep for hospitalized patients in Rasoul-Akram hospital. *Med J Islam Repub Iran 2014;28:73.*

224. Alsma J, van Saase J, Nanayakkara PWB, et al. The Power of Flash Mob Research: Conducting a Nationwide Observational Clinical Study on Capillary Refill Time in a Single Day. *Chest 2017;151:1106-13.*
225. Cambridge Online Dictionary.www.dictionary.cambridge.org.
226. Carney CE, Buysse DJ, Ancoli-Israel S, et al. The consensus sleep diary: standardizing prospective sleep self-monitoring. *Sleep 2012;35:287-302.*
227. Buysse DJ, Yu L, Moul DE, et al. Development and validation of patient-reported outcome measures for sleep disturbance and sleep-related impairments. *Sleep 2010;33:781-92.*
228. Terwee CB, Roorda LD, de Vet HC, et al. Dutch-Flemish translation of 17 item banks from the patient-reported outcomes measurement information system (PROMIS). *Qual Life Res 2014;23:1733-41.*
229. Bano M, Chiaromanni F, Corrias M, et al. The influence of environmental factors on sleep quality in hospitalized medical patients. *Front Neurol 2014;5:267.*
230. Lei Z, Qiongjing Y, Qiuli W, Sabrina K, Xiaojing L, Changli W. Sleep quality and sleep disturbing factors of inpatients in a Chinese general hospital. *J Clin Nurs 2009;18:2521-9.*
231. Gathecha E, Rios R, Buenaver LF, Landis R, Howell E, Wright S. Pilot study aiming to support sleep quality and duration during hospitalizations. *J Hosp Med 2016;11:467-72.*
232. Steiner D, Renetseder F, Kutz A, et al. Performance of the Manchester Triage System in Adult Medical Emergency Patients: A Prospective Cohort Study. *J Emerg Med 2016;50:678-89.*
233. Asplin BR, Magid DJ, Rhodes KV, Solberg LI, Lurie N, Camargo CA, Jr. A conceptual model of emergency department crowding. *Ann Emerg Med 2003;42:173-80.*
234. Liew D, Liew D, Kennedy MP. Emergency department length of stay independently predicts excess inpatient length of stay. *Med J Aust 2003;179:524-6.*
235. Sun BC, Hsia RY, Weiss RE, et al. Effect of emergency department crowding on outcomes of admitted patients. *Ann Emerg Med 2013;61:605-11 e6.*
236. Groarke JD, Gallagher J, Stack J, et al. Use of an admission early warning score to predict patient morbidity and mortality and treatment success. *Emerg Med J 2008;25:803-6.*
237. Morgan RJM, Williams F, Wright MM. An early warning scoring system for detecting developing critical illness. *Clinical Intensive Care 1997;8:100.*
238. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med 2009;6:e1000097.*
239. Moons KG, de Groot JA, Bouwmeester W, et al. Critical appraisal and data extraction for systematic reviews of prediction modelling studies: the CHARMS checklist. *PLoS Med 2014;11:e1001744.*
240. The Area Under an ROC Curve. University of Nebraska Medical Center, NA. (http://gim.unmc.edu/dxtests/ROC3.htm.)
241. Lemeshow S, Hosmer DW, Jr. A review of goodness of fit statistics for use in the development of logistic regression models. *Am J Epidemiol 1982;115:92-106.*
242. Brabrand M, Lassen AT, Knudsen T, Hallas J. Seven-day mortality can be predicted in medical patients by blood pressure, age, respiratory rate, loss of independence, and peripheral oxygen saturation (the PARIS Score): A prospective cohort study with external validation. *PLoS ONE 2015;10.*
243. Coslovsky M, Takala J, Exadaktylos AK, Martinolli L, Merz TM. A clinical prediction model to identify patients at high risk of death in the emergency department. *Intensive Care Med 2015;41:1029-36.*
244. Silke B, Kellett J, Rooney T, Bennett K, O'Riordan D. An improved medical admissions risk system

using multivariable fractional polynomial logistic regression modelling. *QJM 2010;103:23-32.*

245. Kellett J, Deane B. The Simple Clinical Score predicts mortality for 30 days after admission to an acute medical unit. *QJM 2006;99:771-81.*

246. Kellett J, Deane B, Gleeson M. Derivation and validation of a score based on Hypotension, Oxygen saturation, low Temperature, ECG changes and Loss of independence (HOTEL) that predicts early mortality between 15 min and 24 h after admission to an acute medical unit. *Resuscitation 2008;78:52-8.*

247. Stræde M, Brabrand M. External validation of the simple clinical score and the HOTEL score, two scores for predicting short-term mortality after admission to an acute medical unit. *PLoS ONE 2014;9.*

248. O'Sullivan E, Callely E, O'Riordan D, Bennett K, Silke B. Predicting outcomes in emergency medical admissions - Role of laboratory data and co-morbidity. *Acute Med 2012;11:59-65.*

249. Slagman A, Searle J, Vollert JO, et al. Predicting in-hospital mortality using routine parameters in unselected nonsurgical emergency department patients. *Notf Rettungsmed 2015;18:501-9.*

250. Cournane S, Conway R, Byrne D, O'Riordan D, Silke B. Predicting Outcomes in Emergency Medical Admissions Using a Laboratory Only Nomogram. *Comp Math Methods Med 2017;2017.*

251. Kristensen M, Iversen AKS, Gerds TA, et al. Routine blood tests are associated with short term mortality and can improve emergency department triage: a cohort study of >12,000 patients. *Scand J Trauma Resusc Emerg Med 2017;25:115.*

252. Alam N, Vegting IL, Houben E, et al. Exploring the performance of the National Early Warning Score (NEWS) in a European emergency department. *Resuscitation 2015;90:111-5.*

253. Duckitt RW, Buxton-Thomas R, Walker J, et al. Worthing physiological scoring system: Derivation and validation of a physiological early-warning system for medical admissions. An observational, population-based single-centre study. *Br J Anaesth 2007;98:769-74.*

254. Bulut M, Cebicci H, Sigirli D, et al. The comparison of modified early warning score with rapid emergency medicine score: A prospective multicentre observational cohort study on medical and surgical patients presenting to emergency department. *Emerg Med J 2014;31:476-81.*

255. Olsson T, Terent A, Lind L. Rapid Emergency Medicine score: A new prognostic tool for in-hospital mortality in nonsurgical emergency department patients. *J Intern Med (GBR) 2004;255:579-87.*

256. Goodacre S, Turner J, Nicholl J. Prediction of mortality among emergency medical admissions. *Emerg Med J 2006;23:372-5.*

257. Merz TM, Etter R, Mende L, et al. Risk assessment in the first fifteen minutes: A prospective cohort study of a simple physiological scoring system in the emergency department. *Crit Care 2011;15.*

258. Efron B, Tibshirani RJ. An Introduction to the Bootstrap. New York: *Chapman & Hall/CRC; 1993:1-10.*

259. Bech CN, Brabrand M, Mikkelsen S, Lassen A. Risk factors associated with short term mortality changes over time, after arrival to the emergency department. *Scand J Trauma Resusc Emerg Med 2018;26:29.*

260. Altman DG, Bland JM. Missing data. *BMJ 2007;334:424.*

261. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. *J Clin Epidemiol 1996;49:1373-9.*

262. Moons KG, Royston P, Vergouwe Y, Grobbee DE, Altman DG. Prognosis and prognostic research: what, why, and how? *BMJ 2009;338:b375.*

263. Centers for Disease Control and Prevention. National Hospital Ambulatory Medical Care Survey:2011 Emergency Department Summary Tables. (2014). http://www.cdc.gov/nchs/data/

ahcd/nhamcs_emergency/2011_ed_web_tables.pdf.
264. Roberts DC, McKay MP, Shaffer A. Increasing rates of emergency department visits for elderly patients in the United States, 1993 to 2003. *Ann Emerg Med 2008;51:769-74.*
265. Downing A, Wilson R. Older people's use of Accident and Emergency services. *Age Ageing 2005;34:24-30.*
266. van den Akker M, Buntinx F, Metsemakers JF, Roos S, Knottnerus JA. Multimorbidity in general practice: prevalence, incidence, and determinants of co-occurring chronic and recurrent diseases. *J Clin Epidemiol 1998;51:367-75.*
267. Hajjar ER, Cafiero AC, Hanlon JT. Polypharmacy in elderly patients. *Am J Geriatr Pharmacother 2007;5:345-51.*
268. Aminzadeh F, Dalziel WB. Older adults in the emergency department: a systematic review of patterns of use, adverse outcomes, and effectiveness of interventions. *Ann Emerg Med 2002;39:238-47.*
269. Casalino E, Wargon M, Peroziello A, et al. Predictive factors for longer length of stay in an emergency department: a prospective multicentre study evaluating the impact of age, patient's clinical acuity and complexity, and care pathways. *Emerg Med J 2014;31:361-8.*
270. Kreindler SA, Cui Y, Metge CJ, Raynard M. Patient characteristics associated with longer emergency department stay: a rapid review. *Emerg Med J 2016;33:194-9.*
271. Latham LP, Ackroyd-Stolarz S. Emergency department utilization by older adults: a descriptive study. *Can Geriatr J 2014;17:118-25.*
272. Vanpee D, Swine C, Vandenbossche P, Gillet JB. Epidemiological profile of geriatric patients admitted to the emergency department of a university hospital localized in a rural area. *Eur J Emerg Med 2001;8:301-4.*
273. Limpawattana P, Phungoen P, Mitsungnern T, Laosuangkoon W, Tansangworn N. Atypical presentations of older adults at the emergency department and associated factors. *Arch Gerontol Geriatr 2016;62:97-102.*
274. Salvi F, Morichi V, Grilli A, Giorgi R, De Tommaso G, Dessi-Fulgheri P. The elderly in the emergency department: a critical review of problems and solutions. *Intern Emerg Med 2007;2:292-301.*
275. Rutschmann OT, Chevalley T, Zumwald C, Luthy C, Vermeulen B, Sarasin FP. Pitfalls in the emergency department triage of frail elderly patients without specific complaints. *Swiss Med Wkly 2005;135:145-50.*
276. Phillips S, Rond PC, 3rd, Kelly SM, Swartz PD. The failure of triage criteria to identify geriatric patients with trauma: results from the Florida Trauma Triage Study. *J Trauma 1996;40:278-83.*
277. Chang DC, Bass RR, Cornwell EE, Mackenzie EJ. Undertriage of elderly trauma patients to state-designated trauma centers. *Arch Surg 2008;143:776-81; discussion 782.*
278. Baum SA, Rubenstein LZ. Old people in the emergency room: age-related differences in emergency department use and care. *J Am Geriatr Soc 1987;35:398-404.*
279. Schrijver EJ, Toppinga Q, de Vries OJ, Kramer MH, Nanayakkara PW. An observational cohort study on geriatric patient profile in an emergency department in the Netherlands. *Neth J Med 2013;71:324-30.*
280. Hwang U, Morrison RS. The geriatric emergency department. *J Am Geriatr Soc 2007;55:1873-6.*
281. Shankar KN, Bhatia BK, Schuur JD. Toward patient-centered care: a systematic review of older adults' views of quality emergency care. *Ann Emerg Med 2014;63:529-50 e1.*
282. Barfod C, Lauritzen MM, Danker JK, et al. Abnormal vital signs are strong predictors for intensive

care unit admission and in-hospital mortality in adults triaged in the emergency department - a prospective cohort study. *Scand J Trauma Resusc Emerg Med 2012;20:28.*

283. Considine J, Thomas S, Potter R. Predictors of critical care admission in emergency department patients triaged as low to moderate urgency. *J Adv Nurs 2009;65:818-27.*
284. Mackway-Jones K (1997) Manchester Triage Group; Emergency Triage. *BMJ Publishing Group, Londen.*
285. American College of Surgeons Committee on Trauma. Advanced trauma life support course for physicians. (1989) Paper presented at the American College of Surgeons, Chicago, IL.
286. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. *Lancet 1974;2:81-4.*
287. Stenhouse C, Coates S, Tivey M, Allsop P, Parker T (2000) Prospective evaluation of a modified Early Warning Score to aid earlier detection of patients developing critical illenss on a general surgical ward. *British Journal of Anaesthesia 84 (5):663.*
288. Efron B, Tibshirani R (1993) An introduction to the bootstrap. In. Chapman & Hall, New York, pp1-10.
289. Steyerberg EW (2009) Clinical Prediction Models. In. Springer Science + Business, New York, pp356-357. doi:10.1007/978-0-387-77244-8.
290. Steyerberg EW, Harrell FE, Jr., Borsboom GJ, Eijkemans MJ, Vergouwe Y, Habbema JD. Internal validation of predictive models: efficiency of some procedures for logistic regression analysis. *J Clin Epidemiol 2001;54:774-81.*
291. Miller ME, Langefeld CD, Tierney WM, Hui SL, McDonald CJ. Validation of probabilistic predictions. *Med Decis Making 1993;13:49-58.*
292. Dijkland SA, Roozenbeek B, Brouwer PA, et al. Prediction of 60-Day Case Fatality After Aneurysmal Subarachnoid Hemorrhage: External Validation of a Prediction Model. *Crit Care Med 2016;44:1523-9.*
293. RStudio Team (2015). RStudio: Integrated Development for R. RStudio, Inc., Boston, MA URL http://www.rstudio.com/.
294. R Core Team (2015). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/.
295. R Core Team. foreign: Read Data Stored by Minitab, S, SAS, SPSS, Stata, Systat, Weka, dBase, ...(2014). http://CRAN.R-project.org/package=foreign.
296. Harrell FE, Jr. (2014, R package version 4.2-1) rms: Regression Modeling Strategies. http://CRAN.R-project.org/package=rms.
297. McCusker J, Kakuma R, Abrahamowicz M. Predictors of functional decline in hospitalized elderly patients: a systematic review. J *Gerontol A Biol Sci Med Sci 2002;57:M569-77.*
298. Di Bari M, Salvi F, Roberts AT, et al. Prognostic stratification of elderly patients in the emergency department: a comparison between the "Identification of Seniors at Risk" and the "Silver Code". *J Gerontol A Biol Sci Med Sci 2012;67:544-50.*
299. Salvi F, Morichi V, Lorenzetti B, et al. Risk stratification of older patients in the emergency department: comparison between the Identification of Seniors at Risk and Triage Risk Screening Tool. *Rejuvenation Res 2012;15:288-94.*
300. Meldon SW, Mion LC, Palmer RM, et al. A brief risk-stratification tool to predict repeat emergency department visits and hospitalizations in older patients discharged from the emergency department. *Acad Emerg Med 2003;10:224-32.*
301. Baumann MR, Strout TD. Triage of geriatric patients in the emergency department: validity and

survival with the Emergency Severity Index. *Ann Emerg Med 2007;49:234-40.*

302. LaMantia MA, Platts-Mills TF, Biese K, et al. Predicting hospital admission and returns to the emergency department for elderly patients. *Acad Emerg Med 2010;17:252-9.*

303. Grossmann FF, Zumbrunn T, Frauchiger A, Delport K, Bingisser R, Nickel CH. At risk of undertriage? Testing the performance and accuracy of the emergency severity index in older emergency department patients. *Ann Emerg Med 2012;60:317-25 e3.*

304. Yip WL, Fan KL, Lui CT, Leung LP, Ng F, Tsui KL. Utilization of the Accident & Emergency Departments by Chinese elderly in Hong Kong. *World J Emerg Med 2015;6:283-8.*

305. Seymour CW, Liu VX, Iwashyna TJ, et al. Assessment of Clinical Criteria for Sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA 2016;315:762-74.*

306. Carneiro AH, Povoa P, Gomes JA. Dear Sepsis-3, we are sorry to say that we don't like you. *Rev Bras Ter Intensiva 2017;29:4-8.*

307. Goulden R, Hoyle MC, Monis J, et al. qSOFA, SIRS and NEWS for predicting inhospital mortality and ICU admission in emergency admissions treated as sepsis. *Emerg Med J 2018;35:345-9.*

308. Askim A, Moser F, Gustad LT, 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;25:56.*

309. Canet E, Taylor DM, Khor R, Krishnan V, Bellomo R. qSOFA as predictor of mortality and prolonged ICU admission in Emergency Department patients with suspected infection. *J Crit Care 2018;48:118-23.*

310. Hwang SY, Jo IJ, Lee SU, et al. Low Accuracy of Positive qSOFA Criteria for Predicting 28-Day Mortality in Critically Ill Septic Patients During the Early Period After Emergency Department Presentation. *Ann Emerg Med 2018;71:1-9 e2.*

311. Physicians RCo. National Early Warning Score (NEWS): Standardising the assessment of acute illness severity in the NHS. Report of a working party. London: RCP; 2012.

312. Kivipuro M, Tirkkonen J, Kontula T, et al. National early warning score (NEWS) in a Finnish multidisciplinary emergency department and direct vs. late admission to intensive care. *Resuscitation 2018;128:164-9.*

313. Hoikka M, Silfvast T, Ala-Kokko TI. Does the prehospital National Early Warning Score predict the short-term mortality of unselected emergency patients? *Scand J Trauma Resusc Emerg Med 2018;26:48.*

314. Alexander RH, Proctor HJ, American College of Surgeons, Committee on Trauma. Advanced Trauma Life Support Program For Physicians: ATLS. 5th ed. Chicago, IL: American College of Surgeons; 1993.

315. Pedersen AB, Mikkelsen EM, Cronin-Fenton D, et al. Missing data and multiple imputation in clinical epidemiological research. *Clin Epidemiol 2017;9:157-66.*

316. Jo S, Yoon J, Lee JB, Jin Y, Jeong T, Park B. Predictive value of the National Early Warning Score-Lactate for mortality and the need for critical care among general emergency department patients. *J Crit Care 2016;36:60-8.*

317. Shaw J, Fothergill RT, Clark S, Moore F. Can the prehospital National Early Warning Score identify patients most at risk from subsequent deterioration? *Emerg Med J 2017;34:533-7.*

318. Churpek MM, Snyder A, Han X, et al. Quick Sepsis-related Organ Failure Assessment, Systemic Inflammatory Response Syndrome, and Early Warning Scores for Detecting Clinical Deterioration in Infected Patients outside the Intensive Care Unit. *Am J Respir Crit Care Med 2017;195:906-11.*

319. Sbiti-Rohr D, Kutz A, Christ-Crain M, et al. The National Early Warning Score (NEWS) for outcome prediction in emergency department patients with community-acquired pneumonia: results from a 6-year prospective cohort study. *BMJ Open 2016;6:e011021.*
320. Bilben B, Grandal L, Sovik S. National Early Warning Score (NEWS) as an emergency department predictor of disease severity and 90-day survival in the acutely dyspneic patient - a prospective observational study. *Scand J Trauma Resusc Emerg Med 2016;24:80.*
321. Corfield AR, Lees F, Zealley I, et al. Utility of a single early warning score in patients with sepsis in the emergency department. *Emerg Med J 2014;31:482-7.*
322. Gill MR, Reiley DG, Green SM. Interrater reliability of Glasgow Coma Scale scores in the emergency department. *Ann Emerg Med 2004;43:215-23.*
323. Sjoding MW, Luo K, Miller MA, Iwashyna TJ. When do confounding by indication and inadequate risk adjustment bias critical care studies? A simulation study. Crit Care 2015;19:195.
324. Cretikos MA, Bellomo R, Hillman K, Chen J, Finfer S, Flabouris A. Respiratory rate: the neglected vital sign. *Med J Aust 2008;188:657-9.*
325. Asayama K, Aikawa N. Evaluation of systemic inflammatory response syndrome criteria as a predictor of mortality in emergency patients transported by ambulance. *Keio J Med 1998;47:19-27.*
326. Jones GR, Lowes JA. The systemic inflammatory response syndrome as a predictor of bacteraemia and outcome from sepsis. *QJM 1996;89:515-22.*
327. Park HK, Kim WY, Kim MC, Jung W, Ko BS. Quick sequential organ failure assessment compared to systemic inflammatory response syndrome for predicting sepsis in emergency department. *J Crit Care 2017;42:12-7.*
328. Sprung CL, Schein RMH, Balk RA. The new sepsis consensus definitions: the good, the bad and the ugly. *Intensive Care Med 2016;42:2024-6.*
329. Raith EP, Udy AA, Bailey M, et al. Prognostic Accuracy of the SOFA Score, SIRS Criteria, and qSOFA Score for In-Hospital Mortality Among Adults With Suspected Infection Admitted to the Intensive Care Unit. *JAMA 2017;317:290-300.*
330. (UNWTO). WTO. UNWTO tourism highlights, 2014 edition. Madrid: UNTWO; 2014.
331. Freedman DO, Weld LH, Kozarsky PE, et al. Spectrum of disease and relation to place of exposure among ill returned travelers. *N Engl J Med 2006;354:119-30.*
332. Steffen R, deBernardis C, Banos A. Travel epidemiology--a global perspective. *Int J Antimicrob Agents 2003;21:89-95.*
333. Chen LH, Wilson ME. The role of the traveler in emerging infections and magnitude of travel. *Med Clin North Am 2008;92:1409-32, xi.*
334. Wilson ME. The traveller and emerging infections: sentinel, courier, transmitter. *J Appl Microbiol 2003;94 Suppl:1S-11S.*
335. Woodford N. Unwanted souvenirs: travel and multi-resistant bacteria. *J Travel Med 2011;18:297-8.*
336. Woerther PL, Burdet C, Chachaty E, Andremont A. Trends in human fecal carriage of extended-spectrum beta-lactamases in the community: toward the globalization of CTX-M. *Clin Microbiol Rev 2013;26:744-58.*
337. Kumarasamy KK, Toleman MA, Walsh TR, et al. Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study. *Lancet Infect Dis 2010;10:597-602.*
338. Oteo J, Perez-Vazquez M, Campos J. Extended-spectrum [beta]-lactamase producing Escherichia coli: changing epidemiology and clinical impact. *Curr Opin Infect Dis 2010;23:320-6.*
339. Lausch KR, Fuursted K, Larsen CS, Storgaard M. Colonisation with multi-resistant

Enterobacteriaceae in hospitalised Danish patients with a history of recent travel: a cross-sectional study. *Travel Med Infect Dis 2013;11:320-3.*

340. Soraas A, Sundsfjord A, Sandven I, Brunborg C, Jenum PA. Risk factors for community-acquired urinary tract infections caused by ESBL-producing enterobacteriaceae--a case-control study in a low prevalence country. *PLoS One 2013;8:e69581.*

341. Laupland KB, Church DL, Vidakovich J, Mucenski M, Pitout JD. Community-onset extended-spectrum beta-lactamase (ESBL) producing Escherichia coli: importance of international travel. *J Infect 2008;57:441-8.*

342. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev 2015;4:1.*

343. (UNSTATS) UNSD. Composition of macro geographical (continental) regions, geographical sub-regions, and selected economic and other groupings. New York: UNSTATS.

344. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *PLoS Med 2007;4:e296.*

345. Sanderson S, Tatt ID, Higgins JP. Tools for assessing quality and susceptibility to bias in observational studies in epidemiology: a systematic review and annotated bibliography. *Int J Epidemiol 2007;36:666-76.*

346. Tangden T, Cars O, Melhus A, Lowdin E. Foreign travel is a major risk factor for colonization with Escherichia coli producing CTX-M-type extended-spectrum beta-lactamases: a prospective study with Swedish volunteers. *Antimicrob Agents Chemother 2010;54:3564-8.*

347. Kennedy K, Collignon P. Colonisation with Escherichia coli resistant to "critically important" antibiotics: a high risk for international travellers. *Eur J Clin Microbiol Infect Dis 2010;29:1501-6.*

348. Ostholm-Balkhed A, Tarnberg M, Nilsson M, et al. Travel-associated faecal colonization with ESBL-producing Enterobacteriaceae: incidence and risk factors. *J Antimicrob Chemother 2013;68:2144-53.*

349. Kantele A, Laaveri T, Mero S, et al. Antimicrobials increase travelers' risk of colonization by extended-spectrum betalactamase-producing Enterobacteriaceae. *Clin Infect Dis 2015;60:837-46.*

350. Weisenberg SA, Mediavilla JR, Chen L, et al. Extended spectrum beta-lactamase-producing Enterobacteriaceae in international travelers and non-travelers in New York City. *PLoS One 2012;7:e45141.*

351. Angelin M, Forsell J, Granlund M, Evengard B, Palmgren H, Johansson A. Risk factors for colonization with extended-spectrum beta-lactamase producing Enterobacteriaceae in healthcare students on clinical assignment abroad: A prospective study. *Travel Med Infect Dis 2015;13:223-9.*

352. von Wintersdorff CJ, Penders J, Stobberingh EE, et al. High rates of antimicrobial drug resistance gene acquisition after international travel, The Netherlands. *Emerg Infect Dis 2014;20:649-57.*

353. Paltansing S, Vlot JA, Kraakman ME, et al. Extended-spectrum beta-lactamase-producing enterobacteriaceae among travelers from the Netherlands. *Emerg Infect Dis 2013;19:1206-13.*

354. Ruppe E, Armand-Lefevre L, Estellat C, et al. High Rate of Acquisition but Short Duration of Carriage of Multidrug-Resistant Enterobacteriaceae After Travel to the Tropics. *Clin Infect Dis 2015;61:593-600.*

355. Kuenzli E, Jaeger VK, Frei R, et al. High colonization rates of extended-spectrum beta-lactamase (ESBL)-producing Escherichia coli in Swiss travellers to South Asia- a prospective observational multicentre cohort study looking at epidemiology, microbiology and risk factors. *BMC Infect Dis 2014;14:528.*

356. Lubbert C, Straube L, Stein C, et al. Colonization with extended-spectrum beta-lactamase-producing and carbapenemase-producing Enterobacteriaceae in international travelers returning to Germany. *Int J Med Microbiol 2015;305:148-56.*

357. Schwaber MJ, Carmeli Y. Mortality and delay in effective therapy associated with extended-spectrum beta-lactamase production in Enterobacteriaceae bacteraemia: a systematic review and meta-analysis. *J Antimicrob Chemother 2007;60:913-20.*

358. Epelboin L, Robert J, Tsyrina-Kouyoumdjian E, et al. High Rate of Multidrug-Resistant Gram-Negative Bacilli Carriage and Infection in Hospitalized Returning Travelers: A Cross-Sectional Cohort Study. *J Travel Med 2015;22:292-9.*

359. Kaspar T, Schweiger A, Droz S, Marschall J. Colonization with resistant microorganisms in patients transferred from abroad: who needs to be screened? *Antimicrob Resist Infect Control 2015;4:31.*

360. Lepelletier D, Andremont A, Grandbastien B, National Working G. Risk of highly resistant bacteria importation from repatriates and travelers hospitalized in foreign countries: about the French recommendations to limit their spread. *J Travel Med 2011;18:344-51.*

361. Carattoli A. Plasmids and the spread of resistance. *Int J Med Microbiol 2013;303:298-304.*

362. Walsh TR, Weeks J, Livermore DM, Toleman MA. Dissemination of NDM-1 positive bacteria in the New Delhi environment and its implications for human health: an environmental point prevalence study. *Lancet Infect Dis 2011;11:355-62.*

363. van der Bij AK, Pitout JD. The role of international travel in the worldwide spread of multiresistant Enterobacteriaceae. *J Antimicrob Chemother 2012;67:2090-100.*

364. Ruppe E, Armand-Lefevre L, Estellat C, et al. Acquisition of carbapenemase-producing Enterobacteriaceae by healthy travellers to India, France, February 2012 to March 2013. *Euro Surveill 2014;19.*

365. J. P. Acquisition of ESBL- and carbapenemase producing Enterobacteriaceae during travel: The Carriage of Multiresistant Bacteria After Travel (COMBAT) Study. Maastricht: 3rd Euregional Maastricht Symposium on Immune Compromised Traveller; 2014. Available from: http://www.minc.eu/eumict/3rd%20EUMICT_11_Penders.pdf.

366. Morrison BJ, Rubin JE. Carbapenemase producing bacteria in the food supply escaping detection. *PLoS One 2015;10:e0126717.*

367. Arcilla MS, van Hattem JM, Bootsma MC, et al. The Carriage Of Multiresistant Bacteria After Travel (COMBAT) prospective cohort study: methodology and design. *BMC Public Health 2014;14:410.*

368. Wu AR, Fouzdar-Jain S, Suh DW. Comparison Study of Funduscopic Examination Using a Smartphone-Based Digital Ophthalmoscope and the Direct Ophthalmoscope. *J Pediatr Ophthalmol Strabismus 2018;55:201-6.*

369. Volksgezondheidenzorg.info

370. Mercuri M, Sherbino J, Sedran RJ, Frank JR, Gafni A, Norman G. When guidelines don't guide: the effect of patient context on management decisions based on clinical practice guidelines. *Acad Med 2015;90:191-6.*

371. Bjerklund Johansen TE, Cek M, Naber K, et al. Prevalence of hospital-acquired urinary tract infections in urology departments. *Eur Urol 2007;51:1100-11; discussion 12.*

372. van der Donk CF, Beisser PS, Hoogkamp-Korstanje JA, Bruggeman CA, Stobberingh EE, Antibiotic Resistance Surveillance G. A 12 year (1998-2009) antibiotic resistance surveillance of Klebsiella pneumoniae collected from intensive care and urology patients in 14 Dutch hospitals. *J*

Antimicrob Chemother 2011;66:855-8.
373. Khawcharoenporn T, Vasoo S, Ward E, Singh K. High rates of quinolone resistance among urinary tract infections in the ED. *Am J Emerg Med 2012;30:68-74.*
374. Hayward RS, Harding J, Molloy R, et al. Adverse effects of a single dose of gentamicin in adults: a systematic review. *Br J Clin Pharmacol 2018;84:223-38.*
375. Kaloyanides GJ, Pastoriza-Munoz E. Aminoglycoside nephrotoxicity. *Kidney Int 1980;18:571-82.*
376. Ryan A, McGee TJ. Development of hearing loss in kanamycin treated chinchillas. *Ann Otol Rhinol Laryngol 1977;86:176-82.*
377. Cosgrove SE, Vigliani GA, Fowler VG, Jr., et al. Initial low-dose gentamicin for Staphylococcus aureus bacteremia and endocarditis is nephrotoxic. *Clin Infect Dis 2009;48:713-21.*
378. Vardi M, Kochavi T, Denekamp Y, Bitterman H. Risk factors for urinary tract infection caused by Enterobacteriaceae with extended-spectrum beta-lactamase resistance in patients admitted to internal medicine departments. *Isr Med Assoc J 2012;14:115-8.*
379. Dickstein Y, Geffen Y, Andreassen S, Leibovici L, Paul M. Predicting Antibiotic Resistance in Urinary Tract Infection Patients with Prior Urine Cultures. *Antimicrob Agents Chemother 2016;60:4717-21.*
380. Brabrand M, Henriksen DP. CURB-65 Score is Equal to NEWS for Identifying Mortality Risk of Pneumonia Patients: An Observational Study. *Lung 2018;196:359-61.*
381. Alam N, Vegting IL, Houben E, et al. Exploring the performance of the National Early Warning Score (NEWS) in a European emergency department. *Resuscitation 2015;90:111-5.*
382. Chan YL, Liao HC, Tsay PK, Chang SS, Chen JC, Liaw SJ. C-reactive protein as an indicator of bacterial infection of adult patients in the emergency department. *Chang Gung Med J 2002;25:437-45.*
383. Mohammad A, Branicki F, Abu-Zidan FM. Educational and clinical impact of Advanced Trauma Life Support (ATLS) courses: a systematic review. *World J Surg 2014;38:322-9.*
384. Berrevoets MA, Ten Oever J, Sprong T, et al. Monitoring, documenting and reporting the quality of antibiotic use in the Netherlands: a pilot study to establish a national antimicrobial stewardship registry. *BMC Infect Dis 2017;17:565.*
385. Hollyer I, Ison MG. The challenge of urinary tract infections in renal transplant recipients. *Transpl Infect Dis 2018;20:e12828.*
386. Kandil H, Cramp E, Vaghela T. Trends in Antibiotic Resistance in Urologic Practice. *Eur Urol Focus 2016;2:363-73.*
387. Castillo-Tokumori F, Irey-Salgado C, Malaga G. Worrisome high frequency of extended-spectrum beta-lactamase-producing Escherichia coli in community-acquired urinary tract infections: a case-control study. *Int J Infect Dis 2017;55:16-9.*
388. Teunis PFM, Evers EG, Hengeveld PD, Dierikx CM, Wielders CCH, van Duijkeren E. Time to acquire and lose carriership of ESBL/pAmpC producing E. coli in humans in the Netherlands. *PLoS One 2018;13:e0193834.*
389. Arcilla MS, van Hattem JM, Haverkate MR, et al. Import and spread of extended-spectrum beta-lactamase-producing Enterobacteriaceae by international travellers (COMBAT study): a prospective, multicentre cohort study. *Lancet Infect Dis 2017;17:78-85.*
390. Cobussen M, de Kort JM, Dennert RM, Lowe SH, Stassen PM. No increased risk of acute kidney injury after a single dose of gentamicin in patients with sepsis. *Infect Dis (Lond) 2016;48:274-80.*
391. Picard W, Bazin F, Clouzeau B, et al. Propensity-based study of aminoglycoside nephrotoxicity in patients with severe sepsis or septic shock. *Antimicrob Agents Chemother 2014;58:7468-74.*

392. Goto M, Al-Hasan MN. Overall burden of bloodstream infection and nosocomial bloodstream infection in North America and Europe. *Clin Microbiol Infect 2013;19:501-9.*
393. Cross A, Levine MM. Patterns of bacteraemia aetiology. *Lancet Infect Dis 2017;17:1005-6.*
394. Dellinger RP. The Surviving Sepsis Campaign: Where have we been and where are we going? *Cleve Clin J Med 2015;82:237-44.*
395. Kollef MH. Broad-spectrum antimicrobials and the treatment of serious bacterial infections: getting it right up front. *Clin Infect Dis 2008;47 Suppl 1:S3-13.*
396. Gradel KO, Jensen US, Schonheyder HC, et al. Impact of appropriate empirical antibiotic treatment on recurrence and mortality in patients with bacteraemia: a population-based cohort study. *BMC Infect Dis 2017;17:122.*
397. Paul M, Shani V, Muchtar E, Kariv G, Robenshtok E, Leibovici L. Systematic review and meta-analysis of the efficacy of appropriate empiric antibiotic therapy for sepsis. *Antimicrob Agents Chemother 2010;54:4851-63.*
398. Marquet K, Liesenborgs A, Bergs J, Vleugels A, Claes N. Incidence and outcome of inappropriate in-hospital empiric antibiotics for severe infection: a systematic review and meta-analysis. *Crit Care 2015;19:63.*
399. Cain SE, Kohn J, Bookstaver PB, Albrecht H, Al-Hasan MN. Stratification of the impact of inappropriate empirical antimicrobial therapy for Gram-negative bloodstream infections by predicted prognosis. *Antimicrob Agents Chemother 2015;59:245-50.*
400. Fitzpatrick JM, Biswas JS, Edgeworth JD, et al. Gram-negative bacteraemia; a multi-centre prospective evaluation of empiric antibiotic therapy and outcome in English acute hospitals. *Clin Microbiol Infect 2016;22:244-51.*
401. Savage RD, Fowler RA, Rishu AH, et al. The Effect of Inadequate Initial Empiric Antimicrobial Treatment on Mortality in Critically Ill Patients with Bloodstream Infections: A Multi-Centre Retrospective Cohort Study. *PLoS One 2016;11:e0154944.*
402. Thom KA, Shardell MD, Osih RB, et al. Controlling for severity of illness in outcome studies involving infectious diseases: impact of measurement at different time points. *Infect Control Hosp Epidemiol 2008;29:1048-53.*
403. Corona A, Bertolini G, Lipman J, Wilson AP, Singer M. Antibiotic use and impact on outcome from bacteraemic critical illness: the BActeraemia Study in Intensive Care (BASIC). *J Antimicrob Chemother 2010;65:1276-85.*
404. Anderson DJ, Moehring RW, Sloane R, et al. Bloodstream infections in community hospitals in the 21st century: a multicenter cohort study. *PLoS One 2014;9:e91713.*
405. McGregor JC, Rich SE, Harris AD, et al. A systematic review of the methods used to assess the association between appropriate antibiotic therapy and mortality in bacteremic patients. *Clin Infect Dis 2007;45:329-37.*
406. Hernán MA, Robins JM. Causal Inference: Boca Raton: Chapman & Hall/CRC, forthcoming; 2019.
407. SWAB Erasmus MC. 2018. at https://erasmusmc.swabid.nl/.)
408. Verbrugh HA. Mapping antibiotic use and resistance in the Netherlands: SWAB and NethMap. *Neth J Med 2003;61:341-2.*
409. Bloodstream Infection Event (Central Line-Associated Bloodstream Infection and Non-central Line Associated Bloodstream Infection). 2019. (https://www.cdc.gov/nhsn/pdfs/pscmanual/4psc_clabscurrent.pdf.)
410. Trick WE, Zagorski BM, Tokars JI, et al. Computer algorithms to detect bloodstream infections.

Emerg Infect Dis 2004;10:1612-20.
411. Zachariasse JM, Seiger N, Rood PP, et al. Validity of the Manchester Triage System in emergency care: A prospective observational study. *PLoS One 2017;12:e0170811.*
412. Shapiro NI, Wolfe RE, Wright SB, Moore R, Bates DW. Who needs a blood culture? A prospectively derived and validated prediction rule. *J Emerg Med 2008;35:255-64.*
413. Friedman ND, Kaye KS, Stout JE, et al. Health care--associated bloodstream infections in adults: a reason to change the accepted definition of community-acquired infections. *Ann Intern Med 2002;137:791-7.*
414. McGinley A, Pearse RM. A national early warning score for acutely ill patients. *BMJ 2012;345:e5310.*
415. Brink A, Alsma J, Verdonschot R, 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;14:e0211133.*
416. Quan H, Li B, Couris CM, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol 2011;173:676-82.*
417. Brookhart MA, Schneeweiss S, Rothman KJ, Glynn RJ, Avorn J, Sturmer T. Variable selection for propensity score models. *Am J Epidemiol 2006;163:1149-56.*
418. Graham JW, Olchowski AE, Gilreath TD. How many imputations are really needed? Some practical clarifications of multiple imputation theory. *Prev Sci 2007;8:206-13.*
419. Glynn RJ, Schneeweiss S, Sturmer T. Indications for propensity scores and review of their use in pharmacoepidemiology. *Basic Clin Pharmacol Toxicol 2006;98:253-9.*
420. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. *Multivariate Behav Res 2011;46:399-424.*
421. Austin PC. Variance estimation when using inverse probability of treatment weighting (IPTW) with survival analysis. *Stat Med 2016;35:5642-55.*
422. Rassen JA, Glynn RJ, Rothman KJ, Setoguchi S, Schneeweiss S. Applying propensity scores estimated in a full cohort to adjust for confounding in subgroup analyses. *Pharmacoepidemiol Drug Saf 2012;21:697-709.*
423. Paley L, Zornitzki T, Cohen J, Friedman J, Kozak N, Schattner A. Utility of clinical examination in the diagnosis of emergency department patients admitted to the department of medicine of an academic hospital. *Arch Intern Med 2011;171:1394-6.*
424. Council R. https://www.resus.org.uk/resuscitation-guidelines/abcde-approach/.
425. Thim T, Krarup NH, Grove EL, Rohde CV, Lofgren B. Initial assessment and treatment with the Airway, Breathing, Circulation, Disability, Exposure (ABCDE) approach. *Int J Gen Med 2012;5:117-21.*
426. Vincent JL, Ince C, Bakker J. Clinical review: Circulatory shock--an update: a tribute to Professor Max Harry Weil. *Crit Care 2012;16:239.*
427. Atkinson PR, McAuley DJ, Kendall RJ, et al. Abdominal and Cardiac Evaluation with Sonography in Shock (ACES): an approach by emergency physicians for the use of ultrasound in patients with undifferentiated hypotension. *Emerg Med J 2009;26:87-91.*
428. Keikha M, Salehi-Marzijarani M, Soldoozi Nejat R, Sheikh Motahar Vahedi H, Mirrezaie SM. Diagnostic Accuracy of Rapid Ultrasound in Shock (RUSH) Exam; A Systematic Review and Meta-analysis. *Bull Emerg Trauma 2018;6:271-8.*
429. Bonanno FG. Clinical pathology of the shock syndromes. *J Emerg Trauma Shock 2011;4:233-43.*
430. Liu H, Allen J, Zheng D, Chen F. Recent development of respiratory rate measurement technologies.

Physiol Meas 2019.

431. Flenady T, Dwyer T, Applegarth J. Accurate respiratory rates count: So should you! *Australas Emerg Nurs J 2017;20:45-7.*
432. Hill A, Kelly E, Horswill MS, Watson MO. The effects of awareness and count duration on adult respiratory rate measurements: An experimental study. *J Clin Nurs 2018;27:546-54.*
433. Rimbi M, Dunsmuir D, Ansermino JM, Nakitende I, Namujwiga T, Kellett J. Respiratory rates observed over 15 and 30 s compared with rates measured over 60 s: practice-based evidence from an observational study of acutely ill adult medical patients during hospital admission. *QJM 2019;112:513-7.*
434. Schey BM, Williams DY, Bucknall T. Skin temperature and core-peripheral temperature gradient as markers of hemodynamic status in critically ill patients: a review. *Heart Lung 2010;39:27-40.*
435. Bakker J, Nijsten MW, Jansen TC. Clinical use of lactate monitoring in critically ill patients. *Ann Intensive Care 2013;3:12.*
436. Baxter J, Cranfield KR, Clark G, Harris T, Bloom B, Gray AJ. Do lactate levels in the emergency department predict outcome in adult trauma patients? A systematic review. *J Trauma Acute Care Surg 2016;81:555-66.*
437. Jansen TC, van Bommel J, Bakker J. Blood lactate monitoring in critically ill patients: a systematic health technology assessment. *Crit Care Med 2009;37:2827-39.*
438. Lee SW, Hong YS, Park DW, et al. Lactic acidosis not hyperlactatemia as a predictor of in hospital mortality in septic emergency patients. *Emerg Med J 2008;25:659-65.*
439. van den Nouland DP, Brouwers MC, Stassen PM. Prognostic value of plasma lactate levels in a retrospective cohort presenting at a university hospital emergency department. *BMJ Open 2017;7:e011450.*
440. Hohenstein C, Bernhardt M. Elevated serum lactate in emergency department patients predicts hospital admission unrelated to diagnosis - but not more. *Biomarkers 2018;23:88-96.*
441. Hernandez G, Ospina-Tascon GA, Damiani LP, et al. Effect of a Resuscitation Strategy Targeting Peripheral Perfusion Status vs Serum Lactate Levels on 28-Day Mortality Among Patients With Septic Shock: The ANDROMEDA-SHOCK Randomized Clinical Trial. *JAMA 2019;321:654-64.*
442. van Genderen ME, Lima A, Bakker J, van Bommel J. [Peripheral circulation in critically ill patients: non-invasive methods for the assessment of the peripheral perfusion]. *Ned Tijdschr Geneeskd 2013;157:A5338.*
443. Lima AP, Beelen P, Bakker J. Use of a peripheral perfusion index derived from the pulse oximetry signal as a noninvasive indicator of perfusion. *Crit Care Med 2002;30:1210-3.*
444. Monnet X, Guerin L, Jozwiak M, et al. Pleth variability index is a weak predictor of fluid responsiveness in patients receiving norepinephrine. *Br J Anaesth 2013;110:207-13.*
445. Montomoli J, Donati A, Ince C. Acute Kidney Injury and Fluid Resuscitation in Septic Patients: Are We Protecting the Kidney? *Nephron 2019:1-4.*
446. Winters ME, Sherwin R, Vilke GM, Wardi G. Does Early Goal-Directed Therapy Decrease Mortality Compared with Standard Care in Patients with Septic Shock? *J Emerg Med 2017;52:379-84.*
447. Cecamore C, Savino A, Salvatore R, et al. Clinical practice guidelines: what they are, why we need them and how they should be developed through rigorous evaluation. *Eur J Pediatr 2011;170:831-6.*
448. Barth JH, Misra S, Aakre KM, et al. Why are clinical practice guidelines not followed? *Clin Chem Lab Med 2016;54:1133-9.*
449. Benabbas R, Hanna M, Shah J, Sinert R. Diagnostic Accuracy of History, Physical Examination,

Laboratory Tests, and Point-of-care Ultrasound for Pediatric Acute Appendicitis in the Emergency Department: A Systematic Review and Meta-analysis. *Acad Emerg Med 2017;24:523-51.*

450. Gans SL, Pols MA, Stoker J, Boermeester MA. 'Guideline 'Diagnostics in acute abdominal pain in adults', *Ned Tijdschr Geneeskd. 2014;158:A7494*

451. Richtlijn Diagnostische strategie bij kinderen met acute appendictis. *https://richtlijnendatabase.nl/richtlijn/acute_appendicitis/diagnostische_strategie_-_acute_appendicitis_2019/diagnostische_strategie_bij_kinderen_met_acute_appendictis.html*

452. Dezman ZD, Mattu A, Body R. Utility of the History and Physical Examination in the Detection of Acute Coronary Syndromes in Emergency Department Patients. *West J Emerg Med 2017;18:752-60.*

453. NHG standaard Acuut Coronair Syndroom. *https://www.nhg.org/standaarden/samenvatting/acuut-coronair-syndroom*

454. Damman P, van 't Hof AW, Ten Berg JM, et al. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: comments from the Dutch ACS working group. *Neth Heart J 2017;25:181-5.*

455. Wiswell J, Tsao K, Bellolio MF, Hess EP, Cabrera D. "Sick" or "not-sick": accuracy of System 1 diagnostic reasoning for the prediction of disposition and acuity in patients presenting to an academic ED. *Am J Emerg Med 2013;31:1448-52.*

456. Brush JE, Jr., Sherbino J, Norman GR. How Expert Clinicians Intuitively Recognize a Medical Diagnosis. *Am J Med 2017;130:629-34.*

457. Klein JG. Five pitfalls in decisions about diagnosis and prescribing. *BMJ 2005;330:781-3.*

458. Kline JA, Neumann D, Hall CL, Capito J. Role of physician perception of patient smile on pretest probability assessment for acute pulmonary embolism. *Emerg Med J 2017;34:82-8.*

459. Volksgezondheidenzorg.info. *https://www.volksgezondheidenzorg.info/onderwerp/acute-zorg/cijfers-context/gebruik-acute-zorg#node-gebruik-seh-naar-specialisme*

460. Veiligheid.nl. *https://www.veiligheid.nl/.ibmmodres/domino/OpenAttachment/Veiligheid/Website.nsf/FD80D963DD249926C125838C003DF481/asset/Kerncijfers%20Letsels%202017.pdf*

461. Iserson KV, Moskop JC. Triage in medicine, part I: Concept, history, and types. *Ann Emerg Med 2007;49:275-81.*

462. de Magalhaes-Barbosa MC, Robaina JR, Prata-Barbosa A, Lopes CS. Validity of triage systems for paediatric emergency care: a systematic review. *Emerg Med J 2017;34:711-9.*

463. Hong WS, Haimovich AD, Taylor RA. Predicting hospital admission at emergency department triage using machine learning. *PLoS One 2018;13:e0201016.*

464. Singer AJ, Taylor M, LeBlanc D, et al. Early Point-of-Care Testing at Triage Reduces Care Time in Stable Adult Emergency Department Patients. *J Emerg Med 2018;55:172-8.*

465. Abualenain J, Almarzouki A, Saimaldaher R, Zocchi MS, Pines JM. The Effect of Point-of-Care Testing at Triage: An Observational Study in a Teaching Hospital in Saudi Arabia. *West J Emerg Med 2018;19:884-8.*

466. Nannan Panday RS, Minderhoud TC, Alam N, Nanayakkara PWB. Prognostic value of early warning scores in the emergency department (ED) and acute medical unit (AMU): A narrative review. *Eur J Intern Med 2017;45:20-31.*

467. Vincent JL, Martin GS, Levy MM. qSOFA does not replace SIRS in the definition of sepsis. *Crit Care 2016;20:210.*

468. Keep JW, Messmer AS, Sladden R, 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;33:37-41.*

469. Raita Y, Goto T, Faridi MK, Brown DFM, Camargo CA, Jr., Hasegawa K. Emergency department triage prediction of clinical outcomes using machine learning models. *Crit Care 2019;23:64.*
470. de Greeff S, Mouton J, Schoffelen A, Verduin C. NethMap 2019: Consumption of antimicrobial agents and antimicrobial resistance among medically important bacteria in the Netherlands / MARAN 2019: Monitoring of Antimicrobial Resistance and Antibiotic Usage in Animals in the Netherlands in 2018: Rijksinstituut voor Volksgezondheid en Milieu RIVM.
471. Stichting Werkgroep AntibioticaBeleid. *http://www.swabid.nl*
472. Goossens H, Ferech M, Vander Stichele R, Elseviers M, Group EP. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. *Lancet 2005;365:579-87.*
473. Aantal mensen met chronische ziekte bekend bij de huisarts. *https://www.volksgezondheidenzorg.info/onderwerp/chronische-ziekten-en-multimorbiditeit/cijfers-context/huidige-situatie#node-aantal-mensen-met-chronische-aandoening-bekend-bij-de-huisarts*
474. Corrado RE, Lee D, Lucero DE, Varma JK, Vora NM. Burden of Adult Community-acquired, Health-care-Associated, Hospital-Acquired, and Ventilator-Associated Pneumonia: New York City, 2010 to 2014. *Chest 2017;152:930-42.*
475. Capsoni N, Bellone P, Aliberti S, et al. Prevalence, risk factors and outcomes of patients coming from the community with sepsis due to multidrug resistant bacteria. *Multidiscip Respir Med 2019;14:23.*
476. Souverein D, Houtman P, Euser SM, Herpers BL, Kluytmans J, Den Boer JW. Costs and Benefits Associated with the MRSA Search and Destroy Policy in a Hospital in the Region Kennemerland, The Netherlands. *PLoS One 2016;11:e0148175.*
477. Furuya EY, Lowy FD. Antimicrobial-resistant bacteria in the community setting. *Nat Rev Microbiol 2006;4:36-45.*
478. Zumla A, Azhar EI, Hui DS, Shafi S, Petersen E, Memish ZA. Global spread of antibiotic-resistant bacteria and mass-gathering religious events. *Lancet Infect Dis 2018;18:488-90.*
479. Lonely Planet best picks. *https://www.lonelyplanet.com/best-in-travel/*
480. Groupstoday.com. Travel Trends by Age. *https://groupstoday.com/business/404-travel-trends-by-age-demographic.*
481. The unstoppable rise of the Chinese traveller – where are they going and what does it mean for overtourism? *https://www.telegraph.co.uk/travel/comment/rise-of-the-chinese-tourist/*
482. Rottier WC, Bamberg YR, Dorigo-Zetsma JW, van der Linden PD, Ammerlaan HS, Bonten MJ. Predictive value of prior colonization and antibiotic use for third-generation cephalosporin-resistant enterobacteriaceae bacteremia in patients with sepsis. *Clin Infect Dis 2015;60:1622-30.*
483. Nickel CH, Kellett J, Nieves Ortega R, Lyngholm L, Wasingya-Kasereka L, Brabrand M. Mobility Identifies Acutely Ill Patients at Low Risk of In-Hospital Mortality: A Prospective Multicenter Study. *Chest 2019;156:316-22.*
484. Kellett J, Nickel CH, Skyttberg N, Brabrand M. Is it possible to quickly identify acutely unwell patients who can be safely managed as outpatients? The need for a "Universal Safe to Discharge Score". *Eur J Intern Med 2019.*
485. Lyngholm LE, Nickel CH, Kellett J, Chang S, Cooksley T, Brabrand M. A negative d-dimer identifies patients at low risk of death within 30 days: a prospective observational emergency department cohort study. *QJM 2019.*
486. Alsma J. *Unpublished data*
487. Remi J, Pfefferkorn T, Owens RL, et al. The crossed leg sign indicates a favorable outcome after

severe stroke. *Neurology 2011;77:1453-6.*

488. Bazan R, Fernandes T, Braga G, Luvizutto G, Resende L. A new clinical sign probably associated to left hemiplegia with left hemineglect syndrome: the crossed legs. *Arq Neuropsiquiatr 2014;72:418-21.*

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Abbreviations

Abbreviations

95% CI	95% Confidence Interval of the Mean (Lower Bound and Upper Bound)
aAISS	adjusted Acute Illness Severity Score
ABCDE	Airway, Breathing, Circulation, Disability, Exposure
ACE	Angiotensin-Converting Enzyme
AEAT	Appropriate Empirical Antibiotic Therapy
AIC	Akaike Information Criterion
AISS	Acute Illness Severity Score
ALS	Advanced Life Support
AMAU	Acute Medical Assessment Unit
AMU	Acute Medical Unit
ANOVA	Analysis of Variance
AOR	Adjusted Odds Ratio
APACHE II	Acute Physiology, Age, Chronic Health Evaluation II
APOP	Acute Presenting Older Patient
ARISE	Australasian Resuscitation in Sepsis Evaluation
AST	Antibiotic Susceptibility Testing
AT1R	Angiotensin II Type I Receptor autoantibodies
ATLS	Advanced Trauma Life Support
AUC	Area Under the Curve
AVPU	Alert, Verbal, Pain, Unresponsive
Bid	Twice a Day
Bla	Beta-lactamase
BMI	Body Mass Index
BP	Blood Pressure
Bpm	Beats per Minute
BS	Brier Score
BSI	Blood Stream Infection
CART	Classification And Regression Tree
CCI	Charlson Comorbidity Index
CDC	Centres for Disease Control and Prevention
CFS	Chronic Fatigue Syndrome
CHARMS	Checklist for Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies
CI	Confidence Interval

CISNE	Clinical Index of Stable Febrile Neutropenia
CLEARED	Calculation of the Elderly Admission Risk in the Emergency Department
CNS	Central Nerve System
COMBAT	Carriage Of Multiresistant Bacteria After Travel
CPE	Carbapenemase-Producing Enterobacteriaceae
CRP	C-Reactive Protein
CRT	Capillary Refill Time
CRTp	Capillary Refill Time Measured at the Distal Phalanx of the Finger
CRTp15	Peripheral Capillary Refill Time, Application of Pressure 15 Seconds
CRTp5	Peripheral Capillary Refill Time, Application of Pressure 5 Seconds
CRTs	Capillary Refill Time Measured at the Sternum
CRTs15	Sternal Capillary Refill Time, Application of Pressure 15 Seconds
CRTs5	Sternal Capillary Refill Time, Application of Pressure 15 Seconds
CS	Calibration Slope
CSD	Consensus Sleep Diary
CT	Computed Tomography Scan
CTR	Cardiothoracic Ratio
CTX-M	Cefotaximase
CURB-65	Confusion, Urea, Respiratory rate, Blood pressure, Age ≥ 65
cUTI	Complicated Urinary Tract Infection
DBP	Diastolic Blood Pressure
DDAVP	1-Desamoni-8-d-arginine-vasopressine (Desmopressine)
df	Degrees of Freedom
EAU	Emergency Assessment Unit
ECG	Electrocardiogram
ED	Emergency Department
EDMUPS	Medically Unexplained Physical Symptoms in the Emergency Department
EGDT	Early Goal Directed Therapy
EMV	Eye, Motor, Verbal
EPICS	Emergency Processes in Clinical Structures
Erasmus MC	Erasmus University Medical Center, Rotterdam , The Netherlands
ESBL	Extended-spectrum Beta-lactamase
ESBL-E	Extended-spectrum Beta-lactamase Producing Enterobacteriaceae
ESI	Emergency Severity Index
EUCAST	European Committee on Antimicrobial Susceptibility Testing
EWS	Early Warning Score
FiO2	Fraction of Inspired Oxygen
FM	Fibromyalgia

FMR	Flash Mob Research
GCS	Glasgow Coma Scale
GP	General Practitioner
H	Hour
HE	Hypertensive Emergency
HL GOF	Hosmer-Lemeshow Goodness of Fit
HMC	Haaglanden Medical Centre Westeinde, The Hague, The Netherlands
HOTEL	Hypotension, Oxygen Saturation, Low Temperature, ECG Changes, Loss of Independence
HU	Hypertensive Urgency
ICC	Intraclass Correlation Coefficient
ICU	Intensive Care Unit
IQR	Inter Quartile Range
ISAR	Identification of Seniors At Risk
KPC	Klebsiella Pneumoniase Carbapenemase
LC-MS/MS	Liquid Chromatography - Tandem Mass Spectrometry
LOS	Length Of Stay
Lrm	Logistic Regression Model
LRχ2	Likelihood Ratio chi squared
LUMC	Leiden University Medical Center , Leiden, The Netherlands
LVH	Left Ventricular Hypertrophy
MALDI-TOF MS	Matrix Assisted Laser Desorption/Ionization Time-of-Flight Analyser Mass Spectrometry
MAP	Mean Arterial Pressure
MARS	Medical Admissions Risk System
MASCC	Multinational Association for Supportive Care in Cancer
MAU	Medical Assessment Unit
MDR	Multi-drug Resistent
MDRO	Mulit-drug Resistent Organism
MEWS	Modified Early Warning Score
Min	Minute
MLST	Multilocus Sequence Typing
mmHg	Millimetres mercury
MRE	Multidrug-resistant Enterobacteriaceae
MRI	Magnetic Resonance Imaging
MRSA	Methicillin-resistant *Staphylococcus Aureus*
MST	Medisch Spectrum Twente, Enschede, The Netherlands
MTS	Manchester Triage System

MUPS	Medically Unexplained Physical Symptoms
N	Number
NA	Not Applicable
NDM	New Delhi Metallo-beta-lactamase
NEWS	National Early Warning Score
NL	The Netherlands
NPV	Negative Predicting Value
NS	Not Specified
OR	Odds Ratio
OXA	Oxacillinase
pAmp C	Plasmid-borne AmpC
pAmp C-E	Plasmid-mediated Amp C-producing *Enterobacteriaceae*
PaO2	Partial Pressure of Oxygen
PARIS	Systolic Blood Pressure, Age, Respiratory Rate, Loss of Independence, Peripheral Oxygen Saturation
PATHWAY-2	Prevention And Treatment of Hypertension With Algorithm Based Therapy-2
PCI	Percutaneous Coronary Intervention
PCR	Polymerase Chain Reaction
PFGE	Pulsed-Field Gel Electrophoresis
PI	Perfusion Index
POCT	Point-of-Care Testing
POCUS	Point-of-Care Ultrasound
POTS	Postural Orthostatic Tachycardia Syndrome
PPV	Positive Predicting Value
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
ProCESS	Protocolized Care for Early Septic Shock
PROMIS	Patient-Reported Outcomes Measurement Information System
ProMISe	Protocolised Management in Sepsis
PROSPERO	Prospective Register of Systematic Reviews
PSI	Pneumonia Severity Index
PSS	Physiological Scoring System
PVI	Pleth Variable Index
qSOFA	quick Sepsis Related Organ Failure Assessment
RAPS	Rapid Acute Physiology Score
RBC	Red Blood Cell Count
RDW	Red Cell Distribution Width
REMS	Rapid Emergency Medicine Score

Rep-PCR	Repetitve Extragenic Palindromic PCR
Rms	Regression Modeling Strategies
ROC	Receiver Operating Characteristic
RR	Respiratory Rate
S	Seconds
SaO2	Arterial Oxygen Saturation
SBP	Systolic Blood Pressure
SCS	Simple Clinical Score
SD	Standard Deviation
SE	Standard Error
SET	Signal Extraction Technology
SHV	Sulphydryl Variable
SIRS	Systemic Inflammatory Response Syndrome
SOFA	Sepsis Related Organ Failure Assessment
SpO2	Peripheral Oxygen Saturation
SPSS	Statistical Package for the Social Sciences
SSC	Surviving Sepsis Campaign
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
SWAB	Stichting Werkgroep AntibioticaBeleid (Dutch Working Party on Antibiotic Policy)
TEM	Temoniera
TIA	Transient Ischemic Attack
Tid	Three Times a Day
TRST	Triage Risk Screening Tool
UK	United Kingdom
US	United States
USA	United States of America
UTI	Urinary Tract Infections
UZG	Ghent University Hospital, Ghent, Belgium
VSS	Vital Sign Score
WBC	White Blood Cell Count
WMO	Wet Medisch-wetenschappelijk Onderzoek met Mensen (Medical Research Involving Human Subjects Act)
α1AR	Autoantibodies Against Adrenergic Receptors
κ	Kappa Statistics
$\chi 2$	Chi-square Test

List of publications

Manuscripts within this thesis

The value of history, clinical examination and additional testing in the early identification of illness

Chapter 2

Alsma J, van Saase J, Nanayakkara PWB, Schouten W, Baten A, Bauer MP, et al. The Power of Flash Mob Research: Conducting a Nationwide Observational Clinical Study on Capillary Refill Time in a Single Day. *Chest. 2017;151(5):1106-13.*

Chapter 3

Alsma J, den Braber N, Onrust J, Van Loon LM, Van Saase JL, Schuit SC. Axillary Humidity is a Potential Index of Fluid Deficit in Patients Visiting the Emergency Department. *Submitted.*

Chapter 4

Overgaauw N*, **Alsma J***, Brink A, Hameli E, Bahmany S, Peeters LEJ, et al. Drug nonadherence is a common but often overlooked cause of hypertensive urgency and emergency at the emergency department. *J Hypertens. 2019;37(5):1048-57.*

Chapter 5

Alsma J*, van de Wouw J*, Jellema K, Coffeng SM, Tobback E, Delesie L, et al. Medically unexplained physical symptoms in patients visiting the emergency department: an international multicentre retrospective study. *Eur J Emerg Med. 2018.*

Chapter 6

van der Zalm T, **Alsma J,** van de Poll SWE, Wessels MW, Riksen NP, Versmissen J. Postural orthostatic tachycardia syndrome (POTS): a common but unfamiliar syndrome. *Neth J Med. 2019;77(1):3-9.*

Chapter 7

Wesselius HM*, van den Ende ES*, **Alsma J**, Ter Maaten JC, Schuit SCE, Stassen PM, et al. Quality and Quantity of Sleep and Factors Associated With Sleep Disturbance in Hospitalized Patients. *JAMA Intern Med. 2018;178(9):1201-8.*

Prediction Models and Early Warning scores

Chapter 8

Brink A, **Alsma J**, Fortuin AW, Bramer WM, Zietse R, Lingsma HF, et al. Prediction models for mortality in adult patients visiting the Emergency Department: a systematic review. *Acute Med. 2019;18(3):171-183.*

Chapter 9

Brink A, **Alsma J**, Brink HS, de Gelder J, Lucke JA, Mooijaart SP, et al. Development and validation of a prediction model for admission from the emergency department in the older patient population; the CLEARED-tool. *Submitted.*

Chapter 10

Brink A*, **Alsma J***, Verdonschot R, Rood PPM, Zietse R, Lingsma HF, 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;14(1):e0211133.*

Predictors of antibiotic susceptibility

Chapter 11

Hassing RJ*, **Alsma J***, Arcilla MS, van Genderen PJ, Stricker BH, Verbon A. International travel and acquisition of multidrug-resistant Enterobacteriaceae: a systematic review. *Euro Surveill. 2015;20(47).*

Chapter 12

Wijting IEA*, **Alsma J***, Melles DC, Schipper EM, Schuit SCE. Urinary tract infections in a university hospital: pathogens and antibiotic susceptibility. *Neth J Med. 2019;77(6):210-9.*

Chapter 13

Schuttevaer R, **Alsma J**, Brink A, van Dijk W, de Steenwinkel JE, Lingsma HF, et al. Appropriate empirical antibiotic therapy and mortality: conflicting data explained by residual confounding. *PLoS One. 2019 Nov 19;14(11):e0225478*

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Other publications

Lucke JA, de Gelder J, Blomaard LC, Heringhaus C, **Alsma J**, Schuit SCE, et al. Vital signs and impaired cognition in older emergency department patients: The APOP study. *PLoS One. 2019;14(6):e0218596.*

Borgsteede SD, Verwer PEB, Prins G, Wijma RA, de Keijzer K, **Alsma J**, et al. [A body packer with cannabis] Een bodypacker met cannabis. *Ned Tijdschr Geneeskd. 2019;163.*

Benner BJM, **Alsma J**, Feelders RA. Hyponatraemia and hyperpigmentation in primary adrenal insufficiency. *BMJ Case Rep. 2019;12(3).*

Lucke JA, De Gelder J, Blomaard LC, Fogteloo AJ, **Alsma J**, Schuit SCE, et al. CAM-ICU may not be the optimal screening tool for early delirium screening in older emergency department patients: a prospective cohort study. *Eur J Emerg Med. 2018.*

Jainandunsing S, Oei L, Oei EHG, Budde RPJ, **Alsma J**, Hellemond JJV, et al. Cardio-abdominal echinococcosis: A man with a visible pulsating abdominal mass. *IDCases. 2018;11:46-7.*

de Gelder J, Lucke JA, Blomaard LC, Booijen AM, Fogteloo AJ, Anten S, **Alsma J**, et al. Optimization of the APOP screener to predict functional decline or mortality in older emergency department patients: Cross-validation in four prospective cohorts. *Exp Gerontol. 2018;110:253-9.*

Zandee WT, **Alsma J**, Birkenhager TK, den Meiracker AHV, van Hoek M, Versmissen J. [Hypertension en orthostatic hypotension during use of monoamine oxidase (MAO) inhibitors] Hypertensie en orthostatische hypotensie bij gebruik van monoamine-oxidase(MAO)-remmers1. *Tijdschr Psychiatr. 2017;59(6):366-71.*

Zandee WT, Van Hoek M, Birkenhager TK, Van Den Meiracker AH, **Alsma J**, Versmissen J. Pieken en dalen in de bloeddruk bij gebruik van monoamineoxidase(MAO-)remmers. *Focus Vasculair 2016; Juni*

Verheijden NA, Koch BC, Brkic Z, **Alsma J**, Schuit SC. A 45-year-old woman with an anticholinergic toxidrome. *Neth J Med. 2016;74(3):133-5.*

van den Berg B, van den Beukel JC, **Alsma J**, van der Eijk AA, Ruts L, van Doorn PA, et al. [Guillain-Barre syndrome following infection with the Zika virus] Guillain-Barre-syndroom na zikavirus-infectie. *Ned Tijdschr Geneeskd. 2016;160:D155.*

Quax RA, **Alsma J**. On calcium channel antagonist poisoning: towards evidence-based decision making in poisoned patients. *Neth J Med. 2016;74(2):58-9.*

Mevius H, Quax RA, **Alsma J**. Man With Necrotizing Ulcers on the Leg. *Ann Emerg Med. 2016;68(2):244-51.*

Dankbaar ME, **Alsma J**, Jansen EE, van Merrienboer JJ, van Saase JL, Schuit SC. An experimental study on the effects of a simulation game on students' clinical cognitive skills and motivation. *Adv Health Sci Educ Theory Pract. 2016;21(3):505-21.*

Warle-van Herwaarden MF, Valkhoff VE, Herings RM, Engelkes M, van Blijderveen JC, Rodenburg EM, et al. Quick assessment of drug-related admissions over time (QUADRAT study). *Pharmacoepidemiol Drug Saf. 2015;24(5):495-503.*

van Pelt-Sprangers MJ, Geijteman EC, **Alsma J**, Boere IA, Mathijssen RH, Schuit SC. Oromandibular dystonia: a serious side effect of capecitabine. *BMC Cancer. 2015;15:115.*

Alsma J, Bosch FH. Ultrasound for internists: changing bedside examination. *Neth J Med. 2015;73(3):98-9.*

van der Meijden WA, **Alsma J**, van Doorn PA. [A woman with polyneuropathy and white nails] Een vrouw met polyneuropathie en witte nagels. *Ned Tijdschr Geneeskd. 2014;158:A7076.*

Schipper EM, de Graaff LC, Koch BC, Brkic Z, Wilms EB, **Alsma J**, et al. A new challenge: suicide attempt using nicotine fillings for electronic cigarettes. *Br J Clin Pharmacol. 2014;78(6):1469-71.*

Baan J, Bos MM, Gonesh-Kisoensigh SU, Meynaar IA, **Alsma J**, Meijer E, et al. Capecitabine-induced Toxicity: An Outcome Study into Drug Safety. *J Integr Oncol 2014;3(1).*

Alsma J, Schuit SC. 'Capillary refill'-tijd meten in flashmob-onderzoek. De FAMOUS-trial. *Ned Tijdschr Geneeskd. 2014;158:A8218.*

van der Does Y, van Loon LM, **Alsma J**, Govers A, Lansdorp B, Rood PP, et al. Non-invasive blood pressure and cardiac index measurements using the Finapres Portapres in an emergency department triage setting. *Am J Emerg Med. 2013;31(7):1012-6.*

van Dooren Y, **Alsma J**. [A man with a pseudo-athletic posture] Een man met een pseudo-atletisch uiterlijk. *Ned Tijdschr Geneeskd. 2012;156(50):A4752.*

Alsma J, van Rossem RN, Smeets LC, Meynaar IA. A previously healthy 45 yr old male with respiratory insufficiency caused by H1N1 pneumonitis. *Neth J Crit Care 2010. 2010;14:338-42.*

Stoutjesdijk JA, **Alsma J**, Wildschut HI. [Pregnancy termination in the second trimester with vaginally administered dinoprostone followed by intravenous sulprostone, for the indication 'foetal congenital defects'; results of a retrospective study] Zwangerschapsafbreking in het tweede trimester met dinoproston vaginaal gevolgd door sulproston intraveneus, op de indicatie 'foetale congenitale afwijkingen'; resultaten van een retrospectieve studie. *Ned Tijdschr Geneeskd. 2004;148(26):1293-6.*

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Consortium Publications

Alam N, Oskam E, Stassen PM, Exter PV, van de Ven PM, Haak HR, et al. Prehospital antibiotics in the ambulance for sepsis: a multicentre, open label, randomised trial. *Lancet Respir Med. 2018;6(1):40-50.*