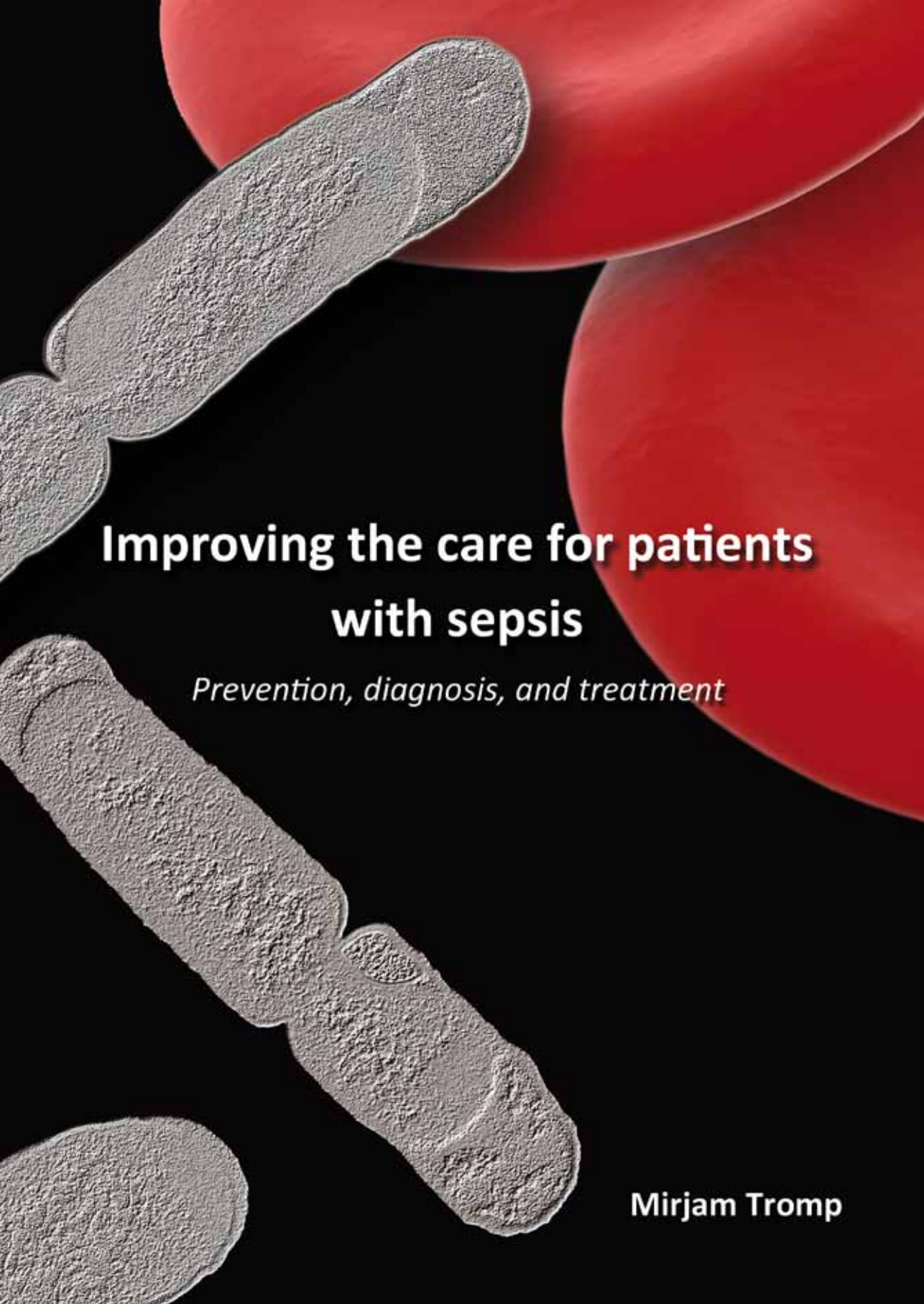

Improving the care for patients with sepsis

Prevention, diagnosis, and treatment

Mirjam Tromp

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Nijmegen, 2012

The studies presented in this thesis have been performed at the Nijmegen Institute for Infection, Inflammation, and Immunity (N4i), and the Scientific Institute for Quality of Healthcare of the Radboud University Nijmegen Medical Centre. The scientific Institute for Quality of Healthcare is part of the Nijmegen Centre for Evidence Based Practice (NCEBP), one of the approved research institutes of the Radboud University Nijmegen and the Netherlands School of Primary Care Research (CaRe), acknowledged by the Royal Dutch Academy of Science (KNAW).

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Wat voor een moeilijkheden je in het
verleden ook gehad mag hebben,
je kunt vandaag een nieuw begin maken
(Boeddha)

Contents

Chapter 1

Introduction and outline of the thesis

Part of the introduction has been published in
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Introduction and outline of the thesis

Sepsis can be defined as the body's response to an infection. An infection is caused by microorganisms (e.g., bacteria, viruses, or fungi) invading the body. Bacterial infections in the lungs (pneumonia), bladder or kidneys (urinary tract infections), skin (cellulitis), abdomen (e.g., appendicitis), and other areas (such as meningitis) can all lead to sepsis. Severe sepsis/septic shock is a life-threatening complication of an infection. Due to associated organ-failure, treatment in an intensive care unit is often indicated.

The documented incidence of sepsis worldwide is 1.8 million each year[1], but this number is confounded by a low diagnostic rate and difficulties in tracking sepsis in many countries. It is estimated that with an incidence of 3 in 1000 the true number of cases each year reaches 18 million, and with a mortality rate of 30% to 50% it becomes a leading cause of death worldwide.[1-6]

In the Netherlands, an estimated 15,500 patients with severe sepsis and 6000 patients suffering from septic shock are annually admitted to an intensive care unit.[3] Intensive treatment and the long recovery period complicate the course of patients with sepsis and are accompanied with high costs. Direct medical costs of severe sepsis are estimated at 19,500 Euros per patient.[6] Costs correlate strongly with the length of stay in the hospital. Annually, an estimated 168,6 million Euros is spent on severe sepsis, which represents 0.5% of all health care costs and 1.7% of the annual hospital budget in the Netherlands.[6] Sepsis represents a burden for both the patient and society.

To eliminate confusion in communication for both clinicians and researchers, standardization of sepsis terminology is necessary. Several editorials and position papers have attempted to provide a framework for standardization and simplification of the sepsis terminology.[7-10] In 1992, the ACCP/SCCM Consensus Conference Committee has offered recommendations for the standardization of the sepsis terminology illustrated in *Figure 1*[11]:

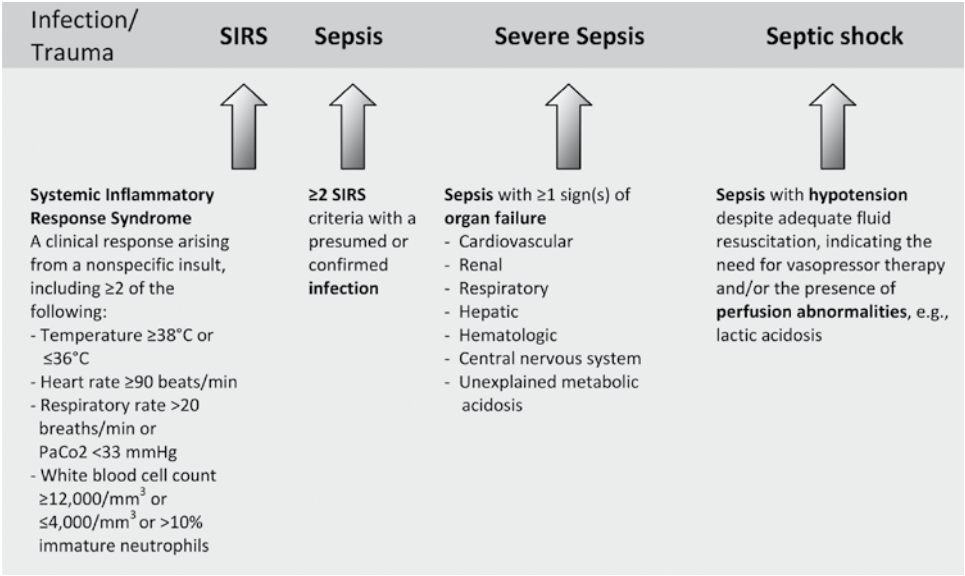
Sepsis: the systemic response to a (strongly suspected or proven) infection, manifested by two or more of the following systemic inflammatory response syndrome (SIRS) criteria, as a result of infection: (1) temperature >38°C or <36°C; (2) heart rate >90 beats per minute; (3) respiratory rate >20 breaths per minute or $PaCO_2$ <32 mmHg; and (4) white blood cell count >12,000/mm^3, <4,000/mm^3, or >10% immature (band) forms.

Severe sepsis: sepsis associated with organ dysfunction, for example impaired renal function.

Septic shock: sepsis with hypotension despite adequate fluid resuscitation indicating the need for vasopressor therapy, along with the presence of perfusion

abnormalities that may include, but are not limited to, lactic acidosis, oliguria, and an acute alteration in mental status. Patients who are receiving inotropic or vasopressor agents may not be hypotensive at the time perfusion abnormalities are measured, but are also considered as suffering from septic shock.

Figure 1. *The relationship of infection, SIRS, sepsis, severe sepsis, and septic shock*



An infection leading to sepsis can be acquired outside the hospital (known as 'community-acquired') or in the hospital (known as 'nosocomial' or 'hospital-acquired'). Hospital-acquired infections are generally more difficult to manage than those acquired in the community, because of the patient's underlying disease, previous use of antibiotics, the presence of drug-resistant bacteria in the hospital, and/or the fact that patients often require an intravenous cannula, urinary catheter, or wound drainage.

Consequently, the presence of hospital-acquired infections is one of the major causes of death and increased morbidity among hospitalized patients.[12;13] It has been estimated that, in the European Union alone, approximately 37,000 lives are lost to hospital-acquired infections each year, with an associated monetary cost of roughly 7 billion Euros, which is mainly attributable to the increased length of hospital stay.[14] In the Netherlands, the prevalence of hospital-acquired infections was 6.6% (74,000 people/year) in the period 2007-2009. The four most common hospital-acquired infections were symptomatic urinary tract infections, post operative wound infections, pneumonia, and (central venous catheter-related) sepsis.[15]

Prevention of sepsis

The strategies to reduce hospital-acquired infections are complex.[16] The performance of (protective) isolation measures, the use of antibiotic prophylaxis in selected surgical patients, and, most importantly, basic hygienic measures including optimal hand hygiene compliance by all health care workers are important strategies to reduce hospital-acquired infections.[17-19] However, although for example hand hygiene compliance by health care workers has been an important issue for years, the compliance rate is still a problem in health care today.[19;20]

To improve the knowledge and compliance to hand hygiene, various improvement strategies have been described. Improving hand hygiene by multifaceted strategies seems superior to using a single strategy.[21] However, most of the effects are small to moderate and often short-lived.[22] A recent study on potential determinants of hand hygiene compliance in the Dutch hospital setting showed that - besides the perception of the health care workers that there is a lack of evidence that hand hygiene is effective in preventing hospital-acquired infections - absence of positive role models and social norms may hinder compliance.[23] Health care workers indicated that creating a stronger social norm and establishing more explicit social control would be important for improving hand hygiene compliance. Therefore, a multifaceted hand hygiene improvement program, including education, feedback, reminders, targeting adequate products and facilities, and social influence activities including the use of role models, should be carried out and its effects on hand hygiene compliance should be evaluated.

Diagnosis and treatment of sepsis

It has become increasingly clear that time is an important factor in patients with severe sepsis or septic shock, since they have a better chance of survival if sepsis is treated adequately at an earlier stage.[24-26] Research has shown that in a hypotensive septic patient, every hour that the first administration of adequate antimicrobial therapy is delayed, is associated with an increase in mortality of 8%.[27] However, the identification of patients with sepsis in daily practice can be difficult as the signs of systemic inflammation response syndrome are not specific. They can also occur in other diseases such as trauma, pancreatitis, and burns.[11;28]

Diagnostic tests

In view of the difficulties with the clinical diagnosis of sepsis, the search for a laboratory value or marker to aid the diagnosis remains an important topic. Rapid tests that provide insight into the etiology of infection may guide the appropriate use of antibiotics and are urgently needed. Although blood cultures are

considered the gold standard for detection of bacteremia, delays between blood sampling and information returned to the clinician is an important disadvantage, but no alternatives are currently available.[29]

Although C-reactive protein and procalcitonin have been most widely used[30], these biomarkers provide limited abilities to distinguish sepsis from other inflammatory conditions, to indicate the severity of sepsis, or to predict outcome. New markers have become available, but their additional value in clinical practice is not clear.

It has been advocated that evaluation of combinations, or a panel of markers, may improve the predictive power, but this has not been thoroughly investigated. Therefore, further evaluation of a combination of different sepsis biomarkers should be carried out.[31-34]

Surviving sepsis campaign

In 2004, the surviving sepsis campaign (SSC) was launched to improve the recognition, diagnosis, management, and treatment of patients with severe sepsis or septic shock. The SSC provides helpful tools and techniques to measure and improve the quality of care for patients with severe sepsis or septic shock, especially for patients in the intensive care unit.

The most important SSC recommendations are summarized in a '6 hour' and '24 hour' bundle: also called the resuscitation bundle and the management bundle.[4;25;26] After introduction of these bundles, a vast amount of articles concerning the early recognition and treatment of patients with severe sepsis and septic shock have been published.[35-47] Recently, the results of the international guideline-based performance program were reported.[41] Patient data and bundle performance data on 14,209 patients from 165 sites worldwide demonstrated that compliance with the SSC bundles was associated with quality improvement in sepsis care and a sustained decrease in mortality.

Also in the Netherlands, the sepsis bundles have been adopted in intensive care units, emergency departments, and nursing wards. A national committee and SSC website were established, facilitating the possibilities to report bundle compliance and patient outcome to the international database. In addition, the Dutch association of hospitals (NVZ), Dutch Federation of University Medical Centres (NFU), Dutch Order of Medical Specialists (OMS), National Expert Centre for Nursing (LEVV), and the Association for Nurses in the Netherlands (V&VN) initiated the National Patient Safety Agency (VMS). VMS aims to reduce the unintentional and avoidable damage to patients in Dutch hospitals with 50% by December 2012. Among other VMS topics, the early diagnosis and treatment of patients with severe sepsis are specific guideline items. The goal of the VMS is to increase compliance with the resuscitation bundle and management bundle

elements to an average of 80%, and to reduce both the in-hospital mortality and the mortality within 30 days after the diagnosis of severe sepsis by 15% compared with mortality data from 2007.

At this moment, the bundle compliance rates and outcome results of patients in the Netherlands are unknown and the collected VMS data are not available yet. To obtain insight in the current care for patients with sepsis in the Netherlands, the Dutch SSC data should be analyzed and compared with international data. Based on these results, possibly further VMS implementation strategies have to be developed.

Professionals' knowledge

Recognition of the systemic inflammatory response syndrome criteria is the first step in the early recognition of patients with sepsis.[9-11] Although clinical signs such as fever, chills, and systolic blood pressure <90 mmHg are associated with the presence of bacteremia[48;49], previous studies have demonstrated that only approximately 30% of physicians correctly identified the systemic inflammatory response syndrome criteria.[50] Even after an active implementation of a sepsis teaching program, only 48% and 67% of the training-grade doctors could define severe sepsis and septic shock, respectively.[51] Also, nurses experience difficulties in recognizing patients with sepsis; lack of detailed knowledge was shown to impair the recognition.[52;53] For example, only about 20% of the nurses thought that a temperature <36°C or a low white blood cell count could be a sign of sepsis.[52]

Since recognizing the clinical signs of sepsis is paramount to prevent treatment delay[50-53], sepsis education is of great importance to enable professionals to timely recognize and treat sepsis. Therefore, the knowledge about systemic inflammatory response syndrome criteria, recognition, and treatment of sepsis should be evaluated frequently, to facilitate further improvements.

Role of nurses in the emergency department

Due to the high mortality rate for patients with severe sepsis and septic shock presenting at the emergency department,[54] this department is an important location for the early recognition and treatment of sepsis. Because nurses are often the first to see and triage a patient, they have a considerable role in observing patients' signs and symptoms. Nevertheless, the role of nurses in the identification and treatment of patients with sepsis has not been formalized in guidelines and is not fully exploited.[24;27;55]

In daily practice, a multidisciplinary protocol for patients with sepsis has been demonstrated to facilitate the recognition and treatment of sepsis.[56-58] However, in many hospitals, and specifically in the emergency department, the role of the nurses is not used to its full potential and the use of these multidisciplinary protocols

is lacking. Therefore, the effects of the implementation of a multidisciplinary care bundle based sepsis protocol in the emergency department should be evaluated.

Antimicrobial treatment

Antimicrobial therapy is the most important treatment in patients with sepsis. Early initiation of appropriate empirical antimicrobial therapy has been shown to improve survival in patients with sepsis and septic shock.[27;59-62] The choice of the empirical antimicrobial therapy in sepsis mainly depends on the suspected site of infection and the antimicrobial susceptibility of the expected pathogens. To include more resistant, but often less prevalent pathogens, the empirical therapy of a severe infection is usually broad-spectrum.[24;63] The downside of this strategy is that the spectrum of antibiotics prescribed often is broader than necessary, or that antibiotics are being prescribed in the absence of a bacterial infection. After culture results are available, the antibiotic therapy should be adjusted to the causative microorganism, but this is frequently delayed or omitted. Antibiotic overuse may have potentially deleterious consequences such as the risk of anaphylactic reactions, antibiotic resistance, and high costs.

Antimicrobial treatment guidelines have been developed to assure effective treatment, to decrease treatment diversity, prevent treatment delay, and reduce the unnecessary use of broad-spectrum antimicrobials, thereby reducing the selective pressure on antimicrobial flora and preventing the development of resistance. Due to geographical differences in pathogens and antimicrobial susceptibility, many countries and hospitals have their own antimicrobial treatment guidelines based on local epidemiological data, existing literature, and expert opinion.

Although many hospitals have implemented local antimicrobial treatment guidelines, there is a wide variation in the reported adherence to this guidelines.[60;63-65] To achieve an improvement in quality of care in patients with sepsis, an evaluation of the current care for patients with (severe) sepsis should be performed. Therefore, each hospital should regularly evaluate the adherence to the antimicrobial treatment guidelines in patients admitted with sepsis.

Aim of this thesis

The three aims of this thesis focus on the prevention, diagnosis, and treatment of sepsis. To improve the prevention of infections and sepsis in the hospital, the effects of implementation of a multidisciplinary hand hygiene improvement program were studied. Second, the potential of different biomarkers to facilitate the diagnosis of sepsis was investigated. Third, the effects of implementation of the surviving sepsis campaign in various hospitals in the Netherlands and the

recognition and treatment of patients with sepsis in the emergency department of our hospital, including the adherence to antimicrobial treatment guidelines, were evaluated.

The specific aims of this thesis are:

- To evaluate the hand hygiene knowledge and hand hygiene compliance in nurses and physicians before and after implementation of a multidisciplinary hand hygiene improvement program;
- To evaluate the predictive value of a single biomarker, biomarker panels, biomarkers combined with clinical signs, and serial determinations of biomarkers in the prediction of bacteremia in patients with sepsis;
- To evaluate the potential of different biomarkers to discriminate between viral and bacterial lower respiratory tract infections in patients with sepsis;
- To evaluate the surviving sepsis campaign bundle compliance in the Netherlands and to compare the results with compliance reports from other countries;
- To evaluate the knowledge about the identification and management of sepsis and the effect of education of internal medicine residents;
- To evaluate the effects of implementation of a nurse-driven, care bundle based, sepsis protocol for the early recognition and treatment of patients with sepsis in the emergency department;
- To evaluate the physicians' adherence to antimicrobial guidelines in patients with sepsis in the emergency department.

Outline of the thesis

Our performed studies are reported in seven different chapters. Following the introduction in this chapter ***(Chapter 1)***, the short-term and long-term effectiveness of a multifaceted hand hygiene improvement program, including education, feedback, reminders, social influence activities including the use of role models, and improvement of hand hygiene facilities, is described in ***Chapter 2***. We measured hand hygiene knowledge and hand hygiene compliance before, directly after, and 6 months after the performance of the hand hygiene improvement program in nurses and physicians.

In ***Chapter 3***, we evaluated the predictive value of four biomarkers (procalcitonin, interleukin-6, lipopolysaccharide binding protein, and C-reactive protein), the combination of the best performing biomarker with one to three other biomarkers (panel analysis), the combination of the best performing biomarker with clinical signs of the patient, and serial determinations of the best performing biomarker in predicting bacteremia in emergency department patients with sepsis.

In addition, in ***Chapter 4***, we determined the value of supplementary laboratory tests (C-reactive protein, lipopolysaccharide binding protein, procalcitonin, interleukin-6, interleukin-18, and soluble triggering receptor expressed on myeloid cells-1) to differentiate between proven viral infections and bacterial infections in patients with lower respiratory tract infections.

In ***Chapter 5***, we describe the compliance with the entire SSC bundles, and change in the completion of the ten individual bundle elements after implementation of the SSC in four hospitals in the Netherlands and compare these results with the published international SSC results.

The short-term and long-term effectiveness of a brief and single teaching intervention on internal medicine residents' knowledge about the identification and management of sepsis is described in ***Chapter 6***. By use of a written questionnaire, we measured sepsis knowledge in internal medicine residents immediately before, 3 hours after, and 4-6 months following a teaching intervention.

The effects of the implementation of a nurse-driven, care bundle based, sepsis protocol in the emergency department is described in ***Chapter 7***. The sepsis protocol consisted of two parts: a sepsis screening list to support the nurses in the emergency department in better recognition of sepsis in patients with a probable infection, and a sepsis performance list, including recommendations for nurses and physicians to initiate diagnosis and treatment. After identifying a patient with sepsis, the responsible nurse should start immediately with the diagnostic procedures such as obtaining blood for chemistry tests and culture, and urine for urinalysis and culture. We measured the effects of implementation of the sepsis protocol on the compliance to measuring serum lactate, taking two blood culture samples before starting antibiotics, performing a chest radiograph, obtaining urine for urinalysis and culture, starting antibiotics within 3 hours, and hospitalizing or discharge the patient within 3 hours.

The adherence to the local antimicrobial treatment guidelines in patients admitted to the emergency department with sepsis is described in ***Chapter 8***. In addition, the *in vitro* susceptibility of the isolated pathogens to the treatment recommended by the guidelines is described in order to investigate whether or not deviations from the protocol were beneficial to the patient.

Chapter 9 provides a summary of results of the included studies in this thesis, and discusses the main findings as well as methodological issues. The discussion ends with the main conclusions and recommendations for future research and practice. Finally, the findings of this thesis are summarized in Dutch ***(Chapter 10)***.

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Chapter 2

The short-term and long-term effectiveness of a multidisciplinary hand hygiene improvement program

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Abstract

Background: Although hand hygiene (HH) compliance has been an important issue for years, the compliance rate is still a problem in health care today.

Methods: This was an observational, prospective, before-and-after study. We measured HH knowledge and HH compliance before (baseline), directly after (post-strategy), and 6 months after the performance of HH team strategies (follow-up).

The study was composed of employed nurses and physicians working in the department of internal medicine of a university hospital. We performed a multifaceted improvement program including HH education, feedback, reminders, social influence activities including the use of role models, and improvement of HH facilities.

Results: Ninety-two nurses and physicians were included. Compared with baseline, there was a significant improvement in the overall mean HH knowledge score at post-strategy (from 7.4 to 8.4) and follow-up (from 7.4 to 8.3). The overall HH compliance was 27% at baseline, 83% at post-strategy, and 75% at follow-up. At baseline, the compliance rate was 17% in nurses and 43% in physicians and significantly improved to 63% in nurses and 91% in physicians at follow-up.

Conclusion: Our multifaceted HH improvement program resulted in a sustained improvement of HH knowledge and compliance in nurses as well as physicians.

Introduction

The presence of health care-associated infections (HAIs) is one of the major causes of death and increased morbidity among hospitalized patients.[1;2] The strategies to reduce HAIs are complex.[3] One important strategy for the prevention of HAIs is optimal hand hygiene (HH) compliance in all health care workers.[4-6]

Although HH compliance has been an important issue for years, the compliance rate is still a problem in health care today.[6;7] In many studies, the effectiveness of different HH improvement strategies are described.[8-12] The improvement of HH because of multifaceted strategies seems higher as compared with using a single strategy. Education with written material, reminders, and continued feedback of performance can have an important effect on HH compliance.[8;9] Unfortunately, most of the effects are small to moderate and often short-term.[10]

A recent study on potential determinants of HH compliance in the Dutch hospital setting showed that, besides the perception of the health care workers that there is a lack of evidence that HH is effective in preventing HAIs, a lack of positive role models and social norms may hinder compliance.[13] Health care workers mentioned that creating a stronger social norm and establishing more explicit social control would be important for improving HH compliance. Strategies with specific activities on social influence are rarely applied in previous studies: role models changed health care workers HH behavior by showing them how to improve HH practices and the best way to perform HH in the unit.[12-14]

Using this information on HH improvement strategies[9-14], we developed a multidisciplinary improvement program, including education, feedback, reminders, and social influence activities including the use of role models, to improve the HH knowledge and compliance in our department of internal medicine. The aim of the current study was to test the short-term and long-term effects of a multifaceted HH improvement program for nurses and physicians, on nurses' and physicians' knowledge of HH guidelines, and their HH compliance.

Methods

Study design

To improve HH knowledge and HH compliance among nurses and physicians, we performed an observational pilot study in the department of internal medicine of a 953-bed university hospital in the Netherlands. Our study consisted of four study phases (*Table 1*), including the performance of a multifaceted HH improvement program (Phase II). HH knowledge tests and HH compliance tests were performed at baseline (Phase I), post-strategy (Phase III), and follow-up (Phase IV).

In view of the observational and anonymous nature of the study, and the performance of non-patient-related strategies, the local medical ethics committee waived the need for written informed consent.

Table 1. *Study phases and performed tests during the study*

Study phase and performed test	Date
Phase I: Baseline (test 1)	
Hand hygiene compliance observations nurses	October 2008
Hand hygiene compliance observations physicians	December 2008
Hand hygiene knowledge questionnaire nurses	December 2008
Hand hygiene knowledge questionnaire staff physicians	January 2009
Phase II: The hand hygiene improvement program	January 2009 - May 2009
Phase III: Post-strategy (test 2)	
Hand hygiene compliance observations nurses	May 2009
Hand hygiene compliance observations physicians	May 2009
Hand hygiene knowledge questionnaire nurses	June 2009
Hand hygiene knowledge questionnaire staff physicians	July 2009
Phase IV: Follow-up (test 3)	
Hand hygiene compliance observations: nurses	November 2009
Hand hygiene compliance observations: physicians	December 2009
Hand hygiene knowledge questionnaire: nurses	December 2009
Hand hygiene knowledge questionnaire: staff physicians	January 2010

Study setting and population

At the department of internal medicine, 45 nurses and 54 physicians are employed. The nurses work at the 32 bed nursing ward (n=42) and the outpatient clinic (n=3). All physicians (30 staff physicians, 24 residents) alternately work at the nursing ward, the outpatient clinic, emergency department, or are involved in medical scientific research and teaching. The nurses at the outpatient clinic were excluded for this study because of their limited patient contact and their dissimilar activities in contrast to the nurses in the nursing ward. Furthermore, 1 nurse and 3 physicians were excluded because of their involvement in the HH improvement strategies. At the start of the study, each patient room included 1 wall-fixed, alcohol-based liquid hand disinfectant dispenser; 1 wall-fixed unmedicated soap dispenser; and 1 wall-fixed paper towel dispenser.

Hand hygiene improvement strategies

We developed an improvement program from current literature: a 'state of the art strategy', which includes education, feedback, reminders, and targeting adequate products and facilities.[8;9] To these, we added strategies with specific activities on social influence. These strategies were built on relevant behavioral science theories and include gaining active commitment and initiative of ward management, modeling by informal role models at the ward, and setting norms and targets within the team.[13-17] All performed strategies are summarized in *Table 2* and were aimed at the nurses as well as the physicians.

Measurements

We measured the HH knowledge of the nurses (n=41) and staff physicians (n=27) at baseline, post-strategy, and follow-up. Furthermore, we measured the HH compliance of nurses and physicians (staff physicians and residents, n=51) in the nursing ward as well as the HH compliance of physicians in the outpatient clinic at baseline, post-strategy, and follow-up.

Hand hygiene knowledge

To obtain data about participants' knowledge regarding the indications for HH, an anonymous questionnaire was developed. The questionnaire consisted of 19 questions (yes/no). Each question described a situation in daily patient care and asked whether HH was necessary. The questionnaire was pilot tested by an infectious disease registered nurse and an infectious disease physician.

Because of the high turnover of the residents and their absence during several educational trainings, only nurses and staff physicians were included in this part of the study.

Table 2. *Performed hand hygiene improvement strategies during the study*

	Date
Education	January 2009 - May 2009
Hospital wide HH promotion meeting for nurses and physicians	
Educational HH website, including knowledge quiz on indications for HH	
Educational training on prevention of hospital-acquired infections	
Educational training on HH technique	
HH brochure including practical indications about HH	
Daily business meeting for nurses about practical HH cases	
Reminders	January 2009 - May 2009
Poster 1 and 4: The importance of HH	
Poster 2 and 5: Nurses' HH performance and own formulated goals	
Poster 3: Physicians' HH performance and own formulated goals	
Performance feedback	February 2009 - May 2009
Bar chart 1: HH compliance rates at baseline	
Bar chart 2: HH compliance rates at post-strategy	
Examining hands under UV light	
Facilities and products	August 2009 - October 2009
Install clocks in the outpatient clinic to overcome need for watches	
Distribute pin-on watches to nurses and physicians	
Place one electronic alcohol dispenser in the nursing ward	
Place additional alcohol dispensers in the nursing ward	
Appoint role models	January 2009 - January 2010
Demonstrate good HH behavior	
Models social skills in addressing behavior of colleagues	
Instruct and stimulate their colleagues in providing good HH behavior	
Active commitment and initiative of ward management	January 2009 - January 2010
Active commitment and involvement during team sessions	
Prioritizes good HH behavior as specific team goal	
Provides adequate facilities and supports improvement activities	
Supports team members and role models	
Setting norms and targets within the team	February 2009 - May 2009
Team sessions that includes goal setting in HH performance at group level	
Analysis of barriers and facilitators	
Nurses and physicians address each other in cases of undesirable HH behavior	

HH = hand hygiene

Hand hygiene compliance

Based on the five moments for HH[7] and the Dutch national infection prevention guideline, an observation list was developed. In many cases in which professionals go from one patient to another, the 'after patient contact' category is immediately followed by an indication of the 'before' category (generally 'before patient contact') in another patient. Given this overlap, the Dutch guideline on HH in hospital care does not include the HH indication 'hand hygiene before touching a patient'. Furthermore, the HH indications 'after taking care for an infected patient' and 'after removing sterile or non-sterile gloves' are included in the Dutch guideline. The final observation list contained six indications for HH: (1) before clean/aseptic procedure, (2) after body fluid exposure risk, (3) after touching a patient, (4) after touching patient surroundings, (5) after taking care of an infected patient, (6) after removing sterile or non-sterile gloves.

HH compliance was defined as hand disinfection using alcohol-based hand rub or washing hands with soap and water following one of the above-mentioned indications. The observers had to mark the applied HH indication(s) and the performed HH action. In addition, the presence of jewelry and whether the nurses and physicians wore long-sleeved clothes under their short-sleeved uniforms or white coats was observed.[7] All observers were trained during three 2-hour meetings on HH indications, HH actions, and observation techniques. Subsequently, the observation technique of the students and the observation list was pilot tested in a nursing ward of a hospital not participating in our study. Every student performed 20 observations jointly with a 'gold standard' observer. Concordance between the observers was determined by comparing the results of each student with the 'gold standard' observer. For that, we used a 3-step approach. First, we calculated the concordance between the number of recorded HH opportunities of the student nurse and the 'gold standard' observer; next, the concordance between the number of recorded HH indications; and, finally, the concordance between the number of recorded actions. The Wilcoxon rank test showed that neither of the student results differed significantly (α=.05) from the results of the 'gold standard' observer (Z scores of every student on every step between -1.96 and 1.96).

Students from the faculty of health and social studies were responsible for the unobtrusive observations of the nurses. They mentioned the observation of patient safety-related items (such as medication safety and fall prevention) and their own learning experience as explanations for their observations. Two nurse practitioners, one physician assistant, and two staff physicians performed the observations of the physicians in the nursing ward and the outpatient clinic during their daily practice, so the physicians were unaware that their HH was under observation. Because of the closed consulting rooms, in the outpatient clinic only

the presence of jewelry and wearing long-sleeved clothes could be observed. All participants were observed for a maximum number of four occasions for the purpose of including as many different nurses and physicians as possible. All observations took place on week days, during day shifts.

Data analysis

All data were analyzed using SPSS version 16.0 (SPSS Inc, Chicago, IL, USA). Descriptive statistics included percentages, means, and standard deviations.

All questions about HH knowledge were given an equal weight of 1 point per question, and the sum scores were recalibrated to a 0-10 scale. They were analyzed using linear regression, with independent factors period, gender, and nurse/staff physician/resident.

The HH compliance rates were expressed as percentages. To determine the effects of the improvement strategies on the compliance rates, we used a generalized linear model, with linear link function and Bernoulli distribution; such a model evaluates the absolute differences between the percentages in each period, in contrast to a logistic model, which determines odds ratios. The logistic approach was not used because odds ratios overestimate rate ratios when the occurrence of the dependent variable is not rare. Fixed factors included strategy period and gender. To account for the fact that the professionals (nurses and physicians) were observed repeatedly, the random factor 'professional' was included in the model. When the results for all professionals were evaluated, an additional factor that distinguished among the three types of professionals (nurse/staff physician/resident) was included. In a secondary analysis, we investigated whether the effect of the strategies depended on gender and type of professional by including the interaction factors period, gender and period, and nurse/staff physician/resident in the models. Results with $p<0.5$ (2-sided) were considered statistically significant.

Results

Hand hygiene knowledge

At baseline, as well as post-strategy and follow-up, 68 HH knowledge questionnaires were distributed. Forty-four participants (65%) returned the questionnaire at baseline, 41 (60%) at post-strategy, and 39 (57%) at follow-up (*Table 3*). Compared with baseline, there was a significant improvement in the overall mean HH knowledge score at post-strategy (from 7.4 to 8.4) and follow-up (from 7.4 to 8.3). Overall, the questionnaire score was significantly better in nurses than in staff physicians (0.5 points more; 95% confidence interval [CI]: 0.1-1.0). There was no evidence that this difference varied among the periods. There were no statistically significant differences in the overall score for gender.

Table 3. *Hand hygiene knowledge scores and hand hygiene compliance scores in the nursing ward*

Variable	Baseline	Post-strategy	Follow-up
Hand hygiene knowledge			
Questionnaire scores (0-10)			
Overall (standard deviation)	7.4 (±1.2)	8.4 (±1.1)	8.3 (±1.2)
Nurses (n)	7.4 (29)	8.5 (28)	8.8 (25)
Staff physicians (n)	7.2 (15)	8.2 (13)	7.5 (14)
Hand hygiene compliance			
Number of opportunities	99	92	103
Number of indications	115	105	138
Compliance scores (%)			
Overall	27	83	75
Nurses (n)	17 (15)	83 (13)	63 (15)
Physicians (n)	43 (11)	83 (11)	91 (11)

Hand hygiene compliance

Nursing ward

In the nursing ward, a total of 294 HH opportunities were observed. The most frequently observed indications for HH were 'after touching a patient' (51%) and 'after touching patient surroundings' (34%). For physicians, the most frequently occurring HH indication was 'after touching a patient'; for nurses also, 'after touching patient surroundings' was a frequent indication.

The overall HH compliance was 27% at baseline, 83% at post-strategy, and 75% at follow-up (*Table 3*). In the subgroup of nurses, the HH compliance significantly improved with 66% points (95% CI: 47%-86%) to 83% at post-strategy and with 46% points (95% CI: 27%-64%) to 63% at follow-up. In the subgroup of physicians, the HH compliance significantly improved with 41% points (95% CI: 22%-59%) to 83% at post-strategy, and with 48% points (95% CI: 31%-66%) to 91% at follow-up. Overall, the HH compliance of the physicians was significantly better than the nurses' compliance: 16% points (95% CI: 2%-29%) better compliance in residents and 24% points (95% CI: 7%-39%) better compliance in staff physicians. There was no evidence that this difference depended on the period. Overall, there was no significant difference in compliance rate for gender. For both groups, the compliance for 'not wearing jewelry' and 'not wearing long-sleeved clothes' was already high at baseline (≥90%) and did not change at post-strategy and follow-up.

Outpatient clinic

The compliance rate for 'not wearing jewelry' significantly improved from 51% at baseline to 79% at post-strategy and to 91% at follow-up. Overall, women were significantly more compliant to 'not wearing jewelry' than men (20%; 95% CI: 2%-37%). The compliance rate for 'not wearing long-sleeved clothes' improved from 57% at baseline to 85% at post-strategy and to 86% at follow-up. After adjustment

for type of professional and gender, the differences were 34% (95% CI: 16%-51%) and 28% (95% CI: 11%-44%), respectively. Overall, men were significantly more compliant to not wearing long-sleeved clothes than women (33%; 95% CI: 17%-49%). There was no evidence that the differences between men and women's compliance rates depended on the period. Overall, no statistically significant differences in compliance rates for 'not wearing jewelry' and 'not wearing long-sleeved clothes' between staff physicians and residents were found.

Discussion

Our study showed that overall as well as in the subgroups of nurses and physicians, a considerable increase in the HH knowledge (about 1 point increase at post-strategy and at follow-up) and in HH compliance (about 50% increase at post-strategy and at follow-up) was achieved.

In line with Naikoba and Hayward's conclusion,[8] we developed a multifaceted strategy. It is impossible to conclude which components were – to what degree – responsible for our achieved improvement. However, there was only a relatively small increase in HH knowledge – knowledge was already rather high at baseline (>7), relative to the low initial compliance and the large increase in compliance. Based on this information, one might conclude that only providing education on the indications for HH would have been insufficient.

Our study showed that our strategies were highly effective for the nurses as well as the physicians. In contrast to other studies,[4;18] the overall compliance in our study was significantly higher in physicians than in nurses. Possibly differences in observed HH indications have influenced the HH compliance results among the subgroups.

Although the HH improvement program in our study was mostly focusing on the nurses and staff physicians, and not on the residents, there was no significant difference between the staff physicians' and residents' compliances. Probably, the staff physicians functioned as role models for the residents.[19;20]

For measuring the HH compliance, we used unobtrusive observations: the gold standard as defined by the World Health Organization.[7] By mentioning the observation of patient safety-related items and their own learning experience as explanations for their observations and by performing observations during the researchers' daily practice, the nurses and physicians were unaware of the true reason for the observations. Nevertheless, observation bias and the Hawthorne effect cannot be excluded.

Some possible limitations of our study must be considered. Sixty-eight nurses and staff physicians anonymously received the HH questionnaire. Approximately 60% of the distributed HH questionnaires were completed and compared;

there could be a matter of selection bias. Moreover, the HH compliance was anonymously observed. Although all participants were equally likely to have been selected for observation during the study periods, selection bias cannot be ruled out.

The effectiveness of HH on the prevention of HAIs depends not only on compliance but also on the HH technique.[21] Although HH technique training was part of the program, it was not evaluated in this study.

Finally, the physicians' HH compliance in the outpatient clinic was not observed. Sladek et al. concluded in their study that the observational setting had an effect on HH compliance: HH was significantly more likely during ward rounds than during clinics.[22] Therefore, we highlighted during our improvement program that HH is important with inpatients just as with outpatients. However, the effect on the HH compliance in the outpatient clinic remains unclear.

In conclusion, our HH improvement program for nurses and physicians had large positive effects on the HH knowledge and HH compliance, and these positive effects sustained after 6 months follow-up. This multifaceted HH improvement program will be tested in a multicenter controlled trial.

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Chapter 3

Serial and panel analyses of biomarkers do not improve the prediction of bacteremia compared to one procalcitonin measurement

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Abstract

Objectives: We evaluated the value of a single biomarker, biomarker panels, biomarkers combined with clinical signs of sepsis, and serial determinations of biomarkers in the prediction of bacteremia in patients with sepsis.

Methods: Adult patients visiting the emergency department because of a suspected infection with at least two of the following symptoms: temperature >38.3°C or <36°C, heart rate >90/min, respiratory rate >20/min, chills, altered mental status, systolic blood pressure <90 mmHg, MAP <65 mmHg, and hyperglycemia in the absence of diabetes mellitus were included. Procalcitonin (PCT), interleukin-6 (IL-6), lipopolysaccharide-binding protein (LBP), C-reactive protein (CRP) were measured, and two blood cultures were taken. The analyses included: 1) To determine the biomarker with the highest predictive value for bacteremia and to examine the predictive value of this biomarker in combination with other biomarkers; 2) Analysis of the best biomarker data in combination with clinical signs of sepsis; and 3) Analysis of serial determinations of the best biomarker.

Results: Of 342 included patients, PCT had the best predictive value for bacteremia with an area under the curve of 0.80, sensitivity 89%, specificity 58%. The predictive value of a combination of PCT plus a panel of other biomarkers, clinical signs, or analysis of serial PCT levels did not lead to a significant improvement of the predictive value of PCT alone.

Conclusions: The ability of PCT to predict bacteremia in patients with sepsis does not further improve when combined with IL-6, LBP, CRP, clinical signs, or serial measurements. Naturally, this does not exclude that a panel of other biomarkers may lead to different results.

Introduction

It is becoming increasingly clear that early identification of patients with sepsis is important but difficult because signs of systemic inflammatory response syndrome (SIRS) are not specific[1;2] and the predictive value of single biomarkers is limited.[3] Although blood cultures are considered the gold standard for the detection of bacteremia, delays between blood sampling and information returned to the clinician is an important disadvantage, but no alternatives are currently available.[4]

To improve survival in patients with sepsis and septic shock, early initiation of appropriate empirical antimicrobial therapy is essential.[5-9] The choice of the empirical antimicrobial therapy in sepsis mainly depends on the suspected site of infection and the antimicrobial susceptibility of the expected pathogens. To include more resistant but often less prevalent pathogens, the empirical therapy of a severe infection is usually broad-spectrum.[5;10] The downside of this strategy is that the prescribed antibiotics are often more broad-spectrum than necessary[11] or even are used in the absence of a bacterial infection.[12;13] This may have potentially deleterious consequences such as anaphylactic reactions, antibiotic resistance, and high costs. Rapid tests that provide insight in the etiology of infection may guide appropriate use of antibiotics and are urgently needed.

To improve diagnosis and management of sepsis, the usefulness of single biomarkers (e.g., C-reactive protein (CRP), procalcitonin (PCT), interleukin-6 (IL-6), and lipopolysaccharide-binding protein (LBP)) are described in many studies.[3;11-28] Of many biomarkers tested, some appear to have a sensitivity and specificity value above 90%.[3] Although PCT and CRP have been most widely used[14], these biomarkers have limited abilities to distinguish sepsis from other inflammatory conditions or to predict outcome. In patients with sepsis admitted to the emergency department (ED), PCT had a sensitivity of 0.62 to 0.71, and specificity 0.67 to 0.88.[19;20;22] Therefore, further evaluation of a combination of different sepsis biomarkers is recommended.[19;20;22]

In patients with sepsis, only a few studies have examined the usefulness of biomarker panels.[29-33] Beneficial effects of a panel to predict organ dysfunction, septic shock, and in-hospital mortality[29] and the differentiation between bacterial and viral lower respiratory tract infections[30] have been reported. Also, chills[31] and increasing values during repeated PCT measurements[32] predict the presence of a positive blood culture.

In view of the absence of a reliable biomarker to predict bacteremia[4], we evaluated the predictive value of four single biomarkers (PCT, IL-6, LBP, and CRP), the combination of the best performing biomarker with one up to three other biomarkers (panels), the combination of the best performing biomarker with

clinical signs of the patient and conventional laboratory parameters, and serial determinations of the best performing biomarker in predicting bacteremia in ED patients with sepsis. We selected bacteremia to have a less disputable diagnosis of infection and aimed to find a reliable (panel of) marker(s) to predict the presence or absence of bacteremia, which may lead to a reduction of the number of blood cultures that needs to be taken.

Because PCT and CRP are the most widely used single biomarkers, the value of IL-6 and LBP for the diagnosis and management of sepsis were frequently evaluated in earlier studies, and PCT, IL-6, LBP, and CRP are commercially available, we included these biomarkers in our panel analyses.

Materials and methods

Study design

The present study was a prospective single centre study, performed at the ED of a 953-bed university hospital in the Netherlands. Each year approximately 20,000 patients visit the ED and 3%-4% is admitted because of sepsis, severe sepsis, or septic shock. During the 8 month study period, medical policy at the ED and the nursing wards was solely based on the clinical chemistry test results in combination with a physical examination and additional diagnostic procedures and not on the results of the inflammatory markers described in this manuscript.

Prior to the conduct of this study, the local Medical Ethics Committee was informed. Although they waived the need for a written informed consent, patients were informed about the study and the acquisition of supplementary plasma.

Study population

Inclusion criteria were: patients (≥16 years old) visiting the ED because of a suspected infection, who had at least two of the following clinical signs of sepsis[1;34;35]: temperature >38.3°C or <36°C, heart rate >90/min, respiratory rate >20/min, chills, altered mental status, systolic blood pressure <90 mmHg, MAP <65 mmHg, and hyperglycemia in the absence of diabetes mellitus. For the analysis of serial (3 days) biomarker data, all hospitalized patients admitted to one of the departments of internal medicine (internal medicine, rheumatology, haematology, nephrology, gastroenterology, oncology, and intensive care), were included.

The final confirmed diagnosis at discharge, as described in *Table 1*, was based on a combination of clinical signs and symptoms of sepsis, the presence/absence of an infiltrate on chest X-ray, laboratory parameters, and culture results (e.g., blood, urine, sputum, and wound) obtained during the first 24 hours following ED admission.

Table 1. *Demographic data and infection characteristics of the subjects*

	Overall group n=342	Positive blood cultures n=55	Negative blood cultures n=287	*p*-value
Patient characteristics				
Gender, % female	43.6	49.1	42.5	NS
Age, yrs [median (IQR)]	59 (43 - 70)	59 (48 - 69)	59 (42 - 70)	NS
Administration of antibiotics in the ED [n (%)]	222 (65)	37 (67)	185 (65)	NS
Patients discharged from ED to home [n (%)]	47 (14)	3 (6)	44 (15)	0.05
Patients admitted from ED to ICU [n (%)]	20 (6)	6 (11)	14 (5)	NS
Patients admitted from ED to nursing ward/OR [n (%)]	275 (80)	46 (84)	229 (80)	NS
Patients admitted from nursing ward/OR to ICU [n (%)]	*16*	*2 (4)*	*14 (5)*	*NS*
Length of hospital stay, days [median (IQR)]	6 (3 - 12)	7 (4 - 15)	6 (2 - 12)	0.05
In-hospital mortality rate [n (%)]	18 (5.3)	4 (7.3)	14 (4.9)	NS
Final confirmed diagnosis at discharge [n (%)]				
Lower respiratory/pneumonia	123 (36.0)	12 (21.8)	111 (38.7)	0.02
Urogenital	61 (17.8)	15 (27.3)	46 (16.0)	NS
Intra-abdominal	29 (8.5)	8 (14.5)	21 (7.3)	NS
Circulatory system/catheter infection	14 (4.1)	9 (16.4)	5 (1.7)	0.0001
Skin/soft tissue/wound	12 (3.5)	3 (5.5)	9 (3.1)	NS
Bone/joint	5 (1.5)	1 (1.8)	4 1.4)	NS
Cerebral	6 (1.8)	4 (7.3)	2 (0.7)	0.007
Other/unknown focus	43 (12.7)	3 (5.5)	40 (13.9)	NS
Viral infection	25 (7.3)	-	25 (8.7)	0.02
No infection	24 (7.0)	-	24 (8.4)	0.02
Biomarker results [median (IQR)]				
PCT (µg/L)	0.25 (0.10 - 1.38)	3.98 (0.43 - 13.69)	0.19 (0.09 - 0.73)	0.0001
IL-6 (pg/ml)	97.55 (32.5 - 314.25)	318 (60.2 - 1000)	87.7 (29.1 - 246)	0.0001
LBP (µg/ml)	21.27 (13.47 - 36.03)	31.50 (17.79 - 61.90)	20.26 (12.77 - 32.51)	0.0001
CRP (mg/L)	77.5 (26.0 - 164.25)	164 (44 - 254)	70 (24 - 137)	0.0004

IQR = interquartile range; ED = emergency department; ICU = intensive care unit; OR = operating room

Data collection

In the ED, blood samples were taken for basic clinical chemistry tests (e.g., lactate, blood gas, glucose, CRP, and leukocyte count) and two blood cultures. For measurement of PCT, IL-6, and LBP, an additional blood sample was taken. In the subgroup of hospitalized patients, blood samples were also drawn for standard analysis and for the measurement of the biomarker panel at day 2 and day 3. Samples for PCT, IL-6, and LBP determination were stored at -80°C until analysis.

Patient characteristics included gender, age, hospitalization, final confirmed diagnosis, length of hospital stay, and in hospital mortality. The required data (including the ≥2 clinical signs of sepsis) were collected from the clinical patient databases and medical records.

Blood sampling

Blood was collected in 3 ml Lithium-heparin coated tubes: one tube for PCT, IL-6, and LBP measurements and one tube for basic clinical chemistry tests including CRP. EDTA blood was collected for leukocyte counting. Plasma was obtained by centrifugation of the blood at 4°C and 2200 g for 10 minutes. Plasma for the measurement of PCT, IL-6, and LBP was frozen at -80°C. CRP was measured by use of the Abbott Aeroset® (Abbott Diagnostics, USA) with a detection limit of

5 mg/L. PCT was measured by use of the Kryptor PCT® (Brahms, Hennigsdorf, Germany) with a detection limit of 0.02 µg/L. IL-6 and LBP were measured by use of the Immulite 2500® (Siemens Healthcare diagnostics, Deerfield, IL, USA) with a detection limit of 2.00 pg/ml and 1.2 µg/ml, respectively.

Blood for culture was collected in two sets of bottles (BACTEC plus Aerobic/F); one aerobic and one anaerobic. Directly upon arrival in the laboratory, blood cultures were entered in the BACTEC 9240 automated blood culture system (Bacton Dickinson Microbiology Systems, Cockeysville, MD, USA). Bacteremia was defined as growth of any pathogen in one or both blood culture sets. The isolation of coagulase-negative staphylococci was considered as contamination and therefore not defined as bacteremia.

Data analysis

In order to evaluate the predictive value of the biomarkers, the data analysis was performed in three steps: 1) Analysis of the single markers and a combination of the best performing biomarker with one to three of the other biomarkers (panels); 2) Combination of the best performing biomarker with the clinical signs of sepsis and conventional laboratory parameters; and 3) Analysis of serial data of the best performing biomarker.

Analysis of single biomarkers and their combination

Receiver operator characteristics (ROC) curves were constructed for each single biomarker to evaluate their individual predictive value, together with the sensitivity, specificity, the negative predictive value (NPV), and the positive predictive value (PPV). Subsequently, the ROC curves of PCT, IL6, LBP, and CRP were compared.[38] To investigate whether a combination of biomarkers increases the predictive value compared with the best performing single marker, a multivariate logistic regression analysis was performed, together with a threshold analysis. For the threshold analysis, we developed a program in Matlab (Matlab R2009b, MathWorks Inc., MA, USA) that uses an upper- and a lower- threshold which were defined as follows: when the value of one of the markers was below the lower threshold, the patient was predicted not to have a positive blood culture, except when the value of one of the other markers was above the upper threshold. The algorithm used every combination of cut-off values as thresholds and iteratively searched for the best combination based on sensitivity, specificity, NPV, and PPV. All possible combinations of biomarkers were analysed, resulting in a total of 18 million comparisons.

Analysis of biomarker data combined with clinical signs of sepsis and conventional laboratory parameters

For this analysis, we added the clinical signs of sepsis and conventional laboratory parameters, and combinations thereof to the best performing single marker and again calculated the sensitivity, specificity, NPV, and PPV.
Subsequently, we analyzed if the best performing single marker combined with the number of SIRS criteria (0-4) could further improve the predictive value.

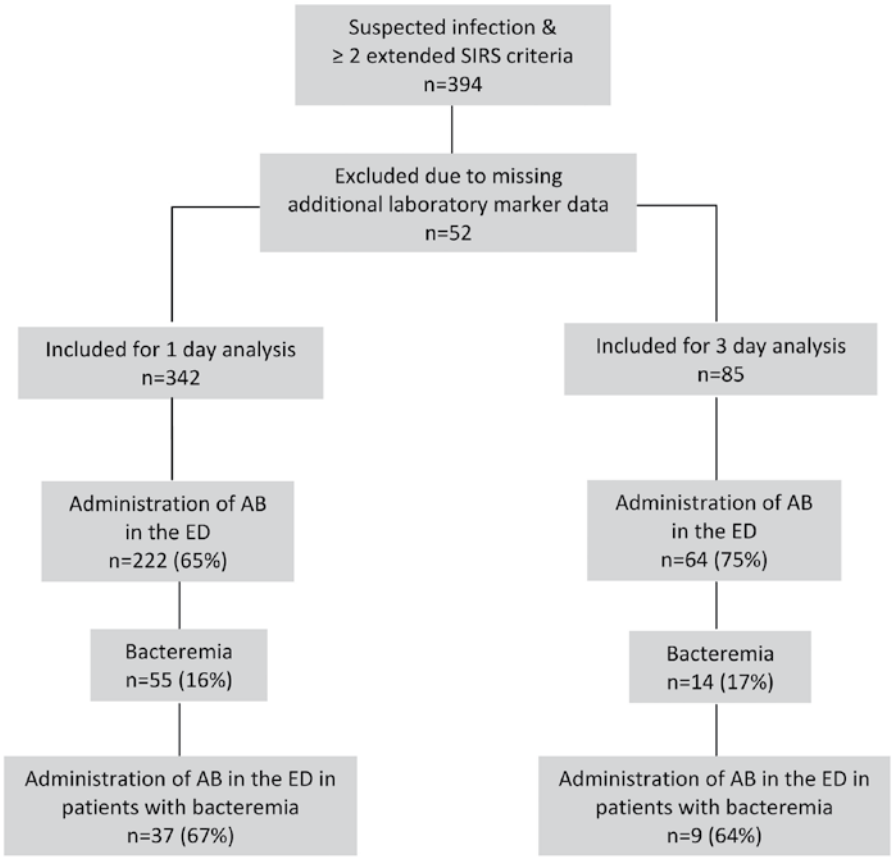
Analysis of serial biomarker data

The best performing biomarker was determined on 3 consecutive days in hospitalized patients. Subsequently, a multivariate logistic regression analysis was performed with the values of the marker on the 3 days. Additionally, two other analysis methods were used. First, a trend analysis, in which all patients were divided into nine different categories depending on their increase or decrease in the determined biomarker on day 2 and day 3 compared to day 1. The predictive value of each category was determined by the area under the curve (AUC) of the ROC and regression plots. Secondly, patients were characterized according to the change in the value of the marker (as a percentage) from day to day (from day 1 to day 2, day 2 to day 3, and day 1 to day 3), and derived whether there was a relation between this change and the presence of bacteremia, again by ROC curve analysis and regression plots.

Statistical analysis

Data are presented as percentages, medians, and interquartile ranges (IQR). Frequency comparison was done by the Chi-squared test. For the analysis of (serial) biomarker data, a multivariate logistic regression analysis and trend analysis was used. All included clinical parameters were changed into dichotomous variables (e.g., presence of temperature >38.3°C yes/no; presence of temperature <36°C yes/no; presence of leukocytes <4 x 10^9/L yes/no; presence of lactate >4 mmol/L yes/no). As the optimal cut-off value of an individual biomarker resulting in the best sensitivity and specificity does not imply that this cut-off value is optimal in the panel analysis, a threshold analysis was conducted in which all possible combinations of cut-off values were tested. Two-tailed *p*-values below 0.05 were considered statistically significant. All statistical calculations were performed in Matlab (Matlab R2009b, Mathworks Inc., MA, USA) and SPSS 18 for windows (SPSS Inc., Chicago, IL, USA).

Figure 1. *Flow-chart of patients included for analysis*



SIRS = systemic inflammation response syndrome; AB = antibiotic treatment; ED = emergency department

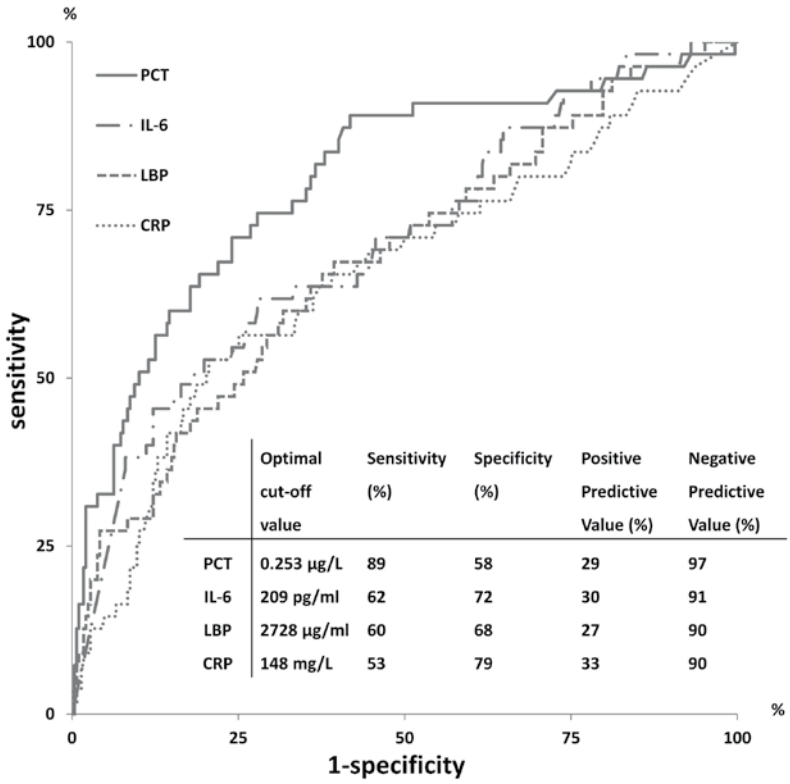
Results

During the study period, 394 patients with a suspected infection and ≥2 clinical signs of sepsis were admitted to the ED (*Figure 1*). We included 342 patients for further analysis. Patient demographics and the single biomarker measurement results are presented in *Table 1*.

In the ED, the administration of antibiotics took place in 222 patients (65%). In the total group of 342 patients, 55 (16%) had proven bacteremia (positive blood culture). The most common causative agents were *E. coli* (29%) and *Streptococcus pneumoniae* (23%).

Thirty-seven patients with proven bacteremia received antibiotics in the ED (67%). There was no significant difference in the administration of antibiotics between the patient group that turned out to have positive blood cultures and the patient group with negative blood cultures.

Figure 2. *ROC curve of the single biomarkers procalcitonin (PCT), interleukin-6 (IL-6), lipopolysaccharide-binding protein (LBP), and C-reactive protein (CRP)*



	Optimal cut-off value	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
PCT	0.253 µg/L	89	58	29	97
IL-6	209 pg/ml	62	72	30	91
LBP	2728 µg/ml	60	68	27	90
CRP	148 mg/L	53	79	33	90

Single biomarkers and their combination

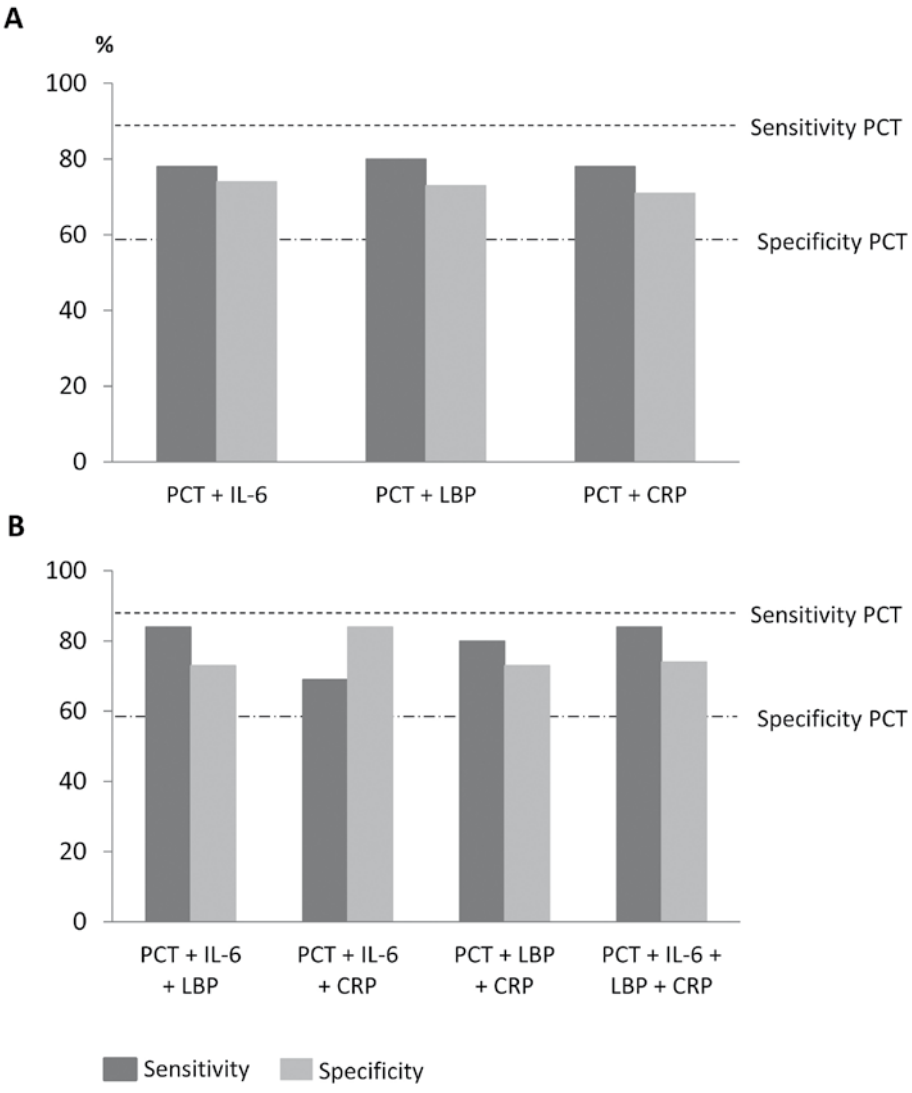
The biomarker concentrations in patients with a positive blood culture were significantly higher than the biomarker results in non-bacteremia patients (all $p<0.05$) (*Table 1*). *Figure 2* represents the single biomarker ROC curves in which the sensitivity, specificity, and cut-off values of the single biomarkers were calculated. The predictive value of PCT with an AUC of 0.80 (95% CI: 0.75-0.84), sensitivity 89% (95% CI: 78%-96%), specificity 58% (95% CI: 52%-64%), was significantly better than that of the other markers (all $p<0.05$). The PCT value associated with the highest AUC is 0.253 µg/L. The sensitivity, specificity, and likelihood ratios for PCT at different cut-offs (0.1 µg/L, 0.25 µg/L, 0.5 µg/L, and 1.0 µg/L) are described in *Table 2*.

Table 2. *Different procalcitonin (PCT) cut-off values with corresponding sensitivity, specificity, and positive and negative likelihood ratio (LR)*

PCT cut-off value	Sensitivity (%)	Specificity (%)	LR+	LR-
>0.1 µg/L	91	29	1.27	0.32
>0.25 µg/L	89	58	2.13	0.19
>0.5 µg/L	75	72	2.67	0.35
>1.0 µg/L	66	78	3.00	0.44

Next, we analyzed if a combination of PCT plus one to three of the other biomarkers could further improve the predictive value of PCT. Although the specificity improved in all combinations, the predictive value of PCT did not further improve because the sum of the sensitivity and specificity (and thereby the AUC) decreased due to a larger decrease in sensitivity in all tested combinations (*Figure 3*).

Figure 3. *Combination of different biomarkers: the sensitivity and specificity of PCT plus one other marker (interleukin-6 (IL-6), lipopolysaccharide-binding protein (LBP), or C-reactive protein (CRP)) (**A**) and the sensitivity and specificity of PCT plus two or three other markers (**B**)*



Biomarker data combined with clinical signs of sepsis and conventional laboratory parameters

In a subgroup of 248 patients (73%), complete documentation of the clinical signs of sepsis and conventional parameters was available (*Table 3*).

Table 3. *The division of clinical signs of sepsis and conventional laboratory parameters in patients with positive blood cultures (n=43) and patients with negative blood cultures (n=205)*

	Overall group n=248	Positive blood cultures n=43	Negative blood cultures n=205	*p*-value
SIRS criteria				
Temperature >38.3°C [n (%)]	211 (85)	33 (77)	178 (87)	NS
Temperature <36°C [n (%)]	8 (3)	1 (2)	7 (3)	NS
Heart rate >90/min [n (%)]	162 (65)	24 (56)	138 (67)	NS
Respiratory rate >20/min [n (%)]	47 (19)	5 (12)	42 (21)	NS
Leukocytes <4 x 10^9/L [n (%)]	28 (11)	4 (9)	24 (12)	NS
Leukocytes >12 x 10^9/L [n (%)]	92 (37)	17 (40)	75 (37)	NS
Other clinical signs/laboratory parameters				
SBP <90 mmHg, MAP <65 mmHg [n (%)]	17 (7)	4 (9)	13 (6)	NS
Chills [n (%)]	88 (36)	21 (49)	67 (33)	0.04
Hyperglycemia in the absence of diabetes mellitus [n (%)]	1 (0.4)	-	1 (0.5)	NS
Altered mental status [n (%)]	19 (8)	4 (9)	15 (7)	NS
Lactate >4 mmol/L [n (%)]	25 (10)	9 (21)	16 (8)	<0.01

Leukocytes <4 or >12 x 10^9/L, chills, and lactate >4 mmol/L had the best predictive value (*Figure 4A*). Combinations of PCT with these three parameters are illustrated in *Figure 4B* and *Figure 4C*. PCT combined with lactate >4 performed best in discriminating between bacteremia and non-bacteremia patients (sensitivity 91%, specificity 57%), but this result was not significantly different from the predictive value of PCT alone. Also, addition of the number of SIRS criteria increased specificity, but sensitivity decreased to the same extent (data not shown). Therefore, the predictive value of PCT as single marker did not further improve by adding the number of SIRS criteria.

Serial biomarker data

In a subgroup of 85 patients that were hospitalized, PCT was measured on day 2 and day 3. Of this subgroup, 14 patients had bacteremia. In addition to the PCT levels on day 1, PCT was also significantly higher on day 2 (p=0.002) and day 3 (p=0.001) in the bacteremia patients compared with non-bacteremia patients. There was no significant difference in percentage change or trend analyses, between bacteremia and non-bacteremia patients (*Figure 5*). Bacteremia was not better predicted when the highest value of the serial PCT determinations was used (data not shown).

Figure 4. *Procalcitonin (PCT) combined with clinical signs and conventional laboratory parameters: the sensitivity and specificity of a single clinical sign of sepsis or conventional laboratory parameter (**A**), PCT plus one clinical sign of sepsis or single conventional laboratory parameter (**B**), and PCT plus two clinical signs of sepsis and/or conventional laboratory parameters (**C**)*

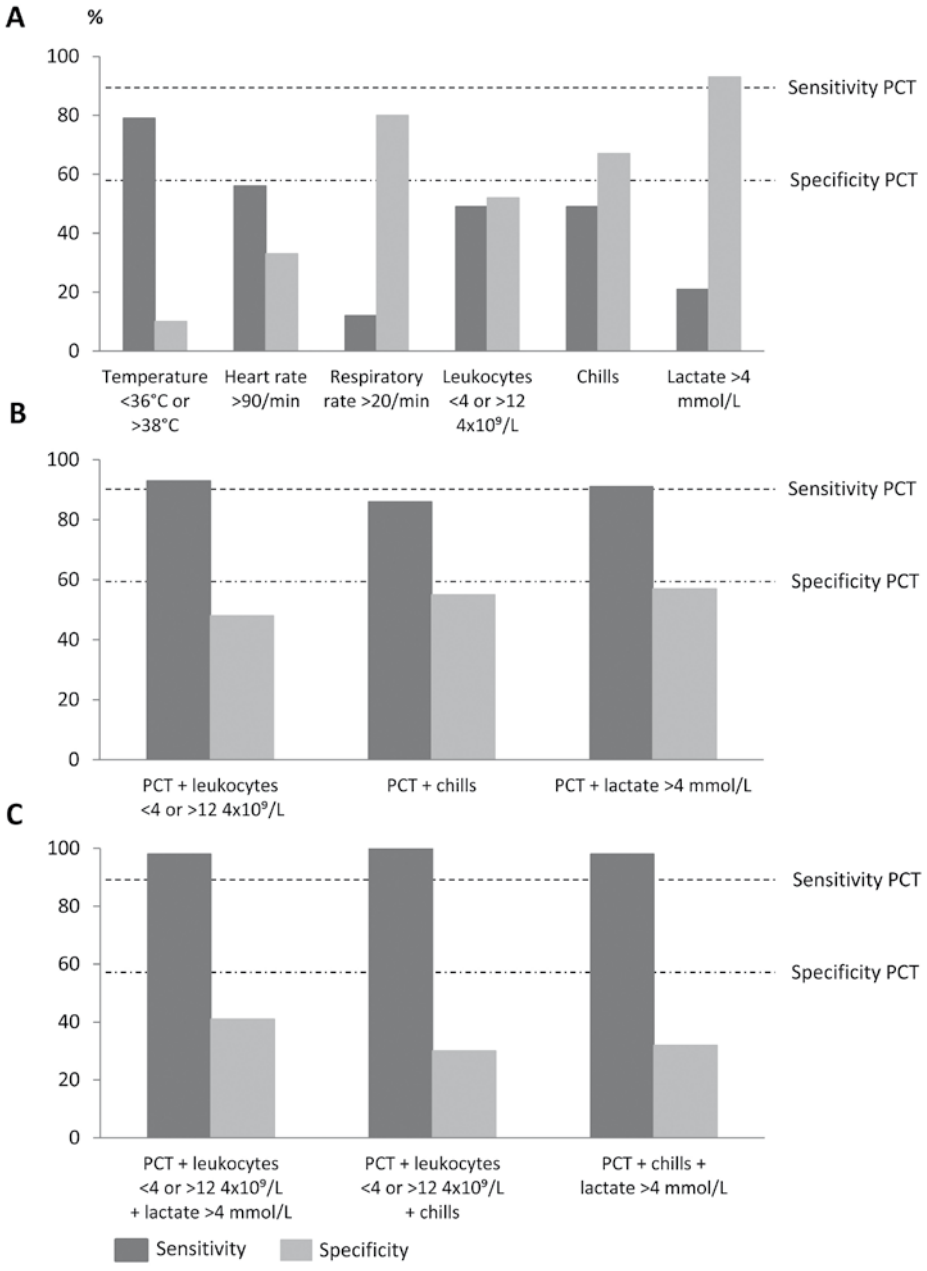
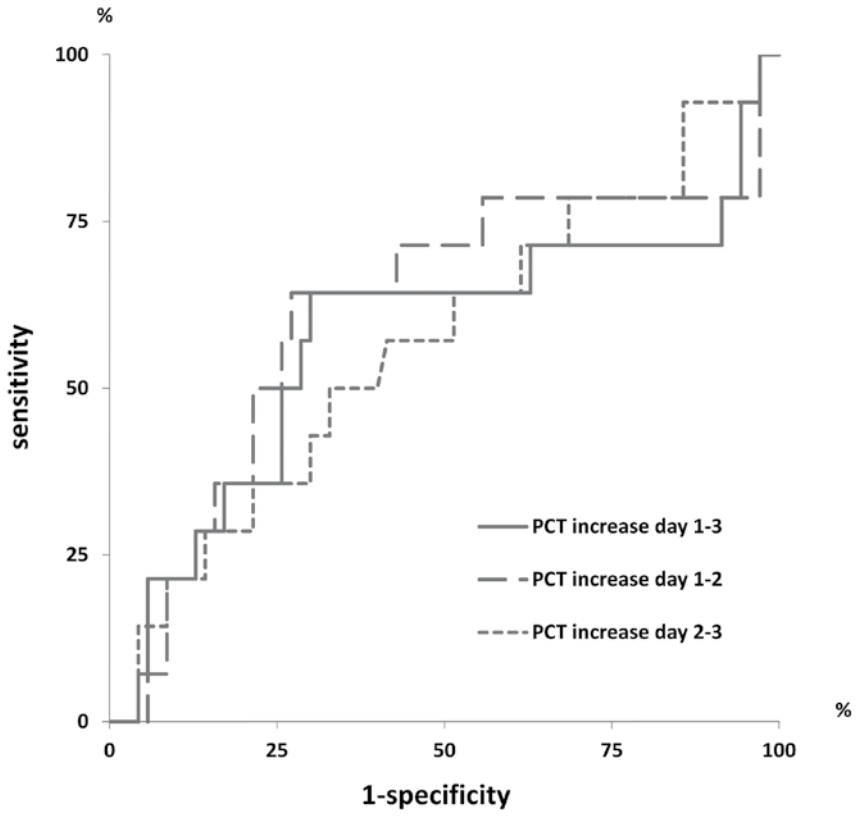


Figure 5. *Serial analysis of procalcitonin (PCT): change in PCT concentration and the presence of bacteremia*



Implications for clinical practice

In the overall patient group, 171 patients (50%) had a PCT value >0.253 µg/L. Hundred-thirty of these patients received antimicrobial treatment. In the patient group with a PCT value <0.253 µg/L (n=171), 92 patients received antibiotics during ED admission.

A total of 55 patients had positive blood cultures. Of this patient group, 6 patients had a PCT value <0.253 µg/L. Nevertheless, 5 out of these 6 patients were treated with antibiotics based on the clinical suspicion of an infection. A PCT value >0.253 µg/L was found in 122 patients with negative blood cultures (43%). Ninety-eight of these patients were treated with antibiotics based on clinical grounds.

A total of 47 patients (14%) were sending home after they visited the ED. Despite negative blood cultures in 44 patients, most of these patients were treated with antibiotics on clinical grounds. In this patient group (n=47), PCT values between

0.02 µg/L and 20.82 µg/L were found. Ten patients had a PCT value >0.253 µg/L.

Afterwards, 3 of the patients who were sending home were found to have positive blood cultures. Interestingly, all these 3 patients had a PCT value >0.253 µg/L. During their ED visit, oral antimicrobial therapy was prescribed in 2 of these 3 patients. Following the culture results, 2 patients were contacted and admitted to the nursing ward.

Following their initial ED visit, a total of 6 out of the 47 patients who were sent home were admitted to one of the nursing wards because of a severe infection within 30 days (including 2 patients with positive blood cultures). In these 6 patients, PCT values between 0.02 µg/L and 2.13 µg/L were found. A PCT value >0.253 µg/L occurred only in the 2 patients with positive blood cultures.

Discussion

Out of four inflammatory biomarkers tested in the present study, PCT was the best single marker for prediction of bacteremia in ED patients suffering from sepsis. The predictive value of PCT did not improve upon addition of one to three other biomarkers, clinical signs of sepsis and conventional laboratory parameters, or serial determinations of PCT.

In agreement with other studies that focused on patients presenting with sepsis in the ED (AUC 0.69-0.84)[19;20;22], we found a comparable AUC of 0.80 to predict positive blood cultures, using PCT as a single inflammatory marker. In an earlier systematic review, PCT was evaluated for its predictive value to diagnose sepsis.[14] Overall, the accuracy of PCT for sepsis diagnosis in critically ill patients resulted in an AUC of 0.78.[14]

In our study, we found that the optimal cut-off value of PCT to predict bacteremia is 0.253 µg/L. Interestingly, this cut-off value was also found and used in earlier studies which investigated PCT to predict bacteremia in patients with community-acquired pneumonia[25], febrile urinary tract infections[26], and patients with growth of coagulase-negative staphylococci.[27] Furthermore, in a recent systematic review of randomized controlled trials and recommendations for clinical algorithms for antibiotic treatment decisions, the measurement of PCT levels for antibiotic decisions in patients with respiratory tract infections and sepsis appears to reduce antibiotic exposure without a negative effect on survival.[28] In this review, a total of 6 studies in the ED setting were identified. Although these studies included specifically patients with respiratory tract infections, all studies used a similar PCT algorithm: no initiation of antibiotic therapy or, if already initiated, discontinuation of antibiotic therapy in patients with PCT levels of <0.25 µg/L.

Earlier studies demonstrated that clinical signs such as fever, chills, and systolic blood pressure <90 mmHg are associated with the presence of bacteremia.[36;37;39;40]

A clinical prediction rule to stratify ED patients according to the likelihood of developing bacteremia appears to enable a physician to make a bedside estimation of the risk of bacteremia.[37] Either one major criterion or two minor criteria may serve as an indication to obtain blood cultures. Furthermore, in a prospective study of 464 consecutive patients in two hospitals, the sensitivity of chills in the prediction of bacteremia was 58% and 73%, and specificity 65% and 62%.[36] We demonstrate that the predictive value of clinical signs of sepsis and conventional laboratory parameters is minimal and combining PCT with these items does not improve the predictive value of PCT. Our results confirm those of an earlier study in which the PPV of the presence of SIRS criteria for predicting bacteremia was only 7%.[41] Our study emphasizes that clinical signs of sepsis do not exert an additional value to the measurement of a single biomarker to predict positive blood cultures. However, this does not imply that the clinical signs of sepsis are not useful in the recognition of patients with bacteremia. To apply a general clinical decision, a good clinical judgment remains necessary and biomarkers must be part of, rather than be used in preference to, a clinical assessment.

Only a few studies have reported improved predictive values when a panel of markers is used.[29-33] Surprisingly, up until now there appears to be no uniform way to calculate the optimal cut-off values for markers used in panel analyses. Importantly, the optimal cut-off value for each single marker may not result in the optimal predictive value of a panel. Therefore, we searched for the best cut-off value of the panel of markers by combining all possible cut-off values of the individual biomarkers based on sensitivity, specificity, NPV, and PPV by variable threshold analyses. Nevertheless, exploring 18 million possible cut-off value combinations did not result in a higher predictive value of the panel in our study. Since all possible combinations of cut-off values were tested, we conclude that panel analysis does not have additional value compared to the determination of the single best marker. To our knowledge, this approach has never been used before and because of its completeness, we would like to recommend it for future studies.

While serial measurements of PCT have proven its value to discriminate between viral and bacterial infections in patients with lower respiratory tract infections[42-45] and to avoid unnecessary use of antimicrobial treatment[42;46], serial measurements of PCT appears not improve the prediction of bacteremia in our study. However, this analysis was based on a subgroup of 85 patients of whom a relatively small number of patients (14) had a proven bacteremia. Furthermore, only patients from one of the departments of internal medicine were included in this part of the study. Therefore, the generalizability of the result of the analysis of serial biomarker data is limited and a more extended clinical research is needed.

Possible limitation of our study is that we included all patients with a suspected infection, who had at least two clinical signs of sepsis. Therefore, also immune-suppressed patients and patients with underlying autoimmune disease or other co-morbidity were included in the study. Furthermore, the use of anti-inflammatory agents, corticosteroids, or other sepsis-modifying agents before enrolment or during the study period was not documented. Theoretically, the levels of PCT, CRP, IL-6, and LBP could be different in the above mentioned patient groups and could have influenced the results of our study. Furthermore, many of the included patients received antimicrobial treatment prescribed by their general practitioner prior to their ED visit. In a study of Müller et al., antibiotic pre-treatment and PCT serum levels were independent predictor for negative and positive blood cultures.[25] Based on this result, antimicrobial pre-treatment may have had an important impact on the biomarker values and on the blood culture results. However, as we wished to evaluate the value of the biomarkers in a daily clinical setting, we chose to study all consecutive patients.

In view of the effects of the use of antibiotic treatment, negative blood culture results do not always exclude the presence of bacteremia. Although the presence of 16% positive blood cultures in our patient group is comparable with findings in other studies, e.g., 8% positive blood cultures in patients with community-acquired pneumonia[25] and 23% in patients with febrile urinary tract infections[26], taking additional cultures may increase this percentage.

Out of four commercially available biomarkers, PCT is the best single biomarker to predict bacteremia in ED patients with sepsis. The value of PCT does not further improve when combined with other biomarkers, clinical signs of sepsis and conventional laboratory parameters, or serial measurements of PCT. Obviously, we cannot exclude the possibility that a panel of PCT plus other biomarkers may lead to different results.

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Chapter 4

Combination of biomarkers for the discrimination between bacterial and viral lower respiratory tract infections

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Abstract

Objectives: To investigate whether additional determinations of plasma lipopolysaccharide binding protein (LBP), procalcitonin (PCT), interleukin-6 (IL-6), interleukin-18 (IL-18), or soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) to C-reactive protein (CRP) improve the discrimination between bacterial and viral lower respiratory tract infections (LRTI).

Methods: Of 342 patients visiting the emergency department because of a suspected infection and ≥2 clinical signs of sepsis, 56 patients with proven bacterial (n=39) or viral (n=17) LRTI were included. The area under the curves (AUC) for the five possible combinations of CRP with one other biomarker were compared with the AUC for CRP alone. Next, the same analysis was performed in the group of patients with a CRP concentration with <95% specificity for bacterial LRTI.

Results: While CRP, PCT, IL-6, sTREM-1, and LBP concentrations were significantly different between patients with bacterial or viral LRTI, the AUC for CRP (0.82, 95% CI: 0.70-0.93) did not increase after combination analysis. After exclusion of patients with a CRP >150 mg/L, biomarker panel analysis did not improve diagnostic accuracy of CRP either.

Conclusions: Combining CRP with LBP, PCT, IL-6, IL-18, or sTREM-1 does not improve differentiation between patients with a bacterial or viral LRTI compared with CRP alone.

Introduction

Morbidity and mortality associated with lower respiratory tract infections (LRTI) remains significant, despite improved diagnostic and therapeutic treatment strategies in recent years.[1] The early initiation of antibiotic therapy has a major impact on the clinical outcome of critically ill patients.[2;3] Several laboratory diagnostic tests are currently used for establishing an etiologic diagnosis. However, difficulty in obtaining relevant specimens, the low sensitivity or specificity of the used tests, high costs, and the absence of test results within the critical window for initiating adequate treatment, often result in prescription of antibiotic therapy in the absence of a bacterial infection. This may have potentially deleterious consequences such as anaphylactic reactions, antibiotic resistance, and high costs.[4] Rapid tests that provide additional insight in the bacterial/viral etiology of infection may guide appropriate use of antibiotics and are urgently needed.

Both C-reactive protein (CRP) and procalcitonin (PCT) concentrations have been used to initiate and monitor the antibiotic use for LRTI.[5;6] However, the specificity of single biomarkers in terms of etiologic distinction between bacterial and viral inflammatory insults remains cumbersome[7;8], and a combination of markers could prove more reliable. The usefulness of IL-18 as a viral marker is supported by the reported high concentrations in HIV, dengue hemorrhagic fever, EBV, and CMV infections.[9-12] Triggering receptor expressed on myeloid cells-1 (TREM-1) is expressed on neutrophils and monocytes upon exposure to bacteria and fungi. Soluble TREM-1 (sTREM-1) has been proposed to be of diagnostic value in bacterial infections.[13] Lipopolysaccharide (LPS)-binding protein (LBP) is an acute phase protein produced by hepatocytes that binds LPS to form a LPS-LBP complex during bacterial infections.[14] In children, LBP has excellent sensitivity for diagnosing invasive bacterial infections.[15] Interleukin-6 (IL-6) is the chief stimulator of the production of most acute phase proteins, such as CRP and LBP. Thus, IL-6 is a potential marker for the early phase of infection.

It is suggested that determination of several biomarkers, or a panel of biomarkers, may improve their predictive value[16-20], but clinical evidence for this notion is scarce.[16-20] Also, differences in the plasma concentrations between, e.g., viral and bacterial infection groups are frequently reported, while the discriminating power for the individual patient remains unclear. Therefore, in the present study we assessed whether combination of the most commonly used biomarker CRP with LBP, PCT, IL-6, IL-18, or sTREM-1 can improve the discriminating ability in patients with a proven bacterial or viral LRTI.

Materials and methods

Study design

This study was a prospective single centre study, performed at the emergency department (ED) of a 953-bed university hospital in the Netherlands between November 2006 and May 2007. During the study, medical policy at the ED and the nursing wards was based on the standard basic clinical chemistry test results, in combination with a physical and additional examination depending on the clinical suspicion, and not on the results of the novel inflammatory markers described in this manuscript. Prior to the conduct of this study, the local Medical Ethics Committee was informed. Although they waived the need for a written informed consent, patients were informed about the study and the acquisition of supplementary plasma.

Study population

The study inclusion criteria were:

1) Patients (≥16 years old) visiting the ED because of a suspected infection, who had at least two of the following clinical signs of sepsis: temperature >38.3˚C or <36˚C, heart rate >90/min, respiratory rate >20/min, chills, altered mental status, systolic blood pressure <90 mmHg, mean arterial pressure <65 mmHg, hyperglycemia (plasma glucose >6.8 mmol/L) in the absence of diabetes mellitus[21];

2) Signs of a LRTI: fever, cough with or without sputum, chest pain, dyspnoea, and altered breath sounds on auscultation, and/or the presence of an infiltrate on chest X-ray;

3) Patients with a microbiologically confirmed bacterial or viral infection. Since the primary goal of this study was not to differentiate between patients with or without infection, but to establish the value of biomarkers in discriminating between bacterial and viral LRTI, we deliberately selected only patients with a microbiologically confirmed bacterial or viral infection.

Data collection

Cultures from sputum and blood, PCR on nose and throat swabs, antigen tests and serology were used to establish a diagnosis. Blood samples were taken for basic clinical chemistry tests and the measurements of the inflammatory mediators. Two blood cultures for microbiological testing were performed. Only CRP results were known to the attending physician. Blood was collected into two 3 ml lithium-heparin coated tubes for PCT, IL-6, LBP, sTREM-1, IL-18, and for basic clinical chemistry tests including CRP. Plasma was obtained by centrifugation of the blood at 4˚C with 2000 rpm for 15 minutes after which the plasma was frozen at -80˚C until measurements took place. CRP was measured by use of the Abbott

Aeroset® (Abbott Diagnostics, Chicago, USA) with a lower detection limit of 5 mg/L. PCT was measured by use of the Kryptor PCT® (Brahms, Hennigsdorf, Germany) with a detection limit of 0.02 µg/L. IL-6 and LBP were measured by use of the Immulite 2500® (Siemens, Breda, The Netherlands) with a lower detection limit of 2 pg/ml and 1.2 µg/ml, respectively. Circulating IL-18 levels were measured using a commercial Luminex assay (BioRad, Hercules, USA) with a lower detection limit of 15 pg/ml. Circulating sTREM-1 was assessed by a commercial ELISA kit (R&D Systems, Minneapolis, USA), according to the instructions of the manufacturer with a lower detection limit of 62.5 pg/ml.

Statistical analysis

Data are expressed as medians with interquartile range. The Mann-Whitney U-test was used to determine the difference of each marker between the two groups of patients. Receiver operating characteristics (ROC) curve statistics were applied for each single marker. Logistic regression analysis was used to estimate the predicted probabilities for CRP alone and in a model with CRP in combination with one of the other five biomarkers. These data were used for the generation of ROC curves. The area under the ROC curves (AUC) for the five possible combinations of CRP with one other biomarker was compared with the AUC for CRP alone. The method described by Hanley and McNeil was used for comparing the AUC.[22] As very high CRP values are highly specific for bacterial infections[23] and no additional biomarkers are needed, we additionally analyzed the combination of markers in the subgroup of patients with a moderately increased CRP that may benefit the most from panel analysis. Therefore, the cut-off value for CRP leading to a specificity >95% for a bacterial LRTI (at the top end of CRP values) was determined. Next, a ROC curve for CRP with one other biomarker was constructed in a similar way as described above for the subgroup of patients with a CRP below this cut-off value. All tests were two-sided, and $p<0.05$ was considered statistically significant. Data were analyzed using SPSS 18 for windows (SPSS Inc., Chicago, IL, USA) and MedCalc version 11.3.1.0 (MedCalc Software, Mariakerke, Belgium).

Results

A total of 342 patients with a suspected infection and ≥2 clinical signs of sepsis were admitted to the ED. Of these patients, 123 had a pulmonary focus for infection of whom 58 had a microbiologically confirmed LRTI. Two patients were excluded because of a fungal infection (*Pneumocystis jirovecii)*. Finally, we included 39 patients with a bacterial LRTI and 17 patients with a viral LRTI for further analysis. No patients with both a bacterial and a viral infection were diagnosed.

With the number of patients included, this study has 80% power to pick up an increase of the AUC of 10% in the whole group and an increase of the AUC of 20% in the subgroup of patients with a CRP concentration <150 mg/L.

The demographic and clinical parameters of the two groups are shown in *Table 1*. Table 2 shows the microbiological data.

Table 1. *Patient characteristics*

Variable	Bacterial infection (n=39)	Viral infection (n=17)
Patient characteristics		
Gender, % male	69	47
Age, years [median (IQR)]	60 (50-70)	54 (32-63)
Number of SIRS criteria [median (IQR)]	2 (2-3)	2 (2-3)
Patients admitted to nursing ward or ICU [n (%)]	35 (90)	16 (94)
Length of hospital stay, days [median (IQR)]	8 (5-20)	7 (3-18)
In-hospital mortality rate [n (%)]	2 (5%)	-
Bacteremia [n (%)]	11 (28%)	-

SIRS = systemic inflammatory response syndrome; IQR = interquartile range; ICU = intensive care unit

Table 2. *Isolated microorganisms*

Bacterial infection (n=39)		Viral infection (n=17)	
Streptococcus pneumoniae	10	Influenza A	5
Coxiella burnetii	9	Influenza B	4
Haemophilus influenzae	6	Respiratory syncytial virus	1
Mycoplasma pneumoniae	3	Metapneumovirus	1
Pseudomonas aeruginosa	3	Parainfluenza virus	3
Staphylococcus aureus	1	Influenza A + respiratory syncytial virus	2
Legionella pneumophila	1	Picornavirus + rhinovirus	1
Citrobacter freundii	1		
Corynebacterium propiquum	1		
Escherichia coli	1		
Streptococcus pneumoniae + *Moraxella catarrhalis*	1		
Haemophilus influenzae + *Pseudomonas aeruginosa*	1		
Staphylococcus aureus + *Streptococcus pneumoniae*	1		

CRP, IL-6, LBP, PCT, and sTREM-1 were significantly higher in the bacterial group compared with the viral group. IL-18 did not differ between the bacterial and the viral group (*Figure 1*).

The ROC for CRP had an AUC of 0.82 (95% CI: 0.70-0.93). The other biomarkers did not have a larger AUC. The combination of CRP with any of the other markers had no significant effect on the AUC compared with CRP alone (*Table 3*).

Table 3. *Area under the curve (AUC) for diagnosing bacterial lower respiratory tract infection of C-reactive protein (CRP) and CRP in combination with other markers (n=56). P-value for the comparison with the AUC for CRP*

Marker	AUC	(95% CI)	*p*-value
CRP	0.82	(0.70-0.93)	
CRP + IL-6	0.84	(0.74-0.95)	0.8
CRP + LBP	0.85	(0.74-0.95)	0.7
CRP + PCT	0.84	(0.73-0.95)	0.7
CRP + IL-18	0.82	(0.70-0.93)	0.6
CRP + sTREM-1	0.83	(0.72-0.94)	0.9

IL-6 = interleukin-6; LBP = lipopolysaccharide binding protein; PCT = procalcitonin; IL-18 = interleukin-18; sTREM-1 = soluble triggering receptor expressed on myeloid cells-1

For CRP, a level of >150 mg/L was highly specific for a bacterial infection (95% CI: 0.80-1.0). However, only 49% (n=19) (95% CI: 0.32-0.65) of the patients with a bacterial LRTI had concentrations >150 mg/L. In the lower range, considerable overlap of CRP concentrations existed between patients with viral (n=17) and bacterial infections (n=20), which had a negative impact on the specificity of the test and impeded the generation of a cut-off value with an acceptable specificity for viral LRTI.

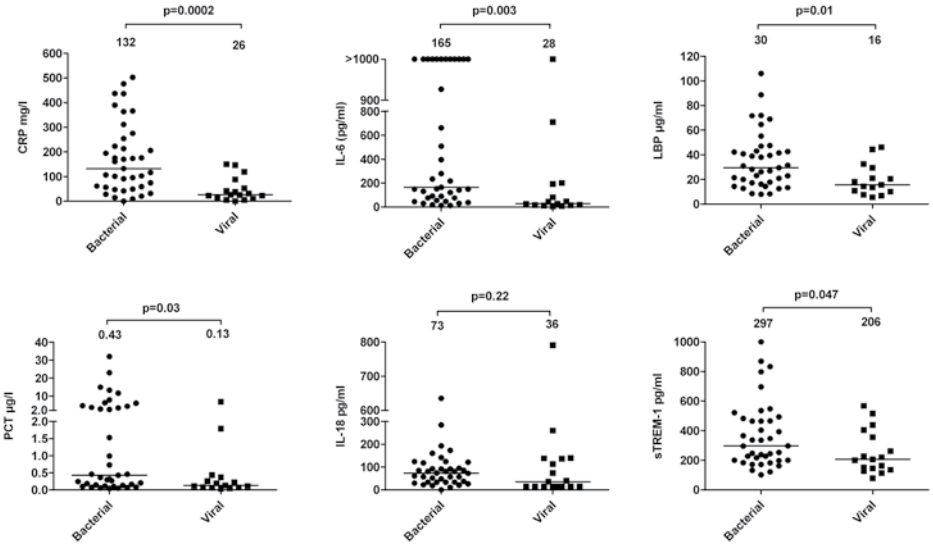
Apart from the patients with a bacterial infection and a CRP >150 mg/L (highly specific for bacterial LRTI), the combination of the CRP-value with any one of the other biomarkers in the remaining patients with a CRP <150 mg/L (n=37) did not increase the AUC to discriminate between a viral and bacterial LRTI in this subgroup of patients (*Table 4*).

Table 4. *Area under the curve (AUC) for diagnosing bacterial lower respiratory tract infection of C-reactive protein (CRP) and CRP in combination with other markers of patients with a CRP <150 mg/L (n=37). P-value for the comparison with the AUC for CRP*

Marker	AUC	(95% CI)	*p*-value
CRP	0.64	(0.45-0.84)	
CRP + IL-6	0.70	(0.53-0.88)	0.8
CRP + LBP	0.68	(0.50-0.86)	0.9
CRP + PCT	0.69	(0.50-0.88)	0.7
CRP + IL-18	0.62	(0.43-0.81)	0.7
CRP + sTREM-1	0.64	(0.46-0.83)	1.0

IL-6 = interleukin-6; LBP = lipopolysaccharide binding protein; PCT = procalcitonin; IL-18 = interleukin-18; sTREM-1 = soluble triggering receptor expressed on myeloid cells-1

Figure 1. *Plasma concentrations of C-reactive protein (CRP), interleukin-6 (IL-6), lipopolysaccharide binding protein (LBP), procalcitonin (PCT), interleukin-18 (IL-18), and soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) in patients with viral lower respiratory tract infection (LRTI) compared with LRTI of bacterial origin (n=56). Horizontal bars represent medians of the concentrations; the median is reported above the scatter plots in the different figures*



Discussion

The main finding of the present study is that while several inflammatory markers are significantly different between a group of bacterial and viral LRTI patients, addition of these markers to CRP was not superior to CRP alone in discriminating between bacterial and viral LRTI in septic patients. CRP as a single biomarker is a useful parameter to suggest the bacterial etiology of an infection, since a concentration >150 mg/L is highly specific for a bacterial infection. However, lower concentrations of CRP are often observed during both viral and bacterial infections. Unfortunately, biomarker panel analysis in this subgroup of patients did not improve diagnostic accuracy of CRP either and are therefore not suitable to guide therapy for the individual patient.

Antibiotics are the cornerstone in the treatment of bacterial infections and early antibiotic administration has been a crucial part of the surviving sepsis campaign.[24] On the other hand, a dramatic increase in antibiotic resistance has emerged without the prospect of development of novel classes of antimicrobial agents.[4;25] Therefore, reduction of the unnecessary use of antibiotics is mandatory.

Unfortunately, symptoms and signs routinely used in the diagnosis of LRTI have limited value in predicting the requirement of antibiotic therapy.[23] As a consequence, a multitude of biomarkers gained a lot of attention in differentiating bacterial from viral infections and prognostication. Among these, CRP and PCT have found their way into daily practice.[5;6] LRTI caused by various classes of microorganism are characterized by different concentrations of PCT and CRP.[16;23;26;27] However, the high a-priori chance of having a bacterial infection[28;29], together with the considerable overlap between the biomarkers in the lower range, complicates the exclusion of a bacterial cause of an infection by the use of individual biomarkers.[16;23;29]

To overcome the problem with single marker analysis, some studies advocated panel analysis.[16-19;29;30] While some promising results have been reported[17;18], studies including only patients with LRTI found no relevant effects of combining markers on diagnostic accuracy.[16;19;29;30] We used the addition of a second biomarker to CRP to examine the discriminatory power of laboratory testing, both in the group as a whole and in a subgroup of patients with relatively moderately increased CRP levels that potentially would benefit most from this approach. In contrast with most previous studies, we included both proven bacterial and viral markers aimed at increasing the discriminative power. For example, IL-18 is a cytokine playing an important role in antiviral immunity[9-12], and was expected to be a sensitive marker for diagnosing viral infections, while other markers are mechanistically related to the immune response against bacterial infections.

Most biomarkers examined in previous studies are stimulated both by bacterial and viral pathogens, but reach higher values during bacterial invasion. Therefore, moderately increased concentrations of these biomarkers can be found in both categories. Combination of these bacterial markers may only be beneficial if they do not correlate well with each other. Furthermore, a potentially suitable biomarker for combination analysis in future studies should demonstrate increased levels during viral infections. Bystanders of viral replication or proteins released upon virus recognition may be reasonable candidates.

There are several limitations of this study. First, the sample size is relatively small, especially for the viral infection group, although our study had enough power to detect a clinically relevant difference between the single and panel analysis. Second, this was a subset analysis of a prospective study in patients with LRTI that had a microbiological diagnosis. For an explorative study, we deliberately included only patients with a confirmed diagnosis. Because of the outbreak of acute Q-fever in the Netherlands between 2007 and 2010 *Coxiella burnetii* infections represented a large part of the bacterial pathogens.

Patients with acute Q-fever are indistinguishable from other bacterial infection on clinical grounds.[31] Furthermore, in the present study the distribution of the inflammatory markers was not importantly influenced by the inclusion of acute Q-fever patients. Third, viral infections predispose to bacterial super infections and these cannot be ruled out in all patients diagnosed as having a viral LRTI. In most of the patients admitted to the hospital, because of the severity of illness, antibiotic treatment was initiated, making it difficult to determine in hindsight the presence or absence of a bacterial co-infection. Fourth, although the results of our study may be different in LRTI patients with <2 clinical signs of sepsis, in general practice the vast majority of patients with a LRTI fulfil ≥2 of these sepsis criteria and consequently satisfy the sepsis definition. Therefore, the results of our study apply to most patients presenting with signs of LRTI to the emergency department. Finally, a group of control patients with other types of non-infectious inflammatory reactions was not included in our cohort, as our primary aim was to investigate whether additional biomarkers could improve the differentiation between viral and bacterial LRTI and not to determine their value to establish the presence of an infection.

In conclusion, while different markers of inflammation show statistically significant higher levels in the group of patients with a bacterial infection compared to the patients with a viral LRTI, the combination of CRP with LBP, PCT, IL-6, IL-18, or sTREM-1 does not improve the prediction of microbiological etiology in patients with LRTI, when compared with CRP as a single marker. Ruling out a bacterial infection remains troublesome and future studies should aim to identify better diagnostic markers.

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Chapter 5

The effects of implementation of the Surviving Sepsis Campaign in the Netherlands

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Abstract

Background: To reduce unintentional and avoidable adverse events in patients in hospitals in the Netherlands, a patient safety agency (VMS) program was launched in 2008. Among the VMS topics, the program 'optimal therapy in severe sepsis', according to the international surviving sepsis campaign (SSC), aims to improve early diagnosis and treatment of sepsis to reduce sepsis mortality by 15% before the end of 2012.

Method: We analyzed compliance data submitted to the international SSC database from the Netherlands and compared these data with published international SSC results.

Results: Data of 863 patients, representing 6% of the international data (n=14,209), were used for analysis. In the Netherlands, the resuscitation bundle compliance improved significantly from 7% at baseline to 27% after 2 years (p=0.002). Internationally, the resuscitation bundle compliance increased significantly from 11% to 31% (p<0.001). In contrast with the international results (18% baseline, 36% after 2 years), the compliance with the management bundle did not improve (24% baseline, 25% after 2 years).

At baseline, hospital mortality was significantly higher compared with internationally (52% versus 37%; p=0.03) and decreased significantly from 52% at baseline to 35% after 2 years (p=0.049). In the Netherlands, the decrease in mortality was significantly more pronounced after implementation of the SSC (p<0.001).

Conclusions: In the Netherlands, following implementation of the SSC guidelines, compliance with the resuscitation bundle increased significantly, while compliance with the management bundle remained unaffected. This was associated with a significant improvement in hospital survival. In view of the VMS program and goals, further implementation of the SSC is warranted.

Introduction

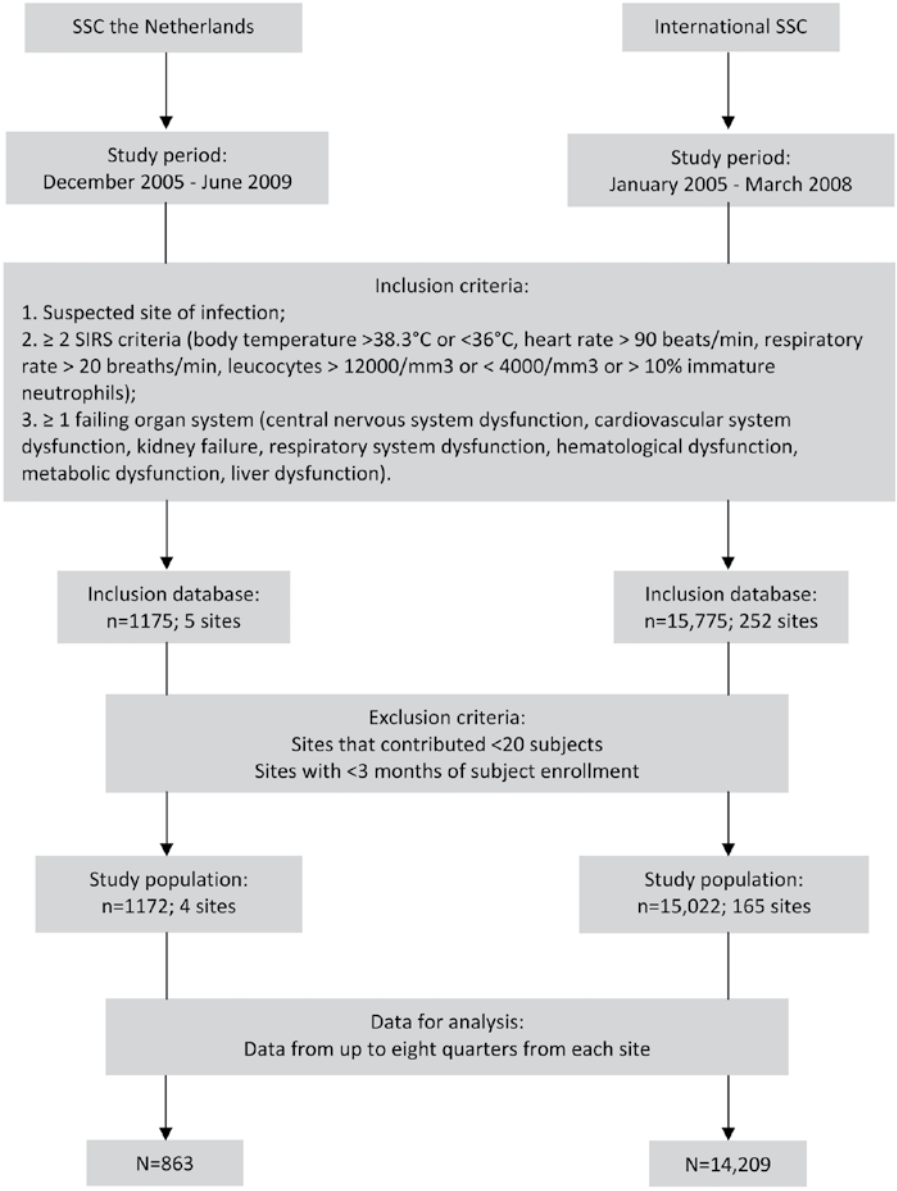
In the Netherlands, it is estimated that 15,500 patients with severe sepsis and 6000 patients suffering from septic shock are annually admitted to an intensive care unit (ICU).[1] With a mortality rate of 30% to 50% severe sepsis/septic shock is the most important cause of death in non-cardiac ICU patients.[2] To provide better guidelines to improve early diagnosis and treatment of severe sepsis and to reduce its mortality, the surviving sepsis campaign (SSC) was launched in 2002.[3;4] The most important SSC guideline recommendations are summarized into two bundles: the resuscitation bundle (six elements to start immediately and to be completed within 6 hours) and the management bundle (four elements to be completed within 24 hours), published in 2004.[3;5] Since then, the sepsis bundles have been adopted in ICUs[6-8], emergency departments[9-11], and nursing wards.[12-18]

In the Netherlands, a national committee and SSC website was established facilitating the possibilities to report bundle compliance and patient outcome to the international database. In addition, the Dutch association of hospitals (NVZ), Dutch Federation of University Medical Centres (NFU), Order of Medical Specialists (Order), National Expert Centre for Nursing (LEVV), and the Association for Nurses in the Netherlands (V&VN) initiated the national patient safety agency (VMS: www.vmszorg.nl). VMS aims to reduce the unintentional and avoidable damage in patients in Dutch hospitals by 50% by December 2012. Among other VMS topics, the early diagnosis and treatment of patients with severe sepsis are specific guideline items. The goal of the VMS is to increase compliance with the resuscitation bundle and management bundle elements to an average of 80% and to reduce both the in-hospital mortality and the mortality within 30 days after the diagnosis of severe sepsis by 15% compared with mortality data from 2007.

Recently, the results of the international guideline-based performance program were published.[12] Patient data and bundle performance data of 14,209 patients from 165 sites worldwide demonstrated that compliance with the SSC bundles was associated with continuous quality improvement in sepsis care and a sustained decrease in mortality.

The aim of our present study was to analyse the data submitted by hospitals in the Netherlands and to compare these results with the international SSC results.

Figure 1. *Study population: SSC database the Netherlands and the international SSC database*



SSC = surviving sepsis campaign

Materials and methods

Study design and population

Patient data and bundle compliance data were collected from December 2005 to June 2009. Inclusion criteria were adult patients (>18 years) admitted to emergency departments, clinical wards, and ICUs with a suspected or proven infection, ≥2 systematic inflammatory response syndrome (SIRS) criteria, and ≥1 failing organ system.[11;18] Participating sites that included ≤20 patients and sites with <3 months of patient enrolment were excluded for this study (*Figure 1*).

The global SSC improvement initiative was reviewed and approved by the Cooper University Hospital Institution Review Board. As patient data were obtained anonymously and no patient-related interventions were carried out, no additional approval from an Ethics Committee was necessary.

Table 1. *Patient characteristics: the Netherlands versus international*[12]

	Subjects, % the Netherlands (n=1172)	Subjects, % International (n=15,022)	*p*-value*
Admission			
From emergency department	28.2	52.4	<0.001
From other unit	57.8	34.8	<0.001
ICU with other diagnosis	14.1	12.8	-
Diagnosis			
Severe sepsis	24.1	28.5	0.001
Septic shock	75.9	71.5	0.001
Site of infection			
Pneumonia	47.2	44.4	-
Urinary tract infection	9.3	20.8	<0.001
Abdominal	36.5	21.1	<0.001
Meningitis	1.8	1.6	-
Skin	3.6	5.9	0.001
Bone	1.0	1.2	-
Wound	5.0	3.8	0.04
Catheter	3.7	4.1	-
Endocarditis	1.7	1.1	-
Device	1.0	1.1	-
Other infection	5.9	12.7	<0.001

*Significant differences between patient characteristics from the Netherlands and the international patient characteristics ($p<0.05$)
ICU = intensive care unit

Data collection and variables

The database used for this study was part of the international SSC database.[12] The relevant patient characteristics included department of admission (from emergency department, from other unit, or ICU with other diagnosis), site of infection, diagnosis, and hospital mortality (*Table 1*). In accordance to country-specific privacy laws, patient age and gender were not collected in the international SSC database and were therefore also not available for our study.

Performance data of the six resuscitation bundle elements and performance data of the four management bundle elements were collected (*Table 2*).

Table 2. *Compliance with the resuscitation and management bundle elements in the Netherlands: percentages per quarter (n=863)*

	Q 1[a] n=62	Q 2[a] n=97	Q 3[a] n=128	Q 4[a] n=117	Q 5[a] n=139	Q 6[a] n=127	Q 7[a] n=93	Q 8[a] n=100
Resuscitation bundle (n)								
1. Measure lactate (863)	71	77	69	76	75	79	86	79
2. Blood cultures before antibiotics (863)	60	52	58	66	58	63	56	70
3. Broad- spectrum antibiotics (863)	50	59	48	47	51	56	50	54
4. Fluids and vasopressors (785)	86	90	80	77	83	81	90	79
5. CVP >8 mm Hg (633)	45	55	55	39	50	54	58	58
6. Scvo2 >70% (629)	8	24	25	24	45	37	38	49
Completion of all resuscitation bundle elements (863)	7	12	13	15	18	21	19	27
Management bundle (n)								
1. Steroid policy (628)	63	82	75	77	73	81	86	91
2. Drotrecogin alfa policy followed (863)	73	62	54	50	46	60	57	72
3. Glucose control (863)	50	50	53	53	61	56	59	47
4. Plateau pressure control (634)	88	80	77	78	75	77	83	84
Completion of all management bundle elements (863)	24	17	20	16	17	26	22	25

[a]Represents each quarter of data submission from each institution during the 2-year data analysis period, regardless of total number of each institutions participation

The bundle element 'drotrecogin alfa policy followed' implies that each hospital has formulated his own drotrecogin alfa policy. If the policy is to treat patients with drotrecogin alfa, a patient that did not receive the drug is classified as not compliant. If the policy is not to administer drotrecogin alfa, and the drug is not given, this is viewed as compliant to the local policy.

If no formal policy is present, the patients that fulfil the criteria but did not receive the drug are scored as not compliant.

All data were organized by quarter, with the first 3 months that a site entered patient data into the database defined as the first quarter, regardless of when those months occurred. Data from up to eight quarters from each site were used to analyse bundle compliances (*Figure 1*). Furthermore, data from the initial quarter (first quarter of data submission from each institution during the 2-year data analysis period) and the final quarter (the last quarter of data submission from each institution during the 2-year data analysis period) were used to compare changes in compliance with the bundle elements between the initial quarter and the final quarter and to compare the data from the Netherlands with the international data.

Outcome measures

The primary outcome measure was change in compliance with the entire resuscitation bundle and management bundle, and change in the completion of the ten individual bundle elements. We included hospital mortality rate as secondary outcome measure.

Statistical analysis

Data are presented as percentages and odds ratios (ORs) with 95% confidence interval (95% CI). To analyse the differences in compliance rates between the quarters, both overall and for each of the ten separate elements, we used the Chi-squared test. In a similar way, we analysed the differences in compliance rates between the Netherlands and the international results. Due to the relatively small number of patients from the Netherlands, the Fisher's exact test was used to analyse the differences between bundle compliance in the initial quarter compared with the final quarter. To determine the effect of the SSC on the compliance rate of the bundles over the study period we used linear regression analysis. To analyse the impact of compliance with the individual bundle elements, a multivariate logistic regression analysis was performed. A two-tailed *p*-value <0.05 was considered statistically significant. Data were analysed using SPSS 16.01 (SPSS Inc., Chicago, IL, USA) and Graph Pad V 5.0 (Graph pad Prism software).

Results

Nationwide, 1172 patients from four different general hospitals were included in the SSC database (*Figure 1*). Internationally, 15,022 patients from 165 different sites were included. In contrast to the international data, where patients were most likely admitted to the ICU through the emergency department, most patients came to the ICU from the general nursing ward in the Netherlands. Furthermore, significantly more septic shock patients were included (*p*=0.001) and the sites of infection were not comparable with the international data (*Table 1*).

Since analysis of the bundle compliance was limited to the first 2 years of patient inclusion at each site, the compliance data of 863 patients, representing 6% of the international analysed data, were used for further analysis. For the international bundle compliance analysis, data of 14,209 patients were available (*Figure 1*).

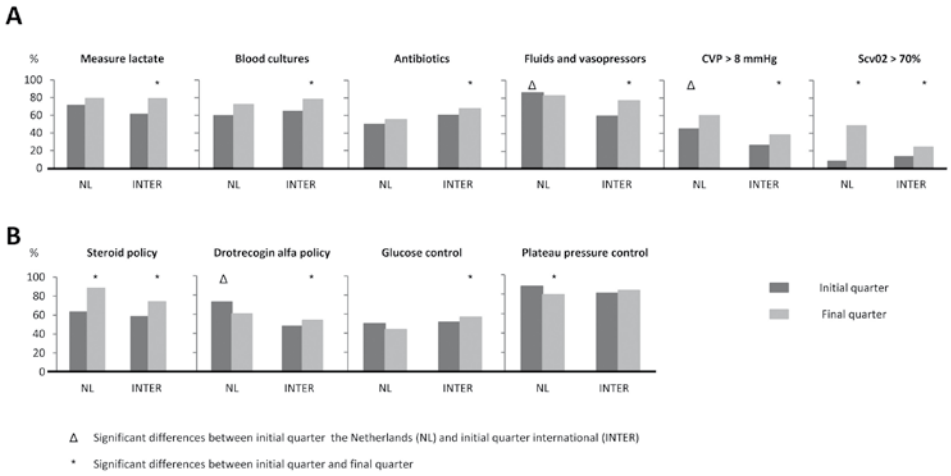
Change in bundle compliance

The compliance with the complete bundles and the individual bundle elements by quarter during 2 years in the Netherlands are represented in *Table 2*. During the first quarter, the compliance rate with the resuscitation bundle and management bundle was 7% and 24% respectively, compared with 11% and 18% internationally.[12]

Although in the initial quarter no significant differences in the overall bundle compliance rate between the Netherlands and the international bundle compliance rate were found (resuscitation bundle *p*=0.27; management bundle *p*=0.25), the compliance with three individual bundle elements ('administration

of fluids and vasopressors', 'achieving a CVP >8 mmHg', and 'drotrecogin alfa policy followed') was significantly higher (p<0.001) in the first quarter in the Netherlands (*Figure 2*).

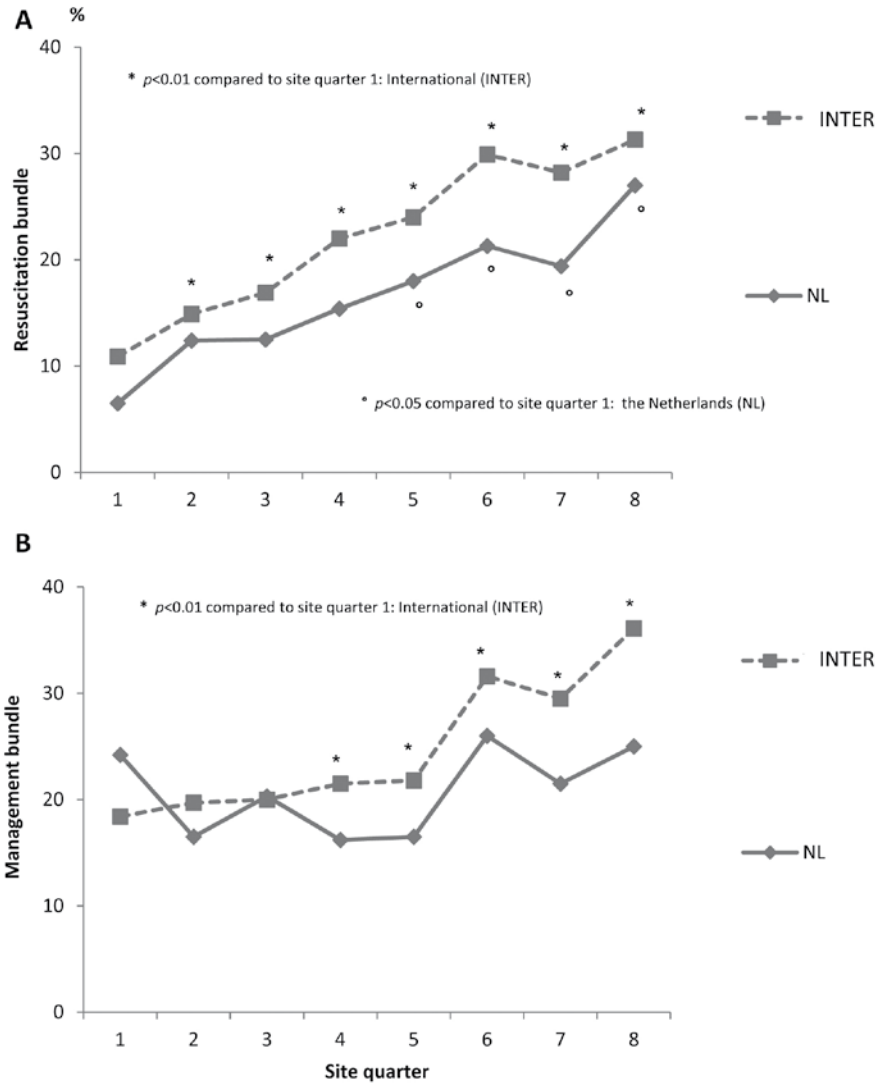
Figure 2. *Changes in compliance with the individual bundle elements in the initial quarter and the final quarter: results from the Netherlands versus the international results*[12]



In the Netherlands, the compliance rate with the complete resuscitation bundle improved significantly to 27% (p=0.002) by the end of 2 years, and statistically significant improvement was achieved by the fifth quarter (*Figure 3A*). Internationally, the compliance with the resuscitation bundle increased to 31% by the end of 2 years, achieving statistical significance (p<0.0001) by the second quarter (*Figure 3A*). For the management bundle no statistically significant differences in compliance rates between baseline and the end of 2 years were found in the Netherlands (*Figure 3B*), while internationally, the compliance with the management bundle significantly increased from 18% to 36% by the end of 2 years.[12]

Changes in compliance with the individual bundle elements between the initial quarter and the final quarter are presented in *Figure 2*. In the final quarter, a significant improvement in the completion of the individual resuscitation bundle element '$Scv0_2$ >70%' (8% to 48%; *Figure 2A*), and the management bundle element 'steroid policy' (63% to 88%; *Figure 2B*) was attained in the Netherlands. Internationally, the completion of all six resuscitation bundle elements and three out of four management bundle elements improved significantly.[12]

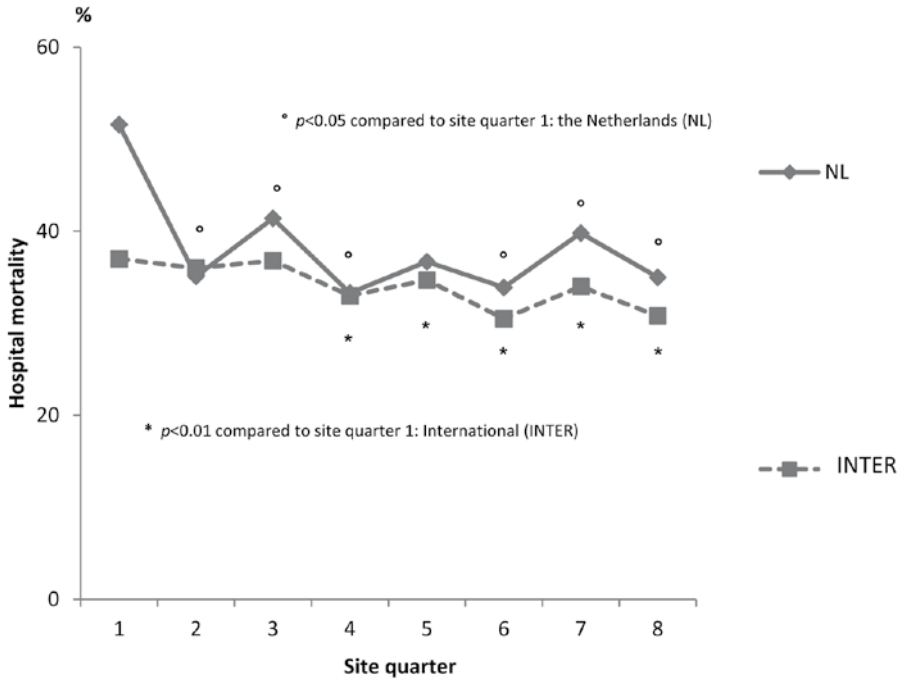
Figure 3. *Change in bundle compliance per quarter over 2 years of data collection: results from the Netherlands (n=863) versus the international results (n=14,209).*[12] *Compliance with the complete resuscitation bundle (**A**), compliance with the complete management bundle (**B**)*



Hospital mortality

Data from the Netherlands showed that the hospital mortality at baseline was 52% and significantly decreased by the end of 2 years to 35% (p<0.05). Internationally, the baseline hospital mortality was 37% and significantly decreased to 31% (*Figure 4*).[12]

Figure 4. *Change in hospital mortality per quarter over 2 years of data collection: results from the Netherlands (n=863) versus the international results (n=14,209)*[12]

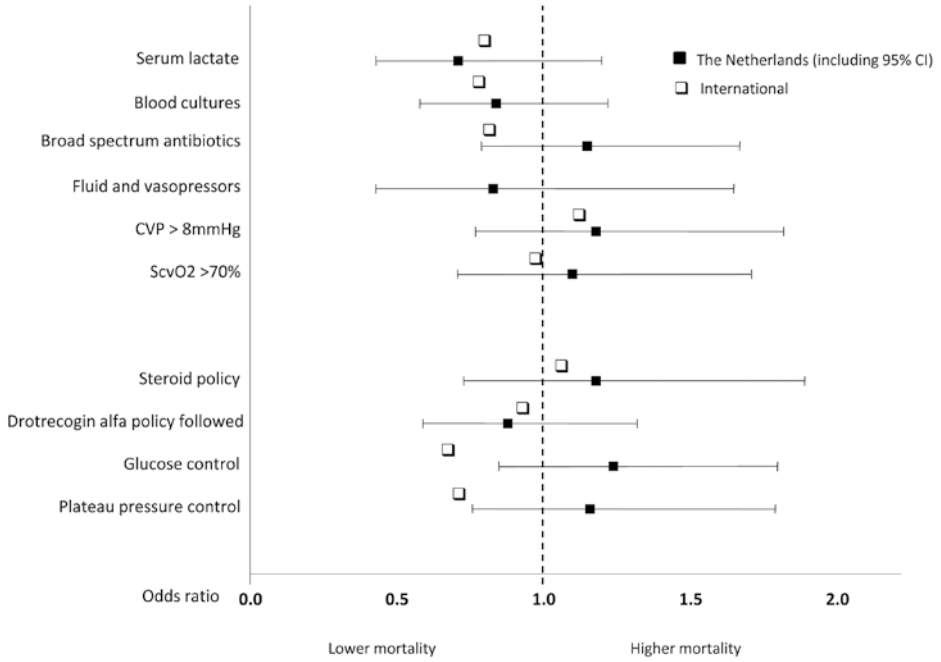


The hospital mortality at baseline was significantly higher in the Netherlands compared with the international hospital mortality (52% versus 37%; p=0.03) and the decrease in hospital mortality in the Netherlands was significantly more pronounced than the achieved decrease in hospital mortality in the international database: 17% versus 6% (p<0.001).

The impact of the individual bundle elements on the unadjusted hospital mortality is represented in *Figure 5*. In the Netherlands, the performance of four out of ten bundle elements contributed to a lower hospital mortality, whereas seven out of nine bundle elements contributed to a lower mortality internationally (the impact of the tenth bundle element 'fluids and vasopressors' on hospital mortality was not known). The beneficial impact of 'glucose control' and 'plateau pressure control' found internationally, was not confirmed in the data from the Netherlands as the 95% CIs do not include the international data point.

Independent of changes in time, of all patients who were treated in the Netherlands in compliance with the resuscitation bundle, mortality was borderline significantly lower (31% versus 39%, p=0.057) compared with the patients who were not.

Figure 5. *Impact of the individual bundle elements on the unadjusted hospital mortality: results from the Netherlands (n=863) versus the international results (n=14,209)*[12]



Discussion

The main finding of our study is that in the included hospitals in the Netherlands the compliance with the resuscitation bundle significantly improved by implementation of the SSC while, in contrast with the international results, the compliance with the management bundle did not improve. The hospital mortality decreased significantly after implementation of the SSC and compared with the international data, the hospital mortality in the Netherlands was significantly higher at baseline and decreased significantly more after implementation of the SSC.

Although the results of the implementation of the SSC bundles have been reported in several studies,[7;8;15;17] we feel it is of importance to report the compliance rates and outcome results of patients in the Netherlands. Our data demonstrate and confirm that focus on the SSC guidelines can improve the care for patients with sepsis in the Netherlands, and that indeed this is associated with a better survival for sepsis patients. Importantly, our study does not describe the effect of implementation of the SSC bundles in all hospitals and data were only collected until June 2009. Since then, it seems likely that the SSC bundles are implemented

in more Dutch hospitals and the bundle compliance further improved because of the performance of several local and national implementation programs related to the VMS safety program.

While the compliance with the resuscitation bundle improved significantly, compliance with the management bundle did not. The management bundle consists of therapies with proven efficacy in patients in the ICU.[3] The lack of improvement in therapies given in the ICU is a striking finding, especially since mainly intensivists are involved in the implementation efforts of the SSC guidelines. Therefore, the implementation of these therapies needs further attention.

Overall, and possibly against general belief, the complete adherence to the bundles was poor at baseline. Despite the implementation of the SSC bundles, the completion of all resuscitation bundle elements as well as all management bundle elements occurred only in approximately a quarter of all patients with severe sepsis and septic shock following implementation. Nevertheless, these results are comparable with international results.[6;7;12;20] In Spain, the implementation of the SSC bundles in 59 medical-surgical ICUs was associated with improved guideline compliance and lower hospital mortality. Compliance with the resuscitation bundle was only 13% at post-intervention and 7% during long-term follow-up. Compliance with the management bundle was 20% at post-intervention and 27% during long-term follow-up.[20] In other studies compliance varies from 4%[6] to 52%.[21]

So far, the cost-effectiveness of the implementation of the SSC bundles in the Netherlands is not known. In Spain, a significant reduction in mortality resulted in an increase in costs per patient of only 1736 Euros, mainly attributable to the increased length of stay.[22]

Several limitations of this study need to be addressed. At baseline, mortality was higher in patients in the Netherlands compared with the international database. Because of the significant differences in case mix (including a higher proportion of patients with septic shock, admitted from the ward, and differences in the site of infection) the relevance of this baseline difference in mortality is not clear. Since we had no access to individual patient data in the international database, adjustments could not be made. In addition, the methods used in other studies are not comparable with the methods used in our study and therefore it is not possible to benchmark the results from the Netherlands with the results from a country with a similar high baseline mortality. Nevertheless, the increase in bundle compliance associated with an improvement in mortality is paramount and in accordance with earlier studies.[7;8;12-14;20-25] The fact that most patients in the Netherlands came from the ward, while most international patients were admitted to the ICU by the emergency department, may be relevant for the initiation of the resuscitation bundle, as sepsis patients are more likely to be treated within

the time frames of the SSC bundles than ward patients. For example emergency department nurses can play a vital role in recognizing and managing patients with severe sepsis.[11]

Although the literature provides a large number of different strategies to implement innovations such as the SSC bundles, e.g., educational meetings, reminders, and feedback, not one of these implementation strategies seems to be superior to the other and most show mixed results.[9-11;15;26;27] Due to the relatively small number of included patients and different implementation strategies per hospital, we were unable to evaluate the effects of the applied implementation techniques on bundle compliance. Furthermore, the expanded attention to severe sepsis and septic shock, changes in hospital practice, changes on the level of the organization, or not SSC related implementation techniques may (also) have contributed to the changes in bundle compliance. Therefore, it is not possible to conclude which factors were (to what degree) responsible for the achieved improvement.

In conclusion, implementation of the SSC bundles and the compliance registration improved insight into the current quality of care for patients with severe sepsis and septic shock. Comparable with other regions of the world, there is room for improvement in the treatment of these patients in the Netherlands. Both national and international improvements in SSC compliance were associated with sustained, continuous quality improvement in sepsis care and better outcome of septic patients, although in an observational study a cause-effect relationship cannot be established.

Especially the lack of improvement of the compliance with the management bundle needs further attention. To achieve a higher SSC bundle compliance and better patient outcome in the Netherlands, sepsis education, repeated evaluation of the SSC bundle compliance, and participation in the VMS safety program is necessary.

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Chapter 6

Internal medicine residents' knowledge about sepsis: effects of a teaching intervention

The Netherlands Journal of Medicine, 2009, 67, 312-315

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P. Pickkers

Abstract

Background: The short- and long-term effects of a single teaching intervention for internal medicine residents are not known. Since sepsis is a prevalent and important disease and both therapeutic and diagnostic interventions have been protocolised, we investigated the effects of a sepsis based single teaching intervention.

Methods: A prospective before-and-after education study was performed among residents who attended a regional professional training for internal medicine. All residents who participated were invited to complete a questionnaire about the assessment of symptoms and the diagnosis and treatment of sepsis. The questionnaire was filled out before, directly after, and 4-6 months after the teaching intervention. The overall questionnaire score was expressed on a 0-10 scale.

Results: A total of 253 questionnaires from 109 training-grade doctors were collected. At baseline, the 'assessment of symptoms of sepsis' score was significantly lower than the 'diagnosis and treatment' score. Following the education session, training-grade doctors' knowledge about sepsis definitions and diagnosis and treatment of sepsis increased from (mean±SD) 6.1±1.6 to 8.2±1.2 (p<.0001). Moreover, 4-6 months after the teaching intervention, this effect was sustained (p<.0001 compared with test I), resulting in a mean score of 7.6±1.1.

Conclusions: Our single teaching intervention resulted in improved and sustained knowledge on the assessment of symptoms and diagnosis and treatment of sepsis.

Introduction

In 2004, the Central College of Medical Specialties (CCMS) of the Royal Dutch Medical Association presented guidelines for modernisation of all postgraduate speciality training programs and since 2006 all these programs should be based on these guidelines. To assess residents' competencies, several methods of evaluation can be applied.[1] Although the organised education for internal medicine residents is substantial, still little is known about its short- and long-term benefits.[2]

Over the last few years, several studies have shown that rapid diagnosis and management of sepsis is critical for successful treatment.[3-6] The surviving sepsis campaign (SSC) provides helpful tools to improve the diagnosis and management of sepsis, especially for patients with severe sepsis and septic shock. However, implementation of these guidelines in daily practice appears to be troublesome.[7-9] As a result, about 30% to 40% of patients do not receive care according to the present scientific evidence and about 20% to 25% of the care provided is not needed or potentially harmful.[10;11]

Use of the SSC tools may be hindered by a variety of barriers to guideline adherence: lack of familiarity, lack of awareness, lack of agreement, lack of outcome expectancy, lack of self-efficacy, lack of motivation/inertia of previous practice, and external barriers.[12] Previous studies have demonstrated that an important reason for not following the SSC guidelines is that the identification of patients with sepsis can be difficult, resulting in treatment delay.[13;14] Only about 30% of physicians correctly identified the diagnostic criteria for systemic inflammatory response syndrome (SIRS).[15] Even after active implementation of a sepsis teaching program, only 48% and 67% of the training-grade doctors could define severe sepsis and septic shock, respectively.[16]

Another reason for not following the SSC guidelines is the lack of knowledge about the management of patients with sepsis.[13;14] Therefore, extensive knowledge about sepsis is an important condition for early identification and management of patients with sepsis. In addition, none of the previous studies have evaluated the knowledge deficiency for different sepsis topics and the short- and long-term effectiveness of a teaching intervention aimed at improving physicians' knowledge about sepsis. We performed the present study in which the potential variety in residents' knowledge about the identification and management of sepsis and the short- and long-term effectiveness of a brief and single teaching intervention were examined.

Materials and methods

Study design and population

We performed a prospective before-and-after education study among internal medicine residents who visited the regional professional training for internal medicine (RODIN) about sepsis. RODIN is part of the training program for internal medicine residents[17] and is organised five times a year at the Radboud University Nijmegen Medical Centre (RUNMC). RODIN is attended by residents from the RUNMC or one of the six affiliated regional community hospitals.

During a brief educational intervention based on the SSC guidelines, an internist-intensivist (PP) gave a lecture about the SSC, diagnosis, and the management of sepsis.

Development of the questionnaire

The questionnaire was based on the two topics of the SSC-based teaching intervention and included ten multiple choice questions: five questions covering assessment of the symptoms of sepsis (topic 1) and five questions about diagnosis and treatment of sepsis (topic 2). In the questionnaire, respondents were presented with short case descriptions. Examples of two questions are shown in *Table 1* (the complete questionnaire is available on request).

Data collection and variables

All data were collected in three periods: immediately before, 3 hours after the education session about sepsis, and 4-6 months following the teaching intervention. Before and directly after the lecture, the residents were asked to fill out the first two questionnaires. All respondents were approached by mail and asked to fill out the third questionnaire. Non-responders received two reminders, including the questionnaire, by e-mail. Relevant respondent characteristics included gender and year of training.

Statistical analysis

Descriptive statistics included frequencies, percentages, means, and standard deviations. All questions were given an equal weight of one point per question. The overall questionnaire score was expressed on a 0-10 scale. Potential differences in the total questionnaire scores between the three tests were analysed using a random-effects model with random-factor respondent and fixed-factor test.

In a secondary analysis, gender and year of experience were added as covariates to investigate whether gender and experience had an impact on the scores. Finally, we investigated whether these factors influenced the learning, by adding the interaction terms with the test to the model.

Table 1. *Questionnaire with five questions covering assessment of the symptoms of sepsis (topic 1) and five questions about diagnosis and treatment of sepsis (topic 2); examples of two questions*

Topic 1: Assessment of symptoms

Which of the following criteria are SIRS criteria?

- Temperature >38°C or <36°C, chills, heart rate >90 beats/min, respiratory rate >20 breaths/min, altered mental status, $PaCO_2$ <4.3 kPa (32 mmHg), white blood cell count >12x10^9/L, <4x10^9/L, or >10% immature (band)forms.
- Temperature >38°C or <36°C, heart rate >90 beats/min, respiratory rate >20 breaths/min, $PaCO_2$ <4.3 kPa (32 mmHg) or respiration, white blood cell count >12x10^9/L, <4x10^9/L, or >10% immature (band)forms.
- Temperature >38°C or <36°C, heart rate >90 beats/min, respiratory rate >20 breaths/min, $PaCO_2$ <4.3 kPa (32 mmHg), white blood cell count >12x10^9/L, <4x10^9/L, or >10% immature (band)forms, hyperglycemia in the absence of diabetes (glucose >6.8 mmol/L).

Topic 2: Diagnosis and treatment of sepsis

When patient's blood pressure and/or organ perfusion does not respond to fluid challenges, you have to start with vasopressor therapy. Which proposition(s) is/are correct?
Proposition I: In case of hypotension in patients with septic shock, norepinephrine or dopamine is first choice vasopressor therapy.
Proposition II: To offer protection to the kidneys, a low dose of dopamine can be used in the treatment of severe sepsis.

- Proposition I as well as proposition II are correct
- Proposition I is correct, proposition II is incorrect
- Proposition I is incorrect, proposition II is correct
- Proposition I and proposition II are both incorrect

Results

A total of 253 questionnaires were collected. Seven of these questionnaires were excluded: four questionnaires could not be linked to follow-up tests and three residents only filled out the questionnaire before or immediately after the education. We used 246 questionnaires for further analysis.

Respondents

A total of 109 internal medicine residents participated, 91 of whom (84%) completed the questionnaire before and immediately after the education. Of these participants 39% were male and 45% had >2 years training experience. The set of all three questionnaires was completed by 64 participants (70%), 33% were male and 42% had a training experience of >2 years.

Questionnaire data

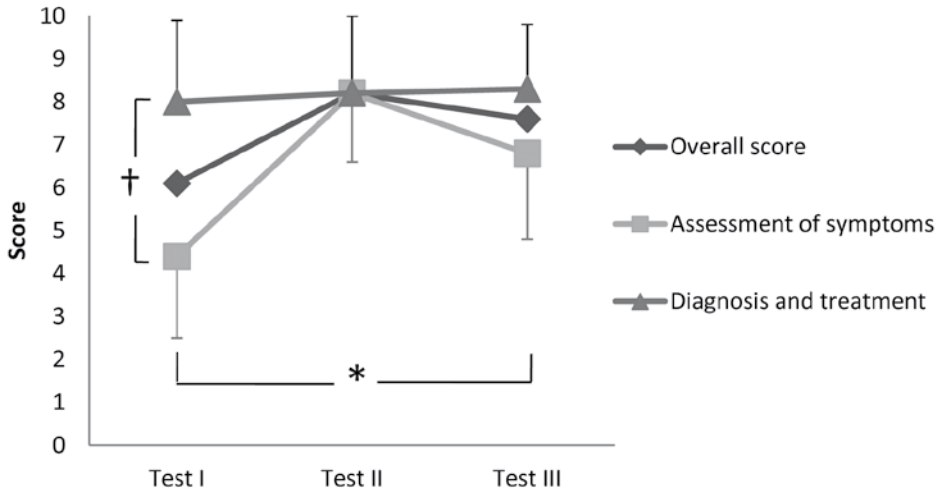
Figure 1 illustrates the mean overall questionnaire scores and the mean scores per topic for all participants in the study. At test I and test II the mean overall questionnaire scores are comparable with the mean scores of the 64 respondents who filled out all three questionnaires: 6.1±1.5 for test I and 8.3±1.1 for test II.

In the subgroup of residents who filled out all three questionnaires, the baseline score of 6.1±1.6 increased to 8.2±1.2 after the lecture (p<.0001). Moreover, 4-6 months after the teaching intervention this improvement was sustained (p<.0001 compared with test I), resulting in a mean score of 7.6±1.1.

At baseline, questions concerning 'diagnosis and treatment' scored significantly better than 'assessment of symptoms' (*Figure 1*). As a result, only the score of 'assessment of symptoms' improved significantly (p<.0001).

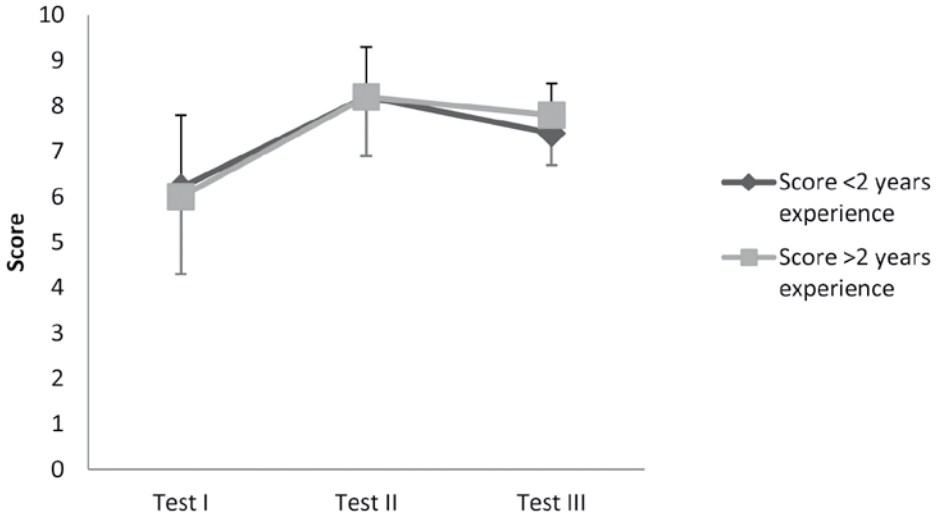
There were no significant differences between male and female residents in baseline score (data not shown). The mean scores for the years of training experience are summarized in *Figure 2*. After adding gender and experience as covariates to the analysis, we found that there was no significant difference between scores or increase in score per gender or year of training (all p>0.05).

Figure 1. *Overall score per test and topic*



** Significant improvement between mean score for test I (6.1±1.6) versus mean score for test II (8.2±1.2), and test I versus test III (7.6±1.1), respectively (both p<0.0001)*
† Significant difference between mean score for assessment of symptoms (4.4±1.8) and diagnosis and treatment (8.0±1.9) at baseline (p<.0001)

Figure 2. *Scores per years of training experience*



Discussion

Identification of patients with sepsis is essential for early diagnosis and treatment. In managing sepsis, delays can be life-threatening.[3-5] Lack of adherence to recommended SSC guidelines is in part caused by lack of knowledge of these guidelines. Through the education of residents about the SSC guidelines, both diagnosis and treatment of sepsis may improve.[18]

We demonstrated that following an educational intervention about sepsis, residents' knowledge about assessment of symptoms of sepsis improved significantly. One of the main findings of this study is that apart from the short-term effects, the improved test results were sustained after 4-6 months. In the first (baseline) questionnaire, the issues relating to the symptoms of sepsis scored significantly lower than those related to the diagnosis and treatment. This might be related to the fact that the SIRS criteria described by Bone[19] demonstrate a high sensitivity, but low specificity for sepsis and may not equal the residents' clinical perception of a septic patient. Interestingly, a previous study showed that a majority of physicians believe that other physicians within their specialty define sepsis differently from themselves: not more than 17% agreed on any one definition.[20] This may explain why we found no association between years of experience and knowledge level at baseline or increase following an educational session. Importantly, only the Bone criteria are acknowledged and it remains important that everyone uses these sepsis definitions correctly. In addition, this finding emphasises our view that the effectiveness of educational activities and

progression of knowledge during the training of residents should be monitored more frequently and more closely.

The issues concerning the treatment of sepsis scored significantly higher at baseline, resulting in the fact that a further increase did not reach statistical significance.

Only a few previous studies have described physicians' and nurses' knowledge about sepsis.[14-16;20] In accordance with our study, these studies showed an inadequate level of knowledge of the signs and symptoms of sepsis. It was demonstrated in one study that knowledge levels increased over time, when a group of residents in 1999 were compared with a different group of residents in 2003.[16] However, it is unclear whether or not this effect is linked to an unidentified more active teaching program as mentioned by the authors, or by other unknown time-dependent factors.

A possible limitation of our study is the fact that we used a questionnaire that, although based on the SSC guidelines, was not formally validated. In addition, repeated use of the same questionnaire may have positively influenced the overall questionnaire score. However, this does not seem likely on account of the decreased overall score 4-6 months after the teaching intervention. Interestingly, compliance to the SSC guidelines in the emergency department significantly improved from 3.0 to 4.2 on a 0-6 scale (number of recommendations that were correctly performed). However, several other implementation strategies were conducted at the same time, and these results cannot be associated with the education of the residents alone.

Conclusion

Our teaching intervention resulted in a sustained improved knowledge on symptoms, diagnosis, and treatment of sepsis. Short- and long-term quantitative determinations concerning the efficiency of educational activities should be performed more often.

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Chapter 7

The role of nurses in the recognition and treatment of patients with sepsis in the emergency department: a prospective before-and-after intervention study

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Abstract

Background: In 2004, the surviving sepsis campaign (SSC), a global initiative to reduce mortality from sepsis, was launched. Although the SSC supplies tools to measure and improve the quality of care for patients with sepsis, effective implementation remains troublesome and no recommendations concerning the role of nurses are given.

Objectives: To determine the effects of a multifaceted implementation program including the introduction of a nurse-driven, care bundle based, sepsis protocol followed by training and performance feedback.

Design and setting: A prospective before-and-after intervention study conducted in the emergency department (ED) of a university hospital in the Netherlands.

Participants: Adult patients (≥16 years old) visiting the ED because of a known or suspected infection to whom ≥2 of the extended systemic inflammatory response syndrome (SIRS) criteria apply.

Methods: We measured compliance with six bundled SSC recommendations for early recognition and treatment of patients with sepsis: measure serum lactate within 6 hours, obtain two blood cultures before starting antibiotics, take a chest radiograph, take urine for urinalysis and culture, start antibiotics within 3 hours, and hospitalize or discharge the patient within 3 hours.

Results: A total of 825 patients were included in the study. Compliance with the complete bundle significantly improved from 3.5% at baseline to 12.4% after our entire implementation program was put in place. The completion of four of six individual elements improved significantly, namely: measure serum lactate (improved from 23% to 80%), take a chest radiograph (from 67% to 83%), take urine for urinalysis and culture (from 49% to 67%), and start antibiotics within 3 hours (from 38% to 56%). The mean number of performed bundle elements improved significantly from 3.0 elements at baseline to 4.2 elements after intervention [1.2; 95% confidence interval: 0.9-1.5].

Conclusions: Early recognition of sepsis in patients presenting to the ED and compliance with SSC recommendations significantly improved after the introduction of a predominantly nurse-driven, care bundle based, sepsis protocol followed by training and performance feedback.

Introduction

Approximately 2% of all hospitalized patients are diagnosed with severe sepsis or septic shock. Intensive care and the long recovery period for patients with sepsis come with considerable costs, and the mortality rate remains high: 30%-40% for patients with severe sepsis and 40%-50% for those with septic shock.[1-3] Rapid diagnosis and management of sepsis are crucial for successful treatment[4]; early goal-directed therapy and antibiotic treatment within 3 hours after admission have proven their value.[5;6]

In 2004, the surviving sepsis campaign (SSC) was launched by the European Society of Intensive Care Medicine, the International Sepsis Forum, and the Society of Critical Care Medicine. The SSC is a global initiative to create an international effort to improve the treatment of sepsis and reduce sepsis mortality. The SSC provides helpful tools and implementation techniques for improving rapid diagnosis and management of sepsis and for measuring and improving the quality of care for patients with sepsis. The most important SSC recommendations are summarized in '6-hours' and '24-hours' bundles, also referred to as the resuscitation and management bundles.[2]

A bundle is a group of three to six care elements related to a disease process. When executed together, the performance of the care elements produce better outcomes then when implemented individually. The individual bundle elements are built on evidence based practice guidelines and provide health care workers with a practical method for implementing evidence-based practice.[7-9] According to the institute for health care improvement (IHI), the creator of the bundle, a bundle should be small and straightforward. The impact of a bundle depends both on the evidence that supports the recommended care process and on the implementation and spread of its recommendations.[10] Various care bundles have been created, including the ventilator care bundle, the central line bundle, and the sepsis bundle.

Although the SSC recommendations, described in the sepsis bundle, focus on those patients with severe sepsis or septic shock, all patients with sepsis need to be screened so that we can recognize those most affected. Since most patients with sepsis present themselves at the emergency department (ED), this department is an important location for early recognition and treatment of sepsis.[11-13] However, implementation of the SSC recommendations at the ED appears to be difficult; the overall level of compliance to the bundle and the compliance to the individual elements remains low.[14-16]

The literature provides a large number of different strategies to implement innovations like the SSC recommendations, e.g., educational meetings, reminders, and audit and feedback. Many studies have assessed the effectiveness of these

strategies for improving patient care and many reviews have summarized them; for example the numerous reviews listed by the Cochrane Effective Practice and Organisation of Care group (http://www.mrw.interscience.wiley.com/cochrane/cochrane_clsysrev_crglist_fs.html). In general, evidence shows that none of these strategies is superior; most show mixed results. Substantial evidence suggests that successful implementation strategies should be based on obstacles and facilitators to change.[17-19]

Various obstacles and facilitators may influence successful implementation of the SSC recommendations. Nurses are often the first to triage a patient, and they have an important role in recognizing patients' signs and symptoms. Nevertheless, the role of nurses is not formalized in guidelines and is not fully exploited at this time.[20;21] In daily practice, a multidisciplinary protocol for patients with sepsis proved to facilitate the recognition and treatment of sepsis.[22-24] However, recognizing patients with sepsis can be difficult; lack of detailed knowledge was shown to impair the recognition.[25;26] For example, only about 20% of the nurses thought that a temperature <36°C or a low white blood cell count could be a sign of sepsis.[26]

Using this information on obstacles and facilitators, we developed an implementation program to implement the SSC recommendations in our ED. As nurses are important in the triage of patients presenting to the ED, we specifically focused on nurses and their role in the recognition and treatment of patients with sepsis. To improve nurses' ability to recognize sepsis and SSC-recommended care, we introduced a care bundle based sepsis protocol and trained ED nurses about the signs and symptoms of sepsis. During the development of the implementation program, it turned out that insight into the performance of the sepsis bundle and the individual elements by the ED nurses was lacking. Therefore, feedback about their performance was part of the implementation program.

The aim of the current study was to determine the effects of our implementation program for following SSC-based recommendations.

Methods

We conducted a prospective before-and-after intervention study in which we carried out two consecutive interventions: the use of a newly developed, nurse-driven, care bundle based, sepsis protocol (intervention 1) and training about sepsis that included feedback about performance before and after the sepsis protocol was introduced (intervention 2).

The study consisted of three dense measurement periods:

Period 1: Before using the new care bundle based sepsis protocol (July 1, 2006 - November 6, 2006);

Period 2: After the sepsis protocol was put to use (November 6, 2006 - June 25, 2007) and before training and performance feedback;

Period 3: After training and performance feedback (June 25, 2007 - October 1, 2007).

In most implementation programs, it is not possible to disentangle the separate effects of the various implementation activities.[19] The two consecutive interventions were followed by measurement periods, so that we could measure the effects of introducing a protocol and the additional effects of training and performance feedback.

Study setting and population

Every year, approximately 20,000 patients visit the ED of a 953-bed university hospital in the Netherlands, where 35 registered nurses are employed. The study inclusion criteria were: adult patients (≥16 years old) visiting the ED because of the presence of a known or suspected infection, to whom at least two of the following diagnostic criteria for systemic inflammation apply: temperature >38.3°C, temperature <36°C, heart rate >90/min, respiratory rate >20/min, chills, altered mental status, systolic blood pressure <90 mmHg, mean arterial pressure <65 mmHg, and hyperglycemia in the absence of diabetes mellitus.[5;27] Patient data were collected from July 1, 2006 until October 1, 2007.

Implementation program

The ED manager and three ED nurses (our 'contact nurses') were involved in the process of developing the implementation program.

Development of a care bundle based sepsis protocol

A sepsis protocol (hereafter referred to as 'protocol') for nurses and physicians in the ED was developed by a multidisciplinary team including an intensivist, ED internist, a surgeon, a medical microbiologist, a clinical pharmacist, ED nurses, and a nurse practitioner. Everybody involved was familiar with the hospital organization, organization of the ED, and the physicians and nurses working in the ED.[28;29] They developed a protocol, based on the SSC care bundle mechanism.[30-32] For the selection of the required bundle elements, two different levels of evidence were used: evidence-based practices described in the present sepsis guidelines[33-35], and expert opinion.

The content of the protocol was discussed with the ED manager and the three contact nurses. The nurses suggested including the hospitalization or discharge of the patient from the ED within 3 hours as an additional bundle element. The final protocol consisted of two parts: a sepsis screening list for nurses and a sepsis performance list, including seven bundle elements.

Sepsis screening list. The screening list was developed to help the nurses identify patients with sepsis. The nurses had to note any focus suspected of being infectious and the two or more systemic inflammatory response syndrome (SIRS) criteria on the screening list. Then the physician had to be informed of the identification of a patient with sepsis.

Sepsis performance list. To guide the nurses and physicians in the ED, we developed a list with seven relevant bundle elements. They were:

1. Measure the serum lactate concentration within 6 hours;
2. Obtain two blood cultures before starting antibiotics;
3. Make a chest radiograph;
4. Take a urine sample for urinalysis and culture;
5. Start antibiotics within 3 hours;
6. Volume resuscitation in case of serum lactate >4.0 mmol/L or hypotension;
7. Hospitalize or discharge the patient within 3 hours.

The nurses and physicians were expected to take elements 1-5 and 7 for all patients included in the protocol. Element 6 (volume resuscitation) was only necessary in case the included patient had a serum lactate >4.0 mmol/L or hypotension.

It was agreed that, after identifying a patient with sepsis, the responsible nurse should start immediately with obtaining blood for chemistry tests and culture, and urine for urinalysis and culture. Furthermore, prior to the implementation of the protocol, we agreed with our radiologists that, in patients included in the protocol, a chest radiograph would be performed without a physician's prescription. Finally, the nurses played an important role in timely obtaining the physician's prescription for antibiotic treatment.

To collect all data and for the general necessity of accurate registration of the performed elements, the nurses had to sign off the performed elements and note the time they were done on the performance list.

After it was fully developed and accepted by all those involved in sepsis care, the protocol was placed on the University Medical Centre (UMC) Intranet website, available to all UMC employees, to facilitate access to it.

Initiation of the sepsis protocol (intervention 1)

The new protocol was formally introduced during the change of duty in the ED on November 6, 2006. From that moment on, the protocol was available to the ED. In addition to the formal introduction, all the ED nurses received an e-mail message with instructions about how to use the screening and performance lists. They were emphatically asked to use the lists each time a patient met the inclusion criteria. If there were any questions, the nurse practitioner in the implementation team could be reached during office hours or by e-mail.

As part of this implementation strategy, the contact nurses were repeatedly requested to motivate and assist the other ED nurses in using the protocol. In the meantime, data collection was started. One of the contact nurses (LP) was frequently consulted about implementation issues, such as incomplete filled out screening and performance lists. The ED nurses' questions were answered personally or by e-mail.

Training and performance feedback (intervention 2)

Six months after initiation of the protocol, training began. Training about sepsis, and the presentation of feedback on performance data of periods 1 and 2, took place during a department meeting for all ED nurses on June 25, 2007. The training focused on sepsis, severe sepsis, septic shock, and the clinical importance of early recognition and treatment. Although they could not provide data to support this, the nurses presumed that their compliance to the bundle was already optimal at baseline. Therefore, the training also included performance feedback. Feedback about the group performance of the bundle elements in the first two periods was presented, as were changes in the performance of each element from the first to the second period. Feedback focused on the elements which the nurses and physicians were generally completing adequately and those that needed more attention. The aim of the presentation was to give the nurses a clear overview of their own practice and to encourage them to improve the diagnosis and management of sepsis. Further, the nurses' experience with applying the protocol in daily practice was evaluated by means of short interviews. Finally, to reach the whole group of nurses in the ED, all of them received the presentation by e-mail, and a poster was presented in the ED. Besides the group training and performance feedback intervention, the contact nurses and nurse practitioner gave regular feedback to the individual ED nurses on their use of the protocol.

To improve the physicians' knowledge about sepsis and the use of the protocol in the ED, the intensivist instructed every new group of ED residents every 2 months. This training started at the end of February 2007. A training program and a conference for medical residents were organized.[36]

Data collection and processing

Data collection included patient data and performance data. The data collection team consisted of a nurse practitioner, an undergraduate, and an internist.

Patient data

The relevant patient characteristics included gender, age, suspected focus of infection, and final documented diagnosis at the time of discharge from hospital. Information about the clinical end points included the length of the hospital stay and the in-hospital mortality rate. The baseline data were collected by retrospectively checking the diagnoses on the ED admission list for patients with sepsis. The required data (including the two or more diagnostic criteria for systemic inflammation) were collected from the clinical patient databases, medical records, and nursing records. The final documented diagnoses were obtained from medical discharge records. After use of the protocol was started, the data were prospectively collected from the screening and performance lists. Missing data were collected from the clinical patient databases, medical records, and nursing records. If, during the study period, a patient with sepsis was registered at the ED more than once, he/she was included in the study each time.

Although most of the patients with sepsis were triaged and included in the protocol by the nurses, some patients were erroneously not included in the protocol by them: the nurse did not recognize a patient with sepsis or forgot to fill out the screening and performance list. To compare the differences in the performance of the bundle elements between those patients included in the protocol by the nurses and those who were not, the patients who were not included in the protocol were still included in the study. To recover patients who were undeservedly not included in the protocol, we retrospectively checked the diagnoses against the ED admission list for patients with sepsis.

Performance data

The goal of the protocol was to improve and evaluate the care of the total group of patients with sepsis, and not only those with severe sepsis or septic shock. Since high serum lactate concentrations and/or hypotension only occurs in a small proportion of the patients with sepsis who present themselves at the ED, early goal-directed therapy was included as a bundle element in the protocol (element 6) but not included as a measure of protocol adherence for this study. Therefore, completion of six bundle elements and compliance with them were measured. Baseline performance data were collected from clinical patient databases, medical records, and nursing records. After use of the protocol was started, all data were collected from the performance lists. Missing data were collected from the clinical patient databases, medical records, and nursing records.

Data analysis

The primary outcome measure was compliance with the bundle of six elements and the completion of the individual elements. The theory behind care bundles is that when several evidence-based interventions are grouped together in a single protocol, it will improve patient outcome. Although the study was not powered to demonstrate a statistically significant effect on the clinical end points, we included the length of the hospital stay and the in-hospital mortality rate as secondary outcome measures.

Descriptive statistics regarding the performance of the bundle of six elements, the performance of the individual elements, length of hospital stay, and mortality rate included frequencies, percentages, medians, and means. The compliance was expressed as a percentage, and the compliance to the bundle was also expressed as the total number of elements that were correctly performed (on a 0-6 scale).

To analyze the differences in compliance between the measurements, both overall and for each of the six separate elements, we used a generalized linear model with a logarithmic link and Bernoulli distribution function. In our secondary, subgroup analysis, we added the impact of the nurses' triage in periods 2 and 3 as a cofactor.

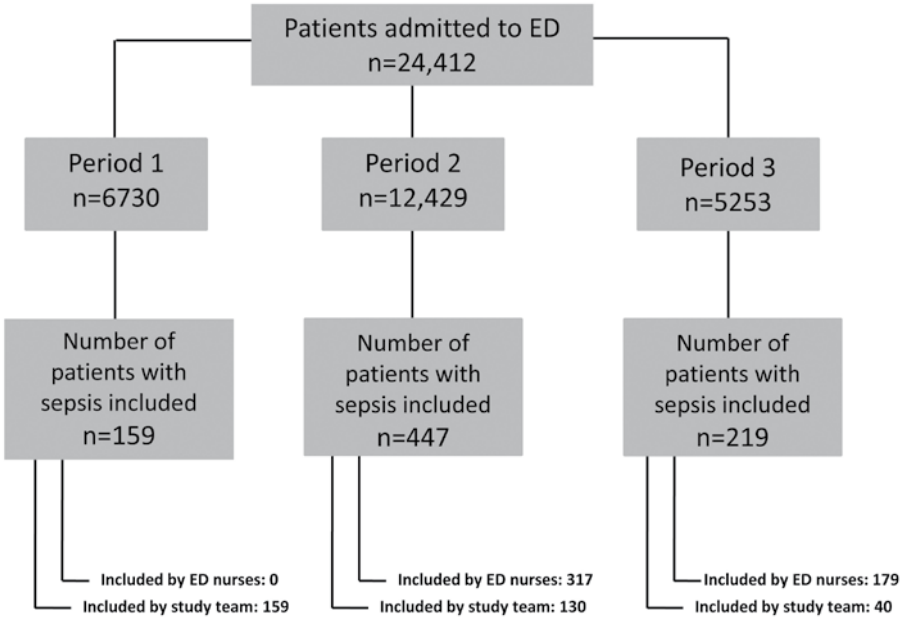
In a similar way, analysis of variance was used to compare the mean of the total number of times that the elements were correctly taken between baseline and the two post-intervention measurements. Each of many nurses treated several patients, which had to be accounted for in the statistical analysis. Therefore, we estimated the intraclass correlation coefficient, based on a mixed model analysis of the cases in which the nurse was known, and we used this coefficient to adjust the results of the analysis of variance of all data.

Results

Patient population

The study included 825 patients presenting with sepsis at the ED (*Figure 1*). There were no statistically significant differences in patient characteristics per period (*Table 1*). Eighty-nine percent of the participants were admitted to a nursing ward or intensive care unit. The ED nurses registered pneumonia and urogenital infection as the most commonly suspected infections. In 680 of the 825 cases (82%), the final diagnosis was a bacterial infection, most commonly in the lungs (33%), followed by urinary tract and/or genitalia infections (21%).

Figure 1. *Overall number of patients presenting to the ED during the study and patients with sepsis included per study period*



ED = emergency department

Table 1. *Characteristics of the patients (n=825)*

Variable	Period 1	Period 2	Period 3
Cases included (n)	**159**	**447**	**219**
Cases included by nurses	-	317	179
Cases with complete data set	-	269	162
Cases included by the researcher	159	130	40
Cases with complete data set	142	119	39
Gender (female)[a]	74 (47)	172 (39)	95 (43)
Age (years)[b]	55 (43-71)	60 (45-71)	59 (43-70)
Patients admitted to nursing ward or ICU[a]	135 (85)	405 (91)	189 (88)
Septic shock[a]	8 (5.0)	18 (4.0)	4 (1.8)
Length of hospital stay (days)[b]	6 (2-12)	7 (3-12)	6 (3-11)
In-hospital mortality rate[a]	10 (6.3)	27 (6.0)	12 (5.5)
Triage nurse's diagnosis in emergency department[a]			
Pneumonia		96 (21.5)	60 (27.4)
Urogenital infection		55 (12.3)	43 (19.6)
Wound infection		19 (4.3)	13 (5.9)
Abdominal infection		18 (4.0)	13 (5.9)
Circulatory system/catheter infection		9 (2.0)	5 (2.3)
Skin/soft tissue		7 (1.6)	6 (2.7)
Bone/joint		8 (1.8)	3 (1.4)
Implant/prosthesis infection		3 (.7)	3 (1.4)
Meningitis		3 (.7)	2 (.9)
Endocarditis		1 (.2)	-
Other/unknown focus		73 (16.3)	38 (17.4)
No clear diagnosis		208 (46.5)	64 (29.2)
Final confirmed diagnosis at discharge[a]			
Pulmonary	34 (21.4)	169 (37.8)	65 (29.7)
Urinary tract/genital	37 (23.3)	81 (18.1)	51 (23.3)
Skin/soft tissue	21 (13.2)	26 (5.8)	24 (11.0)
Abdominal	18 (11.3)	45 (10.1)	25 (11.4)
Circulatory system	7 (4.4)	16 (3.6)	9 (4.1)
Bone/joint	3 (1.9)	11 (2.5)	-
Cerebral	2 (1.3)	7 (1.6)	1 (.5)
Ear/nose/throat	4 (2.5)	6 (1.3)	5 (2.3)
Other focus	-	7 (1.6)	6 (2.7)
Diagnosis not related to infection	14 (8.8)	43 (9.6)	23 (10.5)
No final diagnosis reached	19 (11.9)	36 (8.1)	10 (4.6)

[a] Results expressed as number and (percentage)
[b] Results expressed as median and (interquartile range)
ICU = intensive care unit

Effects on performance of the bundle and the bundle elements

In 731 of 825 cases, information about all six elements was available. In 3.5% of the cases in period 1, all six elements were performed and improved significantly to 10.8% after period 2, and 12.4% after period 3 (*Table 2*).

Table 2. *The performance of the complete sepsis bundle and the six individual bundle elements at baseline (period 1), after introduction of the sepsis protocol (period 2), and after training and performance feedback (period 3) (n=731)*

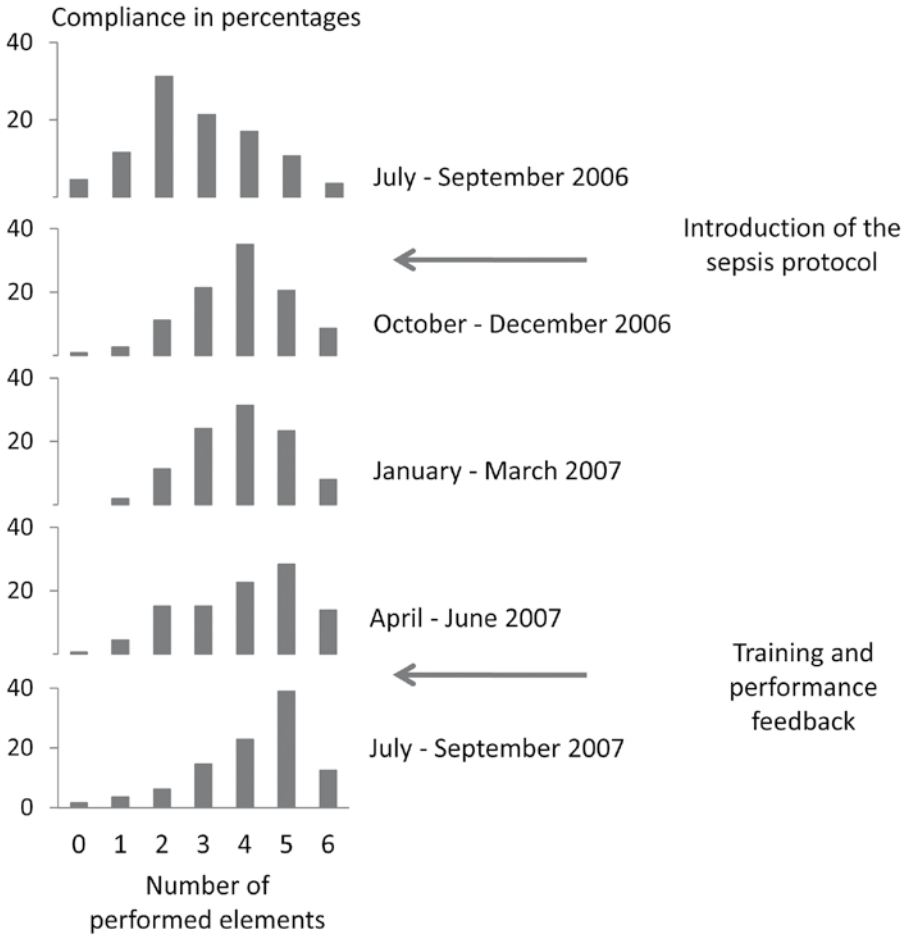
Variable	Usage in period 1 (n=142)	Usage in period 2 (n=388)	Relative incidence (95% CI)[a] of period 2 versus period 1	Usage in period 3 (n=201)	Relative incidence (95% CI)[a] of period 3 versus period 1
Performance of the complete sepsis bundle (all six elements)	3.5%	10.8%	3.1 (1.2-7.6)*	12.4%	3.6 (1.4-9.0)*
Measure lactate within 6 hours	22.6%	73.5%	2.9 (2.5-3.5)*	80.3%	3.9 (3.0-5.2)*
Take two blood cultures before start antibiotics	83.1%	78.6%	0.8 (0.5-1.2)	86.3%	1.2 (0.7-2.0)
Take a chest radiograph	67.3%	88.1%	2.8 (2.0-3.9)*	82.7%	1.9 (1.3-2.7)*
Take urine for urinalysis and culture	49.0%	54.6%	1.1 (0.9-1.3)	66.7%	1.5 (1.2-1.9)*
Start antibiotics within 3 hours	37.7%	49.6%	1.2 (1.1-1.4)*	55.9%	1.4 (1.2-1.7)*
Time from ED admission till administration of antibiotics[b]	2h 25 min (1h 35 min - 3h 0 min)	2h 5 min (1h 20 min - 3h 0 min)		1 h 45 min (1h 15 min - 2h 25 min)	
Admit or discharge patient within 3 hours	44.0%	46.2%	1.0 (0.9-1.2)	48.9%	1.1 (0.9-1.3)
Time from ED admission till admission to a nursing ward or discharge[b]	3h 12min (2h 25 min - 4h 20 min)	3h 15min (2h 25 min - 4h 10 min)		3h 5 min (2h 15 min - 4h 5 min)	

[a] Relative incidence (95% CI (confidence interval)) i.e. the ratio of the percentages (cases with complete data set)
[b] Results expressed as median (interquartile range)
* Significant differences

When analyzing the completion of the individual elements, there was a significant improvement in completing three of six elements after period 2 (*Table 2*), and there was a significant improvement in completing four of the six elements after period 3: measure serum lactate (improved from 23% to 80%), take a chest radiograph (from 67% to 83%), take urine for urinalysis and culture (from 49% to 67%), and start antibiotics within 3 hours (from 38% to 56%).

The mean number of performed bundle elements improved significantly in period 2 versus period 1 (from 3.0 to 3.9, 95% CI: 0.7-1.2) and further increased after period 3 (from 3.9 to 4.2, 95% CI: 0.03-0.5), as *Figure 2* shows.

Figure 2. *Nurses' compliance (%) in the performance of the protocol elements (0-6 elements correctly performed), every 3 months*



The outcome of the analysis of variance of all cases (n=825), is comparable to the outcomes of cases with complete data. Furthermore, no differences between the analysis of variance of all data and the analysis of only the cases for which the nurse was known were found.

Recognition of patients with sepsis

We examined whether patients were erroneously not included in the protocol by the nurses, and it turned out that in period 2, 71% of the cases were included in the protocol by the ED nurses and this percentage further improved to the inclusion of 82% patients with sepsis in period 3 (p=0.005).

Table 3. *Differences between cases included by the ED nurses and cases initially not included by ED nurses, at the level of the performance of the complete sepsis bundle and the six individual bundle elements (n=589)*

Variable	Cases included by ED nurses (n=431) n (%)	Cases initially not included by ED nurses (n=158) n (%)
Performance of the complete sepsis bundle (all six elements)	56 (13.0)	11 (7.0)
Measure lactate within 6 hours	374 (86.8)	75 (47.5)
Take two blood cultures before starting antibiotics	385 (89.3)	99 (62.7)
Take a chest radiograph	375 (87.0)	136 (86.1)
Take a urine sample for urinalysis and culture	280 (65.0)	62 (39.2)
Start antibiotics within 3 hours	241 (55.9)	56 (35.4)
Admit or discharge the patient within 3 hours	207 (48.0)	68 (43.0)

Patients with sepsis and complete data set noted after the start of the sepsis protocol
ED = emergency department

In the patients with sepsis that were erroneously not included in the protocol by the nurses, we also examined whether the compliance with the bundle elements was different. For 589 of the 666 cases included in periods 2 and 3, information about the completion of all six elements was available (88%). The subgroup analysis of the impact of the nurses' inclusion showed that the completion of the six elements in the cases that were included by the nurses was significantly better (1.2 elements more; 95% CI: 1.0-1.4) than the completion of the six elements in the cases that were afterwards included by the study team (*Table 3*).

Effects on the hospital mortality rate and length of hospital stay

The in-hospital mortality rate decreased from 6.3% in period 1 to 5.5% in period 3, which was not significant. The median [interquartile range] length of hospital stay did not change (6 [2-12] to 6 [3-11] days).

Discussion

Our study demonstrates that using a nurse-driven, care bundle based, sepsis protocol followed by training and performance feedback results in improved early recognition and treatment of patients with sepsis who present to the ED. The implementation program resulted in significant improvement of the compliance with the bundle (from 3.5% to 12.4%) and significant changes in four of the six individual elements. The process of obtaining two blood cultures before starting antibiotics did not improve significantly, probably because of the already good compliance at baseline. Further, the median time of hospitalization or discharge of the patient did not improve significantly.

We can improve the quality of care for patients with sepsis by using a relatively simple and inexpensive implementation program. Although care bundles can be a powerful stimulus to focusing the multidisciplinary team on working together to deliver reliable care, the development of a bundle is only one component in an overall improvement strategy.[10] To further improve the recognition of patients with sepsis and the performance of SSC-based recommendations in our ED, additional improvement activities are required.

Interestingly, subgroup analysis showed that compliance with the six bundle elements was significantly better in the cases that the nurses included than in the cases that they did not. This shows that recognizing sepsis with the use of the sepsis screening list alone resulted in better compliance with completion of the six elements. Without the list, some patients with sepsis were initially missed in the nurses' triage, but the attending physicians ultimately identified and treated them.

As nurses are often the first to see and triage a patient, in our view their position in the current organization structure should be exploited to a greater extent. Therefore, the role of the nurses in the development and implementation of the protocol was emphasized in our study. By giving the nurses a greater responsibility in the recognition and treatment of patients with sepsis, the care for these patients obtained a more multidisciplinary character and our study demonstrates that this was associated with an improvement of the quality of care.

In our study, the six bundle elements focused on all patients with sepsis. Most studies about implementation of the SSC bundles specifically focus on patients with severe sepsis and septic shock.[37-39] In our patient group, 3.6% had septic shock. We deliberately included all patients with sepsis because the bundle should be performed in all patients so that we can identify the most affected ones. In addition, the first step to reduce the mortality due to severe sepsis or septic shock is to prevent the progression of sepsis to severe sepsis and septic shock.[40] The early recognition and treatment of patients with sepsis will help achieve this prevention. Our study was not powered to identify a positive effect on patient outcome. However, hospital mortality was low in our patient group and tended to decrease during our study.

Previous studies describe the effects of implementation activities to improve sepsis diagnosis and treatment in the ED. Our results confirm those of a smaller study evaluating the effectiveness of a standardized, SSC-based, set of elements for managing sepsis in the ED of a university medical centre.[41] In this study, 60 patients with septic shock were included before implementation of the standardized set of elements and 60 patients afterwards, and ten process-of-care variables were evaluated. As in our study, formal clinical training was part of the implementation activities. Similarly to our study, several improvements

were reached, e.g., measurement of serum lactate improved from 17% to 78%. Contrary to Micek et al.'s study[41], our study focused on all patients with sepsis, not only on those with septic shock.

Our study is limited in being an uncontrolled study in only a single centre. Our implementation program was tailor-made to the situation of our hospital, so the results cannot be extrapolated. Theoretically it is possible that, in the course of time and based on the last evidence, diagnostic and therapeutic procedures change. Therefore, the possibility of a time effect, independently of our performed implementation strategies, cannot be excluded. However, no changes in hospital practice during the study that may have led to confounding were present, as local and national protocols and guidelines on the treatment of pneumonia, urinary tract infections, and sepsis remained unchanged during the study period.

The sepsis screening and performance list itself may have limitations. The clinical signs included in the sepsis screening list are very sensitive, but not very specific[34;42;43], which may have led to overdiagnosis and overtreatment. Of course this results in unnecessary treatment costs. However, unnecessary costs for a chest radiograph or a urine examination is probably outweighed by the high costs of treatment of patients with severe sepsis or septic shock or the consequences of missing a diagnosis of severe sepsis or septic shock. The fact that 82% of the patients were ultimately diagnosed with an infection indicates that not many patients who were false-positively found to have sepsis were unnecessarily treated with antibiotics. As only the physicians can prescribe antibiotic therapy, it remains the responsibility of the treating physician to decide whether to treat a patient with antibiotics, but better compliance with the bundle led to a more complete and appropriate work-up.

Conclusions

Our data suggest that the use of a predominantly nurse-driven, care bundle based, sepsis protocol combined with training and performance feedback can significantly improve the recognition of patients with sepsis at the ED and the taking of elements based on SSC recommendations for these patients. More attention should be given to the role of nurses in quality improvement of sepsis care. Our pilot study turned out to be both effective and feasible in a university hospital. Future research should aim at testing this promising implementation strategy in a multicenter controlled trial.

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Chapter 8

Non-adherence to antimicrobial treatment guidelines results in more broad-spectrum but not more appropriate therapy

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Abstract

Purpose: Mortality in patients admitted with sepsis is high and the increasing incidence of infections with multiresistant bacteria is a worldwide problem. Many hospitals have local antimicrobial guidelines to assure effective treatment and limit the use of broad-spectrum antibiotics, thereby reducing the selection of resistant bacteria.

We evaluated adherence to the antimicrobial treatment guidelines of our hospital in patients presenting to the emergency department (ED) with sepsis and assessed the *in vitro* susceptibility of isolated pathogens to the guideline-recommended treatment and the prescribed treatment.

Methods: We included all adult patients with a known or suspected infection and ≥2 extended systematic inflammatory response syndrome (SIRS) criteria. Patients who did not receive antimicrobial treatment, presented with infections not included in the guidelines, or had >1 possible focus of infection were excluded.

Results: A total of 276 ED visits (262 patients) were included. Guideline-concordant treatment was prescribed in 168 visits (61%). In case of guideline-disconcordant treatment, 87% was more broad-spectrum than guideline-recommended treatment. A microbiological diagnosis was established in 96 visits (35%). The susceptibility of the pathogens isolated from patients treated with guideline-concordant treatment (n=68) and guideline-disconcordant treatment (n=28) to guideline-recommended treatment (91% versus 89%) and to prescribed treatment (91% versus 93%) was similar (p=0.77 and p=0.79, respectively).

Conclusions: Non-adherence to the guidelines occurred frequently and resulted in more broad-spectrum empirical therapy. This did not result in a higher rate of susceptibility of the isolated pathogens to the prescribed empirical therapy.

Introduction

The mortality rate in patients admitted to the emergency department (ED) with severe sepsis and septic shock is high.[1;2] Early initiation of appropriate empirical antimicrobial therapy has been shown to improve survival in patients with sepsis and septic shock.[3-7] The choice of the empirical antimicrobial therapy in sepsis mainly depends on the suspected site of infection and the antimicrobial susceptibility of the expected pathogens. To include more resistant but often less prevalent pathogens, the empirical therapy of a severe infection is usually broad-spectrum.[4;8]

Antimicrobial treatment guidelines have been developed to assure effective treatment, decrease treatment diversity, prevent treatment delay, and reduce the unnecessary use of broad-spectrum antimicrobials, thereby reducing the selective pressure on antimicrobial resistance. Due to geographical differences in pathogens and antimicrobial susceptibility, many countries and hospitals have their own antimicrobial treatment guidelines based on local epidemiological data, existing literature, and expert opinion. Although many hospitals have implemented local antimicrobial treatment guidelines, there is a wide variation in the reported adherence to these guidelines.[5;8-10]

The local antimicrobial treatment guidelines in our hospital have been developed, adjusted, and evaluated over the years. The goal of our present study is to evaluate the adherence to these guidelines in patients admitted with sepsis and the *in vitro* susceptibility of the isolated pathogens to the treatment recommended in the guidelines. When the prescribed antimicrobial therapy deviated from the therapy advised in the guidelines, we compared the susceptibility of the isolated pathogens to the prescribed treatment and the treatment recommended in the guidelines.

Methods

Study setting

This is a retrospective cohort study of patients admitted with sepsis to the ED of the Radboud University Nijmegen Medical Centre, a 950-bed university hospital in the Netherlands. Every year, approximately 20,000 patients visit this ED, which is staffed by residents from the departments of internal medicine (including cardiology, pulmonology, hematology, general internal medicine, geriatrics, oncology, nephrology, gastroenterology and rheumatology), neurology, and surgery (including orthopedics, urology, and general surgery). Patients admitted to the ED are often referred by their general practitioner to a specific medical specialty, e.g., patients diagnosed with a pneumonia are not exclusively referred to pulmonology but also to other specialties of internal medicine.

All patients (≥16 years old) admitted to the ED between November 6, 2006 and May 9, 2007 with a known or suspected infection and at least two extended systemic inflammatory response syndrome (SIRS) criteria (temperature ≥38.3°C or <36°C, heart rate >90 bpm, respiratory rate >20/min, chills, altered mental status, systolic blood pressure <90 mmHg, mean arterial pressure <65 mmHg, and hyperglycemia in the absence of diabetes mellitus) were eligible for the study.[11] Patients were excluded if they were diagnosed with an infection not included in the local antimicrobial treatment guidelines, if they did not receive antimicrobial therapy, or if the physician considered >1 specific site of infection (the guidelines do not provide an antimicrobial policy for these situations).

Antimicrobial treatment guidelines

Over the years, the antibiotic committee of our hospital, including a pharmacist, a medical microbiologist, and several clinical specialists, have developed antimicrobial treatment guidelines for the most common types of infection. The first version of these guidelines was introduced more than 10 years ago as a booklet and was distributed among all clinicians throughout the hospital. Since then, many guideline revisions have been made. The latest editions of the guidelines have been available as an easily accessible and easy-to-use electronic version on the hospital intranet, available on every computer in the hospital, and a PDA version can be downloaded. *Table 1* represents a summary of the guideline recommendations during the study period.

Data collection

Patient demographics, clinical diagnosis with respect to site of infection, the prescribed antimicrobial therapy at the ED, the medical specialty of the prescribing physician, intensive care unit (ICU) admission within the first 24 hours, and length of stay were retrieved from the patient files. The all-cause 30-day mortality was assessed by chart review. When this follow-up was incomplete, the municipal administration and, when necessary, the general practitioner was consulted.

When the physical examination, laboratory results, and imaging results failed to identify a site of infection, the diagnosis was defined as sepsis of unknown origin. As the choice of therapy is based on the clinical diagnosis as well as factors such as where the infection is contracted (community, hospital, nursing home), previous adverse reactions on antimicrobial therapy, prior antimicrobial use, and culture results, the complete medical charts were reviewed for motivations for therapy adjustments in case of guideline-disconcordant treatment.[12]

Information about culture collection and culture results was retrieved from the laboratory information system. The clinical significance of culture results was assessed taking into account the clinical information and the quality of the

specimen. Bacteria isolated from blood or other sterile body sites were always considered to be significant, except when the isolate is known as a common skin contaminant. In addition, the clinical significance was evaluated by a microbiologist based on culture results, clinical diagnosis, and response to antimicrobial therapy.

Isolates from sputum were considered significant if the sputum sample had <10 squamous cells and >25 leukocytes per low-power field. In patients with a clinical diagnosis of urosepsis, bacteria in concentrations of $>10^5$/ml urine were considered to be significant in the presence of leukocyturia without significant epithelial cells. Clinical significance was evaluated from the patient file if bacterial counts were in the range 10^4-10^5/ml and in case of a monobacterial culture with bacteria $>10^5$/ml in the presence of leukocyturia and epithelial cells. In patients with a diagnosis of skin/wound infection, isolates of true pathogens such as beta-hemolytic streptococci or *Staphylococcus aureus* were considered to be significant, and the significance of Gram-negative bacteria was determined from investigation of the patient file.

Table 1. *Empirical antimicrobial treatment guideline recommendations for the most common infections*

Diagnosis	Guideline-recommended treatment
Urosepsis	Ceftriaxone 1 g every 24 hours after a 2 g loading dose
Recent antibiotic use[a]	Ceftazidime 1 g every 8 hours
Febrile neutropenia	Ceftazidime 2 g every 8 hours
Meningitis	Ceftriaxone 2 g every 12 hours
Listeria risk factors	Ceftriaxone 2g every 12 hours + amoxicillin 2 g every 4 hours
Sepsis of unknown origin	Ceftriaxone 2 g every 24 hours
Recent antibiotic use or hospitalisation[a]	Piperacillin-tazobactam 4.5 g every 8 hours
Cholangitis	Piperacillin 4 g every 8 hours
Skin or soft tissue infection	
Cellulitis	Flucloxacillin 1 g every 4 hours
Erysipelas	Penicillin 1 million UI every 6 hours or clindamycin 600 mg every 8 hours
Pneumonia[b]	
Mild	Doxycycline 100 mg every 24 hours after 200 mg loading dose OR amoxicillin 500 mg every 6 hours
Severe	Penicillin 1 million UI every 4 hours OR penicillin 1 million UI every 4 hours + ciprofloxacin 400 mg every 12 hours
Nursing home or recent antibiotic use[a]	Piperacillin-tazobactam 4.5 g every 8 hours
Aspiration pneumonia	Amoxicillin-clavulanic acid 1.2 g every 6 hours

[a] 'Recent' was not specifically defined in the guidelines
[b] Severity determined by the CURB-65 score: each risk factor scores 1 point: confusion, urea >7 mmol/L (19 mg/dL), respiratory rate ≥30/min, blood pressure systolic ≤90 mmHg and/or diastolic ≤60 mmHg, age 65 years or older
A pneumonia was considered to be mild when the score was 0-1 and severe when the score was ≥2

Guideline adherence

The prescribed antimicrobial therapy was divided into 'guideline-concordant treatment' and 'guideline-disconcordant treatment'. Guideline-concordant treatment was defined as antimicrobial therapy prescribed empirically in accordance with the clinical diagnosis at the ED and the antimicrobial treatment guideline. Complete medical charts were reviewed for motivations for therapy adjustments in case of guideline-disconcordant treatment. When physicians deviated from the guideline-recommended treatment with good motivation, such as the presence of a known allergy or previously cultured pathogens, the therapy was considered to be guideline-concordant.

Antimicrobial susceptibility

Based on the *in vitro* susceptibility results (using Clinical and Laboratory Standards Institute [CLSI] breakpoints) of the isolated pathogens, we evaluated the appropriateness of the guideline-recommended treatment as well as the prescribed therapy. Pathogens were considered resistant to antimicrobial therapy when at least one of the isolated microorganisms categorized as a relevant pathogen was tested resistant by routine *in vitro* susceptibility testing or was intrinsically resistant to the antimicrobial therapy.

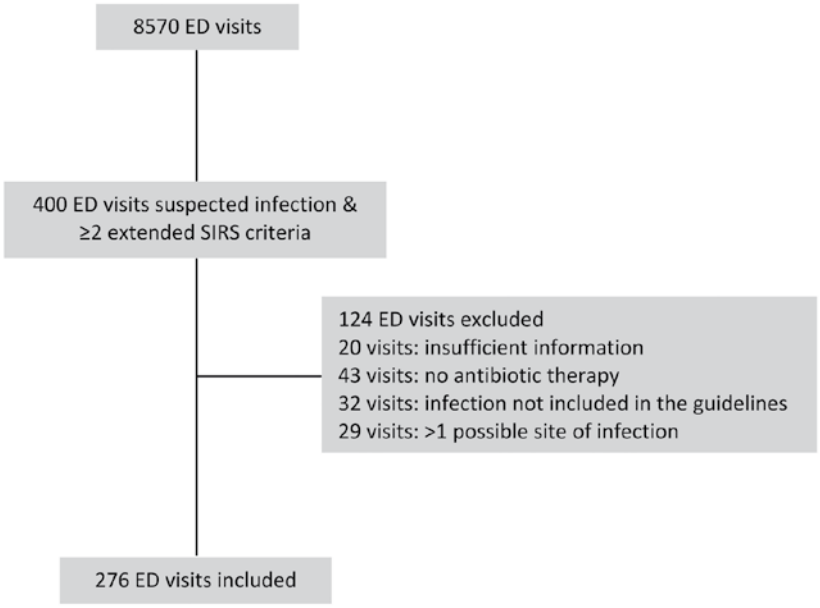
Statistical analysis

We compared the patient demographics and characteristics in patients treated with guideline-concordant treatment and guideline-disconcordant treatment. Categorical variables were analyzed using the Pearson's Chi-squared test and continuous variables were analyzed using Student's *t*-test or the Mann-Whitney U-test, as applicable. A p-value <0.05 was considered to be statistically significant. All calculations were performed using SPSS software, version 16.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Of a total of 400 ED visits with a known or suspected infection and ≥2 extended SIRS criteria, 276 visits (262 patients) were included in the study (*Figure 1*). The mean (± standard deviation [SD]) age was 59±19 years and 63% were male. Blood cultures were positive in 49 patients (18%; contaminated blood cultures not included) and 22 patients were admitted to the ICU within 24 hours after admission (8%). The length of stay, ICU admission within 24 hours, and 30-day all-cause mortality were similar in patients receiving guideline-concordant and guideline-disconcordant treatment (*Table 2*). One patient was lost to follow-up.

Figure 1. *Flow-chart of included emergency department visits*



ED = emergency department; SIRS = systemic inflammatory response syndrome

Table 2. *Patient demographics and characteristics by adherence to guideline-recommended treatment*

Characteristic	Guideline-concordant treatment (n=168)	Guideline-disconcordant treatment (n=108)	*p*-value
Mean age, years ± SD	59 ± 19	60 ± 18	0.55
Male	103 (61%)	72 (65%)	0.46
Nursing home resident	10 (6%)	8 (7%)	0.63
Hospitalization in the last 3 months	51 (30%)	30 (27%)	0.65
Mean C-reactive protein ± SD	135 ± 122	114 ± 112	0.16
Mean lactate ± SD	2.5 ± 1.4	2.3 ± 1.3	0.28
Blood culture obtained	160 (95%)	100 (93%)	0.36
Bacteremia	32 (19%)	17 (16%)	0.48
Median (IQR) LOS (days)	6 (9)	7 (8)	0.90
30-day mortality	17 (10%)	10 (9%)	0.77
ED treatment by			<0.001
General surgery (16)	6 (4%)	10 (9%)	
Orthopedics (2)	0 (0%)	2 (2%)	
Urology (17)	17 (10%)	0 (0%)	
Internal medicine (157)	109 (65%)	48 (44%)	
Neurology (11)	10 (6%)	1 (1%)	
Pulmonology (72)	22 (13%)	50 (45%)	
Otolaryngology (1)	0 (0%)	1 (1%)	

SD = standard deviation; IQR = interquartile range; LOS = length of stay; ED = emergency department

Antimicrobial treatment guideline adherence

The overall adherence to the guideline-recommended treatment was 61% (*Table 3*; n=168). This includes 25 ED visits where the prescribed treatment was considered to be guideline-concordant due to a well-motivated deviation from the guideline-recommended therapy. Adherence was the highest in patients diagnosed with urosepsis and febrile neutropenia (95% and 94%, respectively) and the lowest in patients with pneumonia (43%). Among the patients with pneumonia, adherence was above 50% in patients with severe pneumonia, as defined by the CURB-65 score, patients residing in a nursing home, and patients with recent antibiotic use, whereas adherence in patients with a mild pneumonia was only 34%.[13]

***Table 3**. Adherence to guideline-recommended treatment categorized by clinical diagnosis (n=276)*

Clinical diagnosis	Guideline-concordant treatment (n=168)	Guideline-disconcordant treatment (n=108)
Urosepsis (42)	40 (95%)	2 (5%)
Recent antibiotic use (4)	4	-
Febrile neutropenia (17)	16 (94%)	1 (6%)
Meningitis (6)	5 (83%)	1 (17%)
Sepsis of unknown origin (29)	21 (75%)	8 (25%)
Recent antibiotic use or hospitalisation (4)	3	1
Miscellaneous infections (19)	12 (63%)	7 (37%)
Arthritis (3)	-	3
Clostridium infection (3)	1	2
Diverticulitis (2)	1	1
Pancreatitis (1)	1	-
Post partum fever (1)	1	-
Other abdominal infections (5)	5	-
Epididymitis (1)	1	-
Endocarditis (1)	1	-
Tonsillitis (1)	-	1
Brain abscess (1)	1	-
Cholangitis (7)	4 (57%)	3 (43%)
Skin or soft tissue infection (15)	8 (53%)	7 (47%)
Cellulitis (5)	3	2
Erysipelas (10)	5	5
Pneumonia (142)	62 (44%)	80 (56%)
Mild (66)	23	43
Severe (41)	22	19
Nursing home or recent antibiotic use (31)	16	15
Aspiration (4)	1	3

In 94 of the 108 patients (87%) with guideline-disconcordant treatment, the antimicrobial therapy was more broad-spectrum than the guideline-recommended therapy, and 66 patients were treated with a beta-lactam/beta-lactamase inhibitor instead of a narrow-spectrum beta-lactam. Treatment diversity was the highest among patients diagnosed with a pneumonia: a total of 12 different antibiotic regimens were prescribed in these patients.

Antimicrobial susceptibility

Positive cultures were found in 133 patients. Thirty-seven cultures were interpreted as non-significant or contamination. These cultures consisted of *Candida* species, *Aspergillus* species, or gram negative bacteria interpreted as colonization or contamination from 15 urine and 18 sputum specimens, one wound swab with coagulase-negative staphylococci, two blood cultures with coagulase-negative staphylococci, and one *Propionibacterium acnes* in a biopsy of an intracerebral lesion, later confirmed to be a malignancy. Four cultures that led to a different definite diagnosis than the clinical diagnosis made at the ED were left out of further analysis: two urine cultures diagnostic for urinary tract infection and one *Enterococcus faecalis* bacteremia of unknown source from patients suspected of pneumonia, and a sputum culture from a patient suspected of meningitis. A final microbiological diagnosis was established in 96 patients (35%). *Table 4* shows the pathogens and their susceptibility to guideline-recommended treatment according to clinical diagnosis.

Of the 96 patients with a microbiological diagnosis, 68 received guideline-concordant treatment. The susceptibility of the isolated pathogens to the guideline-recommended treatment was similar in patients with guideline-concordant treatment and guideline-disconcordant treatment (62/68; 91% and 25/28; 89% respectively, p=0.77). Furthermore, the susceptibility of the isolated pathogens to the prescribed therapy was similar in patients with guideline-concordant treatment (62/68; 91%) and guideline-disconcordant treatment (26/28; 93%; p=0.79).

Nine of the 96 isolated pathogens (9%) were resistant to guideline-concordant treatment (*Table 4*). The percentage of pathogens resistant to guideline-recommended treatment was higher when an ED visit was preceded by a hospitalization in the last 3 months (6/26; 23% versus 3/70; 4%; p=0.005).

Discussion

During the study period, the overall adherence to our local antimicrobial treatment guidelines in patients admitted to the ED with sepsis was 61%. However, differences between subgroups were substantial, with high adherence rates in patients with urosepsis and febrile neutropenia, and low rates in patients with pneumonia, skin or soft tissue infection, or cholangitis. The empirical therapy in patients treated with guideline-disconcordant treatment was more broad-spectrum than guideline-recommended treatment in the vast majority of patients. However, this use of more broad-spectrum antimicrobial treatment did not result in a higher rate of *in vitro* susceptibility of the isolated pathogens to the prescribed treatment in the patients with guideline-disconcordant treatment

Table 4. *Isolated pathogens per diagnosis (n=96) and the pathogens which were in vitro resistant to guideline-recommended treatment (n=9)*

	Isolated pathogens (n)	Resistant to guideline therapy (n)
Urosepsis (33)	Enterobacteriaceae (22)	
	E. faecalis (2)	2
	S. aureus (3)	
	H. influenzae (2)	
	polymicrobial (2)	2 (*E. faecalis; A. baumanii*)
	S. epidermidis (1)	
Recent antibiotic use	*E. faecalis* (1)[a]	
Pneumonia (30)	*S. pneumoniae* (13)	
	H. influenzae (2)	
	beta-hemolytic streptococci (3)	
	P. aeruginosa (1)	
	A. baumanii (1)	1
	M. catarrhalis (1)	
	C. propinquum (1)	
	polymicrobial (1)	
Aspiration pneumonia	polymicrobial (1)	1 (*E. coli*)
NH or recent antibiotic use	*S. pneumoniae* (4)	
	H. influenzae (1)	
	S. aureus (1)	
Skin or soft tissue (3)	beta-hemolytic streptococci (3)	
Meningitis (3)	*S. pneumoniae* (3)	
Cholangitis (4)	*P. aeruginosa*	
	K. oxytoca	1
	S. milleri group	
	polymicrobial	
Sepsis of unknown origin (12)	Enterobacteriaceae (8)	
	S. aureus (1)	
	C. canimorsus (1)	
	polymicrobial (1)	1 (ESBL *E. coli* and *E. faecalis*)
Febrile neutropenia (6)	Enterobacteriaceae (2)	
	polymicrobial (2)	1 (*E. faecalis*)
	P. aeruginosa (1)	
	S. pneumoniae (1)	
Miscellaneous infections (5)		
Endocarditis	*S. aureus* (1)	
Arthritis	*S. aureus* (1)	
C.difficile infection	*C. difficile* (1)	
Other abdominal infections	*E. faecium* (1)	
Postpartum fever	*S. agalactiae* (1)	

[a] This patient was treated with ceftazidime and teicoplanin based on recent culture results and recent antibiotic use: this regimen was considered to be guideline-concordant treatment
NH = nursing home resident; ESBL = extended-spectrum beta-lactamase

compared to the patients with guideline-concordant treatment. In addition, the isolated pathogens were equally susceptible to the guideline-recommended therapy in both treatment groups. These results indicate that non-compliance to the guideline does not result in a clinical benefit for patients admitted with sepsis.

A small but significant proportion (9%) of isolated pathogens were resistant to the guideline-recommended therapy. These pathogens were mostly cultured from recently hospitalized patients. This is in keeping with an earlier study that identified frequent contacts with the health care system, especially recent hospitalization, prior to admission as an important risk factor for ineffective empirical therapy in patients admitted with a bloodstream infection.[14]

A more broad-spectrum empirical therapy for this specific group of patients needs to be considered.

Although many hospitals have their own antimicrobial treatment guidelines, little is known about the adherence to these guidelines in patients with sepsis. A high adherence of 90% to local antimicrobial therapy guidelines in patients with a suspected or documented infection (pneumonia, cellulitis or erysipelas, urosepsis, febrile neutropenia, or meningitis) has been described.[8] However, the investigated guidelines were developed by internal medicine specialists for their own use in patients admitted to the internal medicine wards or the ICU. In contrast, we investigated the adherence to local antimicrobial treatment guidelines developed for use in the entire hospital, in patients admitted to the ED and treated by many different physicians and disciplines.

Our adherence data are in agreement with other studies that investigated compliance to treatment guidelines in patients admitted with a pneumonia and reported adherence rates of between 41% and 77%.[3;5;9;10]

The obvious downside of the unnecessary use of broad-spectrum therapy is the increase in the selective pressure on bacteria, thereby, promoting the emergence of resistant pathogens.[15;16] Over the last few decades, a dramatic increase of bacterial resistance has emerged with the increasing use of broad-spectrum antimicrobials, whereas, on the other hand, the development of new antimicrobial agents is declining.[17] The use of antimicrobial treatment guidelines based on local epidemiology, followed by de-escalation of the empirical antimicrobial therapy based on culture and susceptibility results, is one of the most important strategies to reduce the use of broad-spectrum antimicrobial therapy and prevent and control the emergence of bacterial resistance. The adherence rate to our local antimicrobial treatment guidelines illustrates the need for ongoing communication about culture and susceptibility results in relation to the prescribed antimicrobial treatment and the antimicrobial treatment guidelines. Previous research has demonstrated that antimicrobial treatment guideline adherence can be improved by close collaboration with representatives of the involved departments and feedback on antimicrobial use in combination with educational training sessions for physicians.[18]

Our study has several limitations. First, it was a retrospective cohort study, which implicates that reasons for prescribing guideline-disconcordant treatment were only taken into account when they were recorded in the patients' medical charts. Furthermore, the study results reflect the epidemiology and guideline adherence of a single centre; several subgroups such as patients with cholangitis and meningitis were very small, and the miscellaneous infections were very diverse. However, the goal of our study was to provide an overview of the antimicrobial treatment guideline adherence and the appropriateness of prescribed treatment

among all patients admitted to the ED of our hospital with sepsis, and we do believe that our data provide insights into daily clinical practice. The reasons for non-adherence to antimicrobial treatment guidelines were beyond the scope of the current study, but factors identified in other studies will most likely be applicable in our setting.[19] For example, fear for an unfavourable outcome with narrow-spectrum guideline-recommended treatment and a lack of agreement with guidelines have been identified as the main barriers to prescribing empirical antibiotic treatment according to the recommended guidelines in patients with community-acquired pneumonia.[20]

Non-adherence to guideline-recommended treatment predominantly resulted in more broad-spectrum empirical therapy. However, pathogens isolated in patients treated with guideline-disconcordant treatment were equally susceptible to guideline-recommended therapy and the actually prescribed treatment. To minimize treatment diversity and the inappropriate use of broad-spectrum antimicrobials, prescribers should be aware that a more broad-spectrum empirical treatment does not result in more effective treatment, but does increase the selection of antimicrobial resistance. A multidisciplinary effort should be made to improve compliance with local antimicrobial treatment guidelines.

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Chapter 9

Summary and general discussion

Summary and general discussion

Worldwide, as well as in the Netherlands, severe sepsis (acute organ dysfunction secondary to infection) and septic shock (severe sepsis plus hypotension not reversed with fluid resuscitation) are major health care problems. When sepsis proceeds into severe sepsis, it is often initially managed by a non-intensive care medical team, e.g., on a general hospital ward. The severity of this condition is illustrated by the fact that an important proportion of these patients ultimately need further treatment in an intensive care unit. Severe sepsis accounts for 20% of all admissions to intensive care units and is the leading cause of morbidity and mortality for critically ill patients.[1-3]

In a study by Zhen et al.[4], the mortality among septic shock patients admitted via the emergency department was 25.8% compared to 59.3% for patients admitted via the hospital ward. Use of mechanical ventilation during the first 24 hours of shock was 44% in emergency department patients and 70% in hospital ward patients and was independently associated with increased mortality. Infections in the hospital ward group were likely more difficult to treat due to the presence of multi-drug resistant organisms, other infectious patients, and patients' co-morbidity, and this may have played a role in the increased mortality.

Similar to multi-trauma, acute myocardial ischemic infarction, or stroke, the speed and appropriateness of therapy administered in the initial hours after severe sepsis develops are paramount to influence outcome.[1-3;5;6] However, despite the presence of evidence-based clinical practice guidelines to optimize care for patients with sepsis, the mortality related to severe sepsis and septic shock remains high.

In this thesis, the results of seven studies aimed at improving the quality of care for patients with sepsis are presented. This final chapter provides a summary of results of the studies included in this thesis, and discusses the main findings as well as methodological issues. Finally, this chapter ends with the main conclusions and recommendations for future research and practice.

Prevention of sepsis

Optimal hand hygiene compliance by all health care workers is one of the most important strategies for the prevention of hospital-acquired infections and sepsis. Reducing hospital-acquired infections would be expected to decrease the incidence of sepsis, severe sepsis, and septic shock, thereby reducing hospital costs.[4;7]

In ***Chapter 2***, the effects of the implementation of a multifaceted hand hygiene improvement program for nurses and physicians in a department of internal medicine is described. We performed an observational, prospective before-and-

after strategy study. The hand hygiene knowledge and hand hygiene compliance of nurses and physicians was measured before (baseline), directly after (post-strategy), and 6 months after the implementation of hand hygiene team strategies (follow-up).

Education, feedback, reminders, social influence activities including the use of role models, and improvement of hand hygiene facilities were included in the hand hygiene improvement program. We obtained data about participants' knowledge regarding the indications for hand hygiene. Based on five relevant moments for hand hygiene according to the Dutch national infection prevention guideline, an observation list was developed to measure the hand hygiene compliance.

Compared to baseline, there was a significant improvement in the overall mean hand hygiene knowledge score at post-strategy (from 7.4 to 8.4) and follow-up (8.3). The overall hand hygiene compliance was 27% at baseline, 83% at post-strategy, and 75% at 6 months follow-up. In conclusion, a multifaceted improvement strategy including education, feedback, reminders, social influence activities including the use of role models, and improvement of facilities leads to sustainably improvement of adherence to recommended practices in nurses as well as physicians.

Our study was part of a multicenter controlled trial which included 67 different hospital wards in three hospitals. A total of 37 departments were randomized to a state of the art group (multifaceted strategy including education, feedback, reminders and improvement of facilities) and 30 departments were randomized to the team and leaders-directed group (state of the art strategy supplemented with interventions based on social influence and leadership, comprising specific team and leaders-directed activities). During the study, 10,785 hand hygiene opportunities were observed among 2733 different nurses. The compliance in the state of the art group increased from 23% at baseline to 42% at post-strategy and to 46% at follow-up (6 months after strategy delivery). The hand hygiene compliance in the team and leaders-directed group improved from 20% at baseline to 53% at post-strategy and remained 53% at follow-up. The difference between both groups showed an Odds Ratio of 1.64 (95% CI: 1.33-2.02) in favor of the team and leaders-directed group (submitted data). These results are in accordance, although less pronounced, with the results of our pilot study. The fact that not only the nurses, but also the physicians were included in our multifaceted improvement program, may account for this difference as this was not the case in all wards included in the project. Probably, the physicians functioned as role models for the nurses and vice versa.

During the implementation of guidelines (including hand hygiene guidelines), individual factors can be experienced as barriers by the members of the target group, e.g., employees are not aware of the guideline, they are not aware of the

exact content, they do not agree with the guideline, or they have no confidence in their own professionalism. Also, when there is a lack of confidence that the guideline will lead to better results or if there is a lack of motivation to change, a successful implementation will be hampered.[8;9] In addition, social factors within teams and networks of care givers and within the organization related to the department or hospital influence the success of implementation.[10-14] To achieve successful implementation, a strategic approach is necessary in which the various barriers that prevent optimal hand hygiene performance are determined and dealt with. In our study, as well as in the study by Huis et al., the multifaceted improvement strategy was specifically built upon barriers (as described above) that may be present.[8-14]

Although a multimodal and multidisciplinary improvement strategy, including creating a stronger social norm and establishing more explicit social control, appears to be a good approach to sustainably improve guideline compliance rates, we did not achieve the essential 100% adherence to the hand hygiene guidelines at follow-up. Consequently, after participating in our improvement program, hand hygiene performance may still be hindered by unknown barriers to guideline adherence in our specific target group, as was also described in earlier studies.[15;16] Our study was limited by not specifically searching for potential barriers to change hand hygiene compliance at follow-up.

Another limitation of our study was that the effect on clinical outcomes and the cost-effectiveness of implementing the hand hygiene guidelines was not assessed, as the power of our study was not sufficient to do so. However, earlier studies already have shown that low hand hygiene rates lead to unacceptably high rates of health care-associated infections, resulting in unnecessary excess mortality and morbidity in the population and increased health care costs due to increased length of hospital stay and more complex care.[17] Furthermore, Huis et al. concluded in their multicenter study that optimizing hand hygiene compliance through a team and leaders-directed strategy is cost-effective as compared to a state of the art strategy (submitted data). Currently, a cluster-randomized trial on the cost-effectiveness of a multi-component strategy to improve hand hygiene compliance and reduce health care-associated infections is performed.[18] This will be the first randomized clinical trial to investigate the effects of a hand hygiene strategy program on the number of health care-associated infections.

The ultimate target of our study was to sustainably improve hand hygiene performance among nurses and physicians. In a recent study by Jamal et al., strong leadership, stakeholder engagement, the improvement of facilities, education, monitoring of staff, and contemporaneous feedback of performance data were included in a hand hygiene implementation program.[19] Hand hygiene increased from 23% in 2006 to 87% in 2011. Furthermore, a significant decline

in hospital-acquired infections was also noted as hand hygiene rates improved. Major improvements were noted after installation of alcohol-based hand rub and when the performance feedback system was formalised.[19]

To further evaluate and improve the hand hygiene compliance in the department of internal medicine and other hospital wards, the continuation and development of new, barrier based implementation strategies, including a performance feedback system, is necessary. Furthermore, functioning of the health care workers is usually evaluated on a yearly basis. Compliance to clinical guidelines, including hand hygiene, should become part of that evaluation.

Diagnosis and treatment of sepsis

Diagnostic tests

Rapid diagnosis and management of sepsis is critical for a successful outcome. However, in view of the difficulties with the clinical diagnosis, the search for laboratory values or markers to aid the diagnosis and to predict the severity and prognosis of sepsis remains an important topic.

To study patients with an unequivocal diagnosis of infection, we used the presence of bacteremia as the primary outcome and evaluated the predictive value of four single biomarkers, the combination of the best performing biomarker with one to three other biomarkers (panels), the combination of the best performing biomarker with clinical signs of the patient, and serial determinations of the best performing biomarker in predicting bacteremia in emergency department patients with sepsis ***(Chapter 3)***. Adult patients visiting the emergency department for a suspected infection with two or more clinical signs of sepsis (temperature >38.3°C or <36°C, heart rate >90/min, respiratory rate >20/min, chills, altered mental status, systolic blood pressure <90 mmHg, MAP <65 mmHg, and hyperglycemia in the absence of diabetes mellitus) were included.

Procalcitonin (PCT), interleukin-6 (IL-6), lipopolysaccharide-binding protein (LBP), and C-reactive protein (CRP) were measured, and two blood cultures were taken. The analyses included: 1) To determine the biomarker with the highest predictive value for bacteremia and to examine the predictive value of this biomarker in combination with other biomarkers; 2) Analysis of the best biomarker data in combination with clinical signs of sepsis; and 3) Analysis of serial determinations of the best biomarker.

In this study, we included 342 patients of which 55 patients (16%) had proven bacteremia. Of all patients included, PCT had the best predictive value to predict bacteremia with an area under the curve of 0.80, sensitivity 89%, and specificity 58%, and performed significantly better than the other markers did. The PCT cut-off value associated with the highest area under the curve is 0.253 μg/L.

Although the other markers measured were also found to be significantly higher in the group of patients with positive blood culture results, this does not imply that these markers are of additional value in an individual patient. We demonstrated that the predictive value of a combination of PCT plus a panel of other biomarkers, clinical signs, or analysis of serial PCT levels did not lead to a significant improvement compared to the predictive value of PCT alone, illustrating that the other markers are not of additional use to predict bacteremia.

Although the PCT cut-off value of 0.253 µg/L was also found and used in earlier studies that investigated PCT to predict bacteremia in patients with community-acquired pneumonia, febrile urinary tract infections, and patients with blood cultures positive for coagulase-negative staphylococci, our study was performed in patients with sepsis evoked by infections of different body sites. Possibly, in a more homogeneous group of patients, e.g., patients with lower respiratory tract infections, inflammatory markers related to the specific pathways of the innate immune response to viral and bacterial infections may result in a better predictive value of viral and bacterial discrimination. This assumption was investigated in ***Chapter 4***. The aim of this single-centre observational study was to investigate whether the addition of five different biomarkers to a single CRP measurement improves the discrimination between bacterial lower respiratory tract infections and viral lower respiratory tract infections. The additional biomarkers included LBP, PCT, IL-6, IL-18, and soluble triggering receptor expressed on myeloid cells-1 (sTREM-1).

Out of 342 patients presenting at the emergency department with sepsis, 56 patients with proven bacterial (n=39) or viral (n=17) lower respiratory tract infections were identified. The areas under the curves for the five possible combinations of CRP with one other biomarker were compared with the area under the curve for CRP alone. Next, the same analysis was performed after the exclusion of patients with a CRP concentration with more than 95% specificity for bacterial lower respiratory tract infection.

While concentrations of PCT, IL-6, sTREM-1, and LBP were significantly different between patients with a bacterial or viral lower respiratory tract infection, the area under the curve for CRP alone did not further improve following combination analyses. A CRP concentration >150 mg/L was highly specific for a bacterial infection (95% CI: 0.81-1.0). After exclusion of the patients with a CRP concentration >150 mg/L, the area under the curve for CRP was 0.64 (95% CI: 0.45-0.83), but also in this subgroup, in which CRP does not discriminate adequately, panel analyses did not have an additional value to CRP alone.

From the results of these two studies we concluded that the ability of PCT to predict bacteremia in patients with sepsis did not further improve when combined with IL-6, LBP, CRP, clinical signs, or serial measurements.

Second, the combination of CRP with LBP, PCT, IL-6, IL-18, or sTREM-1 does not further improve differentiation between patients with a bacterial or viral lower respiratory tract infection compared with CRP alone.

Possible limitation of these studies is that also immune-suppressed patients and patients with underlying autoimmune disease or other comorbidity were included. Furthermore, the use of anti-inflammatory agents, corticosteroids, or other sepsis-modifying agents before enrolment or during the study period was not documented. Theoretically, the biomarker levels could be different in the above mentioned patient groups and could have influenced the results of our studies. Furthermore, many of the included patients received antimicrobial treatment prescribed by their general practitioner prior to their ED visit. In a study of Müller et al., antibiotic pre-treatment and PCT serum levels were independent predictor for negative and positive blood cultures.[20] Based on this result, antimicrobial pre-treatment may have had an important impact on the biomarker values and on the blood culture results. However, as we wished to evaluate the value of the biomarkers in a daily clinical setting, we chose to study all consecutive patients.

Although our results might be seen as disappointing, it does not exclude the possibility that other markers perform better. Nevertheless, it does temper the high expectations of the predictive value of various markers in the differentiation of infections and their potential role in the confirmation of a diagnosis. Based on the results of earlier studies[21;22] and our own extensive analyses, it appears likely that an optimal biomarker or panel of biomarkers to predict bacteremia will probably not be found in the near future.

Currently, other indications for biomarkers are being explored. For example, PCT is investigated in clinical algorithms to aid termination of antibiotic treatment decisions in specific patient groups such as patients with respiratory tract infections or febrile urinary tract infections.[23-26] Apart from the search for markers to aid the diagnosis in patients suspected to suffer from an infection, the results of these trials, which are expected in the near future, may result in other applications of the markers used.

Surviving sepsis campaign

To improve the recognition, diagnosis, management, and treatment of patients with severe sepsis or septic shock, the surviving sepsis campaign (SSC) was launched in 2004. The SSC provides helpful tools and techniques to measure and improve the quality of care for patients with severe sepsis or septic shock, especially for patients in the intensive care unit. The most important SSC recommendations are summarized in a '6 hour' and '24 hour' bundle: also called the resuscitation bundle and the management bundle.

Chapter 5 describes the compliance with the SSC bundles, and change in the

completion of the ten individual bundle elements after implementation of the SSC in four hospitals in the Netherlands. Furthermore, these results were compared with the international SSC results.

The database used for this study was part of the international SSC database. The compliance data on 863 patients, representing 6% of the international data, were used for the analysis. In the Netherlands, compliance to the complete resuscitation bundle improved significantly from 7% at baseline to 27% after 2 years. Internationally, compliance to the resuscitation bundle increased significantly from 11% to 31%, a comparable result. In contrast with the international results (18% at baseline, 36% after 2 years), the compliance with the management bundle did not improve in the Netherlands (24% at baseline, 25% after 2 years). As the management bundle elements are mainly to be performed in the intensive care unit, this indicates that more attention to compliance to protocols for the treatment of critically ill patients in the intensive care unit is warranted.

At baseline, the Dutch hospital mortality was significantly higher compared with the international hospital mortality data (52% versus 37%), possibly related to important baseline differences in the patient population admitted to the intensive care unit in the Netherlands compared to other countries. For example, internationally, more patients were admitted to the intensive care unit from the emergency department while in the Netherlands most patients were admitted from hospital wards. Furthermore, internationally, significantly more patients were included because of sepsis based on a urinary tract infection (with a better prognosis) compared with the patients in the Netherlands.

The hospital mortality of Dutch SSC patients decreased significantly from 52% at baseline to 35% after 2 years. This decrease in mortality in the Netherlands was significantly more pronounced compared with the international data.

In conclusion, the compliance registration provided insight into the current quality of care for patients with severe sepsis and septic shock in hospitals in the Netherlands. Although the adherence to the overall resuscitation bundle significantly improved after its implementation, further improvement of compliance to the individual bundle elements and the management bundle is necessary.

Since 2007, the Dutch national patient safety program, called 'Safety Management System' (VMS: www.vmszorg.nl), has been developed. This program is to be implemented in all general- and university hospitals in the Netherlands by the end of 2012. VMS aims to reduce the unintentional and avoidable harm to patients in Dutch hospitals with 50% by December 2012. One of the VMS topics is *the treatment of severe sepsis*. The goal of the VMS is to increase compliance with the resuscitation bundle and management bundle elements to an average of 80% and to reduce both the absolute in-hospital mortality and the mortality within 30

days after the diagnosis of severe sepsis by 15% compared with mortality data from 2007. Although our study was mainly performed before the official start of the VMS patient safety program, implementation of this national program probably further facilitated the outcomes of our study: it is likely that the bundle compliance was influenced by the performance of several local and national implementation programs related to the VMS safety program.

While the goal of the national patient safety program is to implement the VMS topics in all hospital departments in all Dutch hospitals, only four general hospitals in the Netherlands were included in our study. Therefore, the generalizability of our results may be limited.

In our study, the effect on clinical outcomes and the cost-effectiveness of implementing the sepsis guidelines was not assessed. However, earlier studies have reported that early management of septic shock in the emergency department using current guideline recommendations is not only associated with a better clinical outcome[1;27], but also results in a meaningful reduction of the median per-patient cost (from $21,985 to $16,103) after successfully implementing the sepsis bundles.[28] Another study assessing cost-effectiveness demonstrated an increase in mean hospital costs of $8800 per patient (driven by an increased intensive care unit length of stay), and an incremental cost of $11,274 per life-year saved and a cost of $16,309 per quality-adjusted life year gained.[29]

Our study showed that, also in the Netherlands, it is possible to improve the compliance to the sepsis bundle elements. However, the bundle compliance is still far from optimal. To better understand the success of the individual hospitals, to analyze which improvement strategy was most effective, and to further implement the sepsis bundles in the hospitals, it is important to know the exact nature of the improvement activities. One of the weaknesses of our study is, however, that probably multiple – but unknown – improvement strategies were performed by the various hospitals, making it difficult to attribute success to specific strategies and to learn from each other.

Professionals' knowledge

The short-term and long-term effectiveness of a brief and single teaching intervention on residents' knowledge about the identification and management of sepsis is described in ***Chapter 6***. By use of a written questionnaire, we measured sepsis knowledge immediately before, 3 hours after, and 4-6 months following the teaching intervention. The questionnaire was based on the two topics of the SSC-based teaching intervention and included ten multiple-choice questions: five questions covering assessment of the symptoms of sepsis and five questions about diagnosis and treatment of sepsis.

A total of 253 questionnaires were collected. At baseline, the 'assessment of symptoms of sepsis' score (4.4) was significantly lower than the 'diagnosis and

treatment' score (8.0). Following the education session, training-grade doctors' knowledge about sepsis definitions and diagnosis and treatment of sepsis increased significantly from 6.1±1.6 to 8.2±1.2. Moreover, 4-6 months after the teaching intervention this effect sustained, resulting in a mean score of 7.6±1.1. After adding gender and years of training experience as covariates to the analysis, we found that there was no significant difference between scores or increase in score per gender or year of training.

Our single teaching intervention resulted in improved and sustained knowledge on the assessment of symptoms and diagnosis and treatment of sepsis. As the diagnosis and treatment score was already high at baseline, we concluded that the sepsis education of internal medicine residents should mainly be focused on the assessment of symptoms of sepsis.

Before we implemented the sepsis bundles in the emergency department of our hospital, it appeared that the identification of sepsis itself was a major barrier to implement the SSC guidelines.[16;30-32] A recent review concerning the implementation of early goal-directed therapy for septic patients in the emergency department confirmed this notion.[33] Operational and system issues were described to significantly influence the success of implementing sepsis protocols or bundles. In agreement with our findings, three of the seven studies that were reviewed reported that under-recognition of sepsis was one of the main barriers to treatment. Delaying a diagnosis of sepsis could potentially delay life-saving care. Findings also indicated that facilities that incorporated collaboration among departments, preplanning, and/or education of emergency department and intensive care unit nursing staff were most successful in implementing the surviving sepsis campaign recommendations.[33] These findings support the importance of our educational activities that focused on internal medicine residents' and emergency department nurses' knowledge about sepsis.

To further improve the physicians' knowledge about sepsis and the use of the sepsis guidelines in the emergency department and hospital wards, every new group of emergency department residents should be instructed and sepsis education should become part of the standard educational program for internal medicine residents. Furthermore, assessment of the effects of educational moments during the training of internal medicine residents should be performed more frequently to determine which kind of training is effective and which is not.

Limitation of our study is that we did not evaluate the effects of our education program during residents' daily practice. Consequently, we cannot conclude if the performance of a teaching intervention itself practically leads to the earlier identification and management of patients with sepsis in the emergency department and general hospital ward. Therefore, further research should aim at testing the effects of our teaching intervention on clinical decision-making.

Role of nurses in the emergency department

Although the surviving sepsis guidelines provide a comprehensive review of the medical management of patients with sepsis and septic shock, they are silent on the nursing care that is essential for optimal outcome of these patients.[1;5;6] Expert nursing knowledge and skills are required for both the identification of the deteriorating patient as a result of newly developed sepsis and the ongoing provision of optimal care to the known severe sepsis patient. Aitken et al. formulated sixty-three recommendations relating to the nursing care of severe sepsis patients.[34] The recommendations are related to infection prevention, infection management, initial resuscitation, hemodynamic support, and other supportive nursing care. Goal of the study was to provide a series of recommendations based on the best available evidence to guide clinicians providing nursing care to patients with severe sepsis. Consensus was reached on many aspects of nursing care for the severe sepsis patient.

We investigated the effects of implementation of a nurse-driven, care bundle based, sepsis protocol in the emergency department, described in ***Chapter 7***. The sepsis protocol for nurses and physicians in the emergency department was developed by a multidisciplinary team. The sepsis protocol was based on the SSC care bundle mechanism. For the selection of the required bundle elements, two different levels of evidence were used: evidence based practices described in the present sepsis guidelines and expert opinion. The final protocol consisted of two parts: a 'sepsis screening list' to support the nurses in the emergency department to better recognize sepsis in patients with a probable infection and a 'sepsis performance list', including recommendations for nurses and physicians. We measured compliance with six bundled recommendations in 825 patients with sepsis before implementation of the sepsis protocol (period 1; n=159), during the implementation phase (period 2; n=447), and after training and performance feedback (period 3; n=219). Compliance with the complete bundle significantly improved from 3.5% at baseline to 12.4% after our entire implementation program was put in place. The completion of four of six individual elements improved significantly: measurement of lactate (improved from 23% to 80%), ordering a chest radiograph (from 67% to 83%), obtaining urine for urinalysis and culture (from 49% to 67%), and starting antibiotics within 3 hours (from 38% to 56%). The mean number of performed bundle elements improved significantly from 3.0 elements at baseline to 4.2 elements after intervention.

Our study showed that we can improve the quality of nursing care for sepsis by using a relatively simple and inexpensive implementation program. Besides the use of care bundles, we also used other implementation strategies such as the use of a sepsis screening list, education, and feedback. Regrettably, it was impossible to conclude which components were – to what degree – responsible for our achieved improvement.

In a sub analysis we examined whether patients were erroneously not included in the sepsis protocol by the nurses, and it turned out that in period 2, 71% of the cases were included in the protocol by the nurses and this percentage further improved to the inclusion of 82% patients with sepsis in period 3. Possibly, the early recognition of patients with sepsis further improved due to the training and performance feedback intervention. Overall, the completion of the six elements in the cases that had been identified by the nurses (periods 2 and 3) was significantly better (1.2 elements more; 95% CI: 1.0-1.4) than the completion of the six elements in the cases that were identified afterwards by the study team. Although care bundles can be a powerful stimulus to focusing the multidisciplinary team on working together to deliver reliable care, the development of a bundle is only one component in an overall improvement strategy.

During our study, we did not specifically analyze the barriers that influence the compliance to the sepsis bundles. However, in advance, we did try to anticipate possible barriers that would hamper the implementation of the sepsis bundles. We formed a multidisciplinary implementation team, involving the emergency department manager, and gave the nurses an important role in the early recognition and treatment of patients with sepsis, followed by training and performance feedback.

In conclusion, our study confirmed that nurses indeed should have a more prominent role in the recognition and treatment of patients with sepsis. By giving them a greater responsibility in screening for sepsis and the early performance of diagnostic tests, patients with sepsis were recognized earlier and therefore received the necessary care, e.g., antimicrobial therapy and fluid resuscitation, at an earlier stage. To further improve the recognition of patients with sepsis and the performance of sepsis guidelines-based recommendations, additional improvement activities are required.

Although the sepsis protocol 6 years after its introduction in our emergency department is still used in current practice, the adherence to the sepsis bundles has not been evaluated recently. To easily obtain and analyze the necessary bundle performance data, translating the paper version of the sepsis registration form into an electronic registration system is required.

Our study is limited in being an uncontrolled study in the emergency department of only a single centre. Our implementation program was tailor-made to the situation of our hospital and the emergency department, so the results cannot be extrapolated. Therefore, future research should aim at testing this promising implementation strategy in emergency departments, general hospital wards, and intensive care units in a multicenter controlled trial.

Antimicrobial treatment

The sepsis resuscitation bundle recommends that, in patients with (suspected) severe sepsis, broad-spectrum antibiotics should be administered within 3 hours from time of presentation for emergency department admissions and within 1 hour from time of presentation for non-emergency department intensive care unit admissions. This recommendation is based on numerous studies demonstrating that delayed start of antibiotics is clearly associated with increased mortality.[2;5;35-38] A study by Kumar et al. demonstrated that each hour of delay from the onset of hypotension to administration of appropriate antibiotic treatment was associated with an average increase in in-hospital mortality of 7.5%.[5] Concerning the choice of the antibiotic to be administered, many hospitals have implemented local antimicrobial treatment guidelines. However, there is a wide variation in the reported adherence to these guidelines.

Chapter 8 describes the adherence to the local antimicrobial treatment guidelines in patients admitted in the emergency department with sepsis. In addition, the *in vitro* susceptibility of the isolated pathogens to the treatment recommended in the guidelines was determined. A total of 262 patients were included in this study. In these patients, the prescribed antimicrobial therapy was divided into 'guideline-concordant treatment' and 'guideline-disconcordant treatment'. Guideline-concordant treatment was defined as antimicrobial therapy prescribed empirically in accordance with the clinical diagnosis at the emergency department and the antimicrobial treatment guideline. Based on the *in vitro* susceptibility results of the isolated pathogens, we evaluated the appropriateness of the guideline-recommended treatment as well as the actually prescribed therapy.

Guideline-concordant treatment was prescribed in 168 visits (61%). In case of guideline-disconcordant treatment, 87% of prescriptions were more broad-spectrum than guideline-recommended treatment. Interestingly, this broader-spectrum therapy did not result in a higher rate of *in vitro* susceptibility of the isolated pathogens to the prescribed treatment in the patients with guideline-disconcordant treatment compared to the patients with guideline-concordant treatment.

Although the reasons for non-adherence to antimicrobial treatment guidelines were not included in our study, factors identified in other studies will most likely be applicable in our setting. For example, fear for an unfavorable outcome with narrow spectrum guideline recommended treatment and a lack of agreement with guidelines have been identified as main barriers.[39;40]

The obvious downside of the unnecessary use of broad-spectrum therapy is the increase in the selective pressure on bacteria, thereby promoting the emergence of resistant pathogens. Over the past few decades, a dramatic increase

of bacterial resistance has emerged with the increasing use of broad-spectrum antimicrobials, whereas, on the other hand, the development of new antimicrobial agents is declining. The use of antimicrobial treatment guidelines based on local epidemiology, followed by de-escalation of the empirical antimicrobial therapy based on culture and susceptibility results, is one of the most important strategies to reduce the use of broad-spectrum antimicrobial therapy and prevent and control the emergence of bacterial resistance.

The results from our study showed that non-adherence to the guidelines occurred frequently and resulted in more broad-spectrum empirical therapy, while this did not result in a higher rate of susceptibility of the isolated pathogens to the prescribed empirical therapy. Our study illustrates that the presence of antimicrobial guidelines does not guarantee an optimal adherence to these guidelines and deviation from the guidelines often does not result in a better antimicrobial therapy. Therefore, ongoing communication about culture and susceptibility results in relation to the prescribed antimicrobial treatment and antimicrobial treatment guidelines is needed.

Earlier studies have shown that in about half of the cases, physicians in the hospital are not prescribing antibiotics appropriately.[41;42] Many strategies are available to influence professionals' antibiotic use. In the Cochrane review by Davey et al., several interventions to improve antibiotic prescribing practices for hospitalized patients have been described.[41] Most of the studies included in this review tested persuasive and restrictive methods to reduce unnecessary antibiotic use and most of the interventions were either educational or restrictive. Persuasive methods advised physicians how to prescribe or gave them feedback on how they prescribed. Restrictive methods put a limit on how they prescribed, e.g., physicians had to have approval from an infection specialist in order to prescribe an antibiotic. Although the persuasive strategies were effective, the restrictive strategies seemed to have a larger effect. Only a few studies used multifaceted interventions with both educational and restrictive elements. Interestingly, the use of single interventions showed similar effects compared with multifaceted interventions. In their review, Davey et al. concluded that interventions to improve antibiotic prescribing to hospitalized patients are successful, and can reduce antimicrobial resistance and hospital-acquired infections.[41] However, there was no obvious relationship between the nature of the intervention and success rate. To fully assess the clinical benefits of these intervention methods, more studies are needed.

As described by Hulscher et al., determinants on various levels (cultural, contextual, and behavioral) might influence the prescription of antibiotics and cause antibiotic use to vary in different hospitals. Improvement strategies built on these determinants can make hospital antibiotic use more appropriate.[42]

In view of the increasing costs and the development of multi-resistant bacteria, adherence to antibiotic treatment as described in protocols and guidelines becomes paramount. To improve the adherence to antimicrobial guidelines in hospitals, a guideline adherence improvement program including interventions at the cultural level, contextual level, as well as the behavioral level should be developed and executed. To reduce inaccurately and unnecessary antibiotic use, restrictive strategies should be part of this improvement program.

Main conclusions

- To reach an optimal and sustained implementation result, a multidisciplinary hand hygiene improvement program including education, feedback, reminders, social influence activities including the use of role models, and improvement of facilities is crucial;
- Although the hand hygiene compliance significantly improved after the performance of a multidisciplinary hand hygiene improvement program, further improvement of hand hygiene compliance is necessary;
- The ability of PCT to predict bacteremia in patients with sepsis does not further improve when combined with IL-6, LBP, CRP, clinical signs, or serial measurements;
- The combination of CRP with LBP, PCT, IL-6, IL-18, or sTREM-1 does not improve differentiation between patients with a bacterial or viral lower respiratory tract infection compared with CRP alone;
- The SSC bundle compliance registration improved insight into the current quality of care for patients with severe sepsis and septic shock in hospitals in the Netherlands;
- Although the adherence to the overall resuscitation bundle significantly improved after its implementation, further improvement of compliance to the individual bundle elements and the management bundle is necessary;
- The compliance with the sepsis resuscitation and management bundle is associated with continuous quality improvement in sepsis care and a sustained decrease in mortality;
- Knowledge on the diagnosis and treatment of sepsis is of great importance to enable professionals to timely recognize sepsis;
- By giving nurses in the emergency department a greater responsibility in the screening for sepsis and early ordering of diagnostic tests, patients with sepsis are recognized and treated earlier;
- Only the presence of antimicrobial guidelines does not guarantee an optimal adherence to these guidelines and deviation from the guideline does generally not result in a better antimicrobial therapy.

Implications for future research and practice

With this thesis, a further step in the prevention of hospital-acquired infections (including sepsis), and in the improvement of the recognition and treatment of sepsis has been made. As described in this general discussion, several implications for future research and practice can be deducted from the results of the present thesis.

The main implications for future research and practice include:

- To further evaluate and improve hand hygiene compliance among both nurses and physicians, the continuation and development of new, barrier based, implementation strategies, including a performance feedback system, is necessary;
- More research is needed to overcome barriers to implementing hand hygiene guidelines;
- Compliance to clinical guidelines, including those on hand hygiene, should be part of the yearly evaluation of the health care workers' functioning;
- The effectiveness of implementation of the surviving sepsis campaign guidelines on patient outcomes and the process of care in all hospitals have to be investigated;
- To better understand the success of the individual hospitals, to analyze which improvement strategy was most effective, and to further implement the sepsis bundles in the hospitals, it is important to know the exact nature of the improvement activities;
- More research is needed to overcome barriers to implementing the surviving sepsis campaign guidelines;
- To improve the physicians' knowledge about sepsis and the use of the sepsis guidelines in an emergency department, every new group of emergency department residents should be instructed and sepsis education should be added to the standard educational program for internal medicine residents;
- To conclude if the performance of a teaching intervention itself practically leads to the earlier identification and management of patients with sepsis in the emergency department and general hospital ward, further research should aim at testing the effects of our teaching intervention on clinical decision-making;
- Assessment of the effects of educational moments during the training of internal medicine residents should be performed more frequently to determine which kind of training is effective and which is not;
- Because nurses are often the first to see and triage a patient, nurses should have a more prominent role in the recognition and treatment of patients with sepsis;

- Future research should aim at testing the implementation of a sepsis protocol in emergency departments, general hospital wards, and intensive care units, including the extensive role of nurses, in a larger multicenter randomized controlled trial;
- To further improve the recognition of patients with sepsis and the performance of sepsis guidelines-based recommendations, additional improvement activities are required;
- To easily obtain and analyze bundle performance data, conversion of the paper version of the sepsis registration form into an electronic registration system is required;
- To improve the adherence to antimicrobial guidelines, a guideline adherence improvement program including interventions at the cultural level, contextual level, as well as the behavioral level should be developed and executed;
- In general practice, the prescribed antibiotics are frequently more broad-spectrum than necessary or even are used in the absence of a bacterial infection. To reduce inaccurately and unnecessary antibiotic use, restrictive strategies should be part of a guideline adherence improvement program.

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Chapter 10

Samenvatting

Samenvatting

Sepsis is een ernstige aandoening die wordt gekenmerkt door een algemene ontstekingsreactie van het lichaam ('systemisch inflammatoir respons syndroom' of SIRS) op een bewezen of vermoedelijke infectie. Een infectie kan worden veroorzaakt door micro-organismen (zoals bacteriën, virussen of schimmels) die het lichaam binnendringen. Infecties zoals een bacteriële longontsteking, urineweginfectie of huidinfectie kunnen leiden tot sepsis. 'Ernstige sepsis' treedt op wanneer sepsis leidt tot het falen van één of meerdere organen. Voorbeelden hiervan zijn verminderde urineproductie (nieren), of verwardheid (hersenen). In het geval dat een lage bloeddruk of tekenen van onvoldoende doorbloeding van organen (hypoperfusie) bij een patiënt met ernstige sepsis niet verbeteren na het toedienen van vocht via het infuus, spreekt men van een 'septische shock'. Bij een patiënt met septische shock is de toediening van een vaatvernauwend medicijn (bijvoorbeeld noradrenaline) nodig om de bloeddruk en orgaanperfusie te verbeteren.

Zowel ernstige sepsis als septische shock zijn levensbedreigende complicaties ten gevolge van een infectie en vormen een groot probleem in de gezondheidszorg. Alleen al in Nederland worden jaarlijks ongeveer 15.500 patiënten met ernstige sepsis en 6.000 patiënten met septische shock op een intensive care afdeling opgenomen en behandeld. De kans op overlijden voor patiënten met sepsis is 5-20% en deze kans loopt op tot 30-50% voor patiënten met septische shock. Sepsis vormt hiermee wereldwijd één van de belangrijkste doodsoorzaken.

Infecties die kunnen lijden tot sepsis kan men zowel buiten het ziekenhuis ('community-acquired') als binnen het ziekenhuis ('hospital-acquired') opdoen. Ziekenhuisinfecties komen in alle ziekenhuizen voor en worden meestal veroorzaakt door bacteriën die de patiënt zelf bij zich draagt of die door anderen worden overgedragen, bijvoorbeeld door handcontact of via de lucht. Ziekenhuisinfecties zijn over het algemeen moeilijker te behandelen vanwege een verminderde weerstand van de patiënt door onderliggende ziekten, eerder antibioticagebruik, de aanwezigheid van voor antibiotica ongevoelige bacteriën in het ziekenhuis en de aanwezigheid van een open toegangsweg (porte d'entrée) voor micro-organismen door de aanwezigheid van bijvoorbeeld een infuus, urinekatheter of wonddrain bij de patiënt. Naast het feit dat ziekenhuisinfecties voornamelijk door de toename van het aantal ligdagen in het ziekenhuis veel geld kosten, vormen ziekenhuisinfecties één van de belangrijkste oorzaken van sterfte van in het ziekenhuis opgenomen patiënten.

Hoofdstuk 1 van dit proefschrift betreft een algemene inleiding waarbij de huidige problematiek op het gebied van de preventie, diagnostiek en behandeling van sepsis beschreven wordt.

De drie hoofddoelen van dit proefschrift zijn:

- De evaluatie van het effect van de implementatie van een multidisciplinair handhygiëne verbeterprogramma met als doel het verbeteren van de ***preventie*** van ziekenhuisinfecties;
- De evaluatie van de potentiële meerwaarde van verschillende biomarkers bij het aantonen van een bacteriemie en het onderscheiden van een bacteriële of lagere virale luchtweginfectie met als doel het verbeteren van de sepsis ***diagnostiek***;
- Het beschrijven van de effecten van de implementatie van de 'surviving sepsis campaign' in verschillende ziekenhuizen in Nederland en de evaluatie van de herkenning en behandeling van patiënten met sepsis op de spoedeisende hulp, inclusief een evaluatie van de naleving van de aanwezige antibioticarichtlijnen met als doel het verbeteren van de ***behandeling*** van patiënten met sepsis.

Deze doelen hebben geresulteerd in de uitvoering en beschrijving van 7 studies.

Preventie van sepsis

Ondanks het feit dat patiënten zelf kunnen bijdragen aan het voorkomen van infecties door bijvoorbeeld het regelmatig wassen van de handen en het hoesten in een papieren zakdoek, vormen gezondheidsmedewerkers een belangrijke bron van overdracht van ziekenhuisinfecties van patiënt naar patiënt. Goede handhygiëne bij zorgmedewerkers wordt beschouwd als de belangrijkste maatregel om het risico op overdracht van micro-organismen van medewerkers in de gezondheidszorg naar patiënten te verminderen. De effectiviteit van handhygiëne is in een groot aantal studies aangetoond. Hoewel het verbeteren van handhygiëne bij gezondheidsmedewerkers al jaren een belangrijk aandachtspunt is, worden de richtlijnen voor handhygiëne tot op heden nog steeds niet goed nageleefd.

Ter preventie van in het ziekenhuis opgelopen infecties, waaronder sepsis, is er een ziekenhuisbreed handhygiëne verbeterprogramma voor verpleegkundigen ontwikkeld waarbij gebruik is gemaakt van verbeterstrategieën die voortkomen uit de literatuur (educatie, feedback, reminders en het aanbieden van de benodigde producten en faciliteiten) in combinatie met op sociale invloed gerichte verbeterstrategieën (aanstellen van rolmodellen, actieve betrokkenheid van leidinggevenden en het vaststellen van normen en doelen binnen het team). In ***Hoofdstuk 2*** worden de korte- en lange termijn effecten van de implementatie

van deze handhygiëne verbeterstrategieën bij zowel verpleegkundigen als artsen binnen de afdeling algemeen interne geneeskunde beschreven.

De implementatieperiode vond plaats van januari 2009 tot en met mei 2009. Gedurende de studie werd op drie verschillende momenten de kennis over de handhygiënerichtlijnen en de naleving van deze richtlijnen gemeten: direct voor de uitvoering van de verbeterstrategieën (test 1), direct na de uitvoering van de verbeterstrategieën (test 2) en 6 maanden na uitvoering van de verbeterstrategieën (test 3). Bij zowel test 2 als test 3 was er, in vergelijking met test 1, een significante verbetering in de gemiddelde handhygiënekennisscore. Tijdens test 1 werden de handhygiënerichtlijnen in 27% van de gevallen nageleefd (verpleegkundigen 17% en artsen 43%). Tijdens test 2 en test 3 was er een significante verbetering in de naleving van de handhygiënerichtlijnen: 83% tijdens test 2 en 75% tijdens test 3. Deze resultaten laten zien dat de uitvoering van multiple verbeterstrategieën, inclusief interventies gericht op sociale invloed, hebben geleid tot een verbetering van de kennis over handhygiëne en het naleven van de handhygiënerichtlijnen door zowel verpleegkundigen als artsen.

Diagnostiek en behandeling van sepsis

Gezien de associatie tussen de kans op overlijden en de mate van progressie van de aandoening is de vroegtijdige herkenning en behandeling van patiënten met ernstige sepsis en septische shock van essentieel belang. Eerdere studies hebben aangetoond dat het snel identificeren van patiënten met sepsis – en daarmee het tijdig starten van de juiste behandeling – de kans op overleving van deze patiënten vergroot. Een belemmerende factor bij deze directe herkenning is echter dat de symptomen van sepsis niet specifiek zijn. Verschijnselen als koorts, een hoge hartfrequentie (>90 slagen per minuut) of een snelle ademhalingsfrequentie (>20 per minuut) kunnen bijvoorbeeld ook voorkomen bij traumapatiënten of patiënten met brandwonden.

Diagnostische tests

Hoewel het afnemen van bloedkweken wordt gezien als de 'gouden standaard' voor het vaststellen van een bacteriemie, is de tijd tussen het afnemen van bloedkweken en het bekend worden van de uiteindelijke kweekresultaten een belangrijk nadeel. Om de diagnostiek van sepsis te verbeteren, zou een biomarker van grote klinische en financiële waarde kunnen zijn. Hoewel er de afgelopen jaren al vele studies zijn gedaan naar de rol van biomarkers in de diagnostiek en behandeling van sepsis, is er tot op heden geen optimale diagnostische test beschikbaar.

In ***Hoofdstuk 3*** wordt de waarde van de individuele biomarkers procalcitonine (PCT), interleukine-6 (IL-6), lipopolysaccharide-bindend proteïne (LBP) en C-reactive proteïne (CRP), een combinatie van deze biomarkers, een combinatie van PCT met klinische verschijnselen van sepsis plus aanvullend laboratoriumonderzoek en de waarde van herhaalde afname van PCT gedurende 3 opeenvolgende dagen voor het voorspellen van een bacteriemie beschreven.

Bij 394 volwassen patiënten die de spoedeisende hulp bezochten in verband met een (vermoede) infectie en twee of meer klinische verschijnselen van sepsis (temperatuur >38.3°C of <36°C, hartfrequentie >90/minuut, ademhalingsfrequentie >20/minuut, koude rillingen, acuut veranderd bewustzijn, systolische bloeddruk <90 mmHg, MAP <65 mmHg of hyperglycaemie in de afwezigheid van diabetes mellitus) werd naast het afnemen van twee bloedkweken en de standaard bloedbepalingen (waaronder lactaat, bloedgas, glucose, CRP en leukocytenaantal), extra bloed afgenomen voor de bepaling van PCT, IL-6 en LBP. De data van 342 patiënten konden worden gebruikt voor nadere analyse. Binnen deze patiëntengroep hadden 55 patiënten (16%) een bewezen bacteriemie. De meest voorkomende verwekkers waren *E. coli* (29%) en *Streptococcus pneumoniae* (23%). Hoewel de concentraties van zowel PCT, IL-6, LBP als CRP significant hoger waren in de groep patiënten met een bewezen bacteriemie, had PCT de best voorspellende waarde voor een bacteriemie (oppervlakte onder de curve (AUC) 0.80, sensitiviteit 89%, specificiteit 58%). De PCT afkapwaarde met de hoogste AUC was 0,253 µg/L.

Na de toevoeging van één of meer andere biomarkers, klinische verschijnselen van sepsis plus aanvullend laboratoriumonderzoek of bij afname van PCT gedurende 3 opeenvolgende dagen verbeterde de voorspellende waarde van PCT niet. Op basis van deze studie kan geconcludeerd worden dat PCT de beste marker is voor het voorspellen van een bacteriemie en dat de toevoeging van één of meer andere markers, een combinatie van PCT met klinische verschijnselen van sepsis plus aanvullend laboratoriumonderzoek en herhaalde afname van PCT geen aanvullende waarde heeft.

Sommige ontstekingseiwitten zijn vooral van belang bij een bacteriële infectie en andere bij een virale infectie. Door deze biomarkers als panel te bepalen kan er wellicht een beter onderscheid gemaakt worden tussen bacteriële en virale infecties. ***Hoofdstuk 4*** beschrijft de studie waarin we onderzocht hebben of er op basis van de toevoeging van LBP, PCT, IL-6, IL-18 of soluble TREM-1 (sTREM-1) aan de bepaling van CRP een beter onderscheid gemaakt kan worden tussen de aanwezigheid van een bacteriële of virale lagere luchtweginfectie.

De AUC van de vijf verschillende markers plus CRP werd vergeleken met de AUC van CRP alleen. Na het uitsluiten van patiënten met een CRP >150 mg/L (>95% specificiteit voor een bacteriële lagere luchtweginfectie) werd dezelfde vergelijking nogmaals uitgevoerd.

Van de 342 volwassen patiënten die de spoedeisende hulp bezochten in verband met een (vermoede) infectie en twee of meer klinische verschijnselen van sepsis hadden 39 patiënten een bewezen bacteriële lagere luchtweginfectie en 17 patiënten een bewezen virale lagere luchtweginfectie. In vergelijking met de groep patiënten met een virale lagere luchtweginfectie waren de concentraties van CRP, PCT, IL-6, sTREM-1 en LBP significant hoger bij de patiënten met een bacteriële lagere luchtweginfectie. Van de zes individuele markers had CRP de hoogste AUC (0.82; 95% betrouwbaarheidsinterval: 0.70-0.93) waarbij een combinatie van CRP met één van de andere markers niet heeft geleid tot een significante verbetering van de AUC. Ook het uitsluiten van patiënten met een CRP >150 mg/L liet geen verbetering van de AUC van de verschillende markers in combinatie met CRP zien. Dit onderzoek heeft aangetoond dat de combinatie van CRP met andere markers geen meerwaarde heeft in het maken van een onderscheid tussen bacteriële en virale lagere luchtweginfecties ten opzichte van de bepaling van CRP alleen.

Surviving sepsis campaign

De surviving sepsis campaign (SSC) is een internationaal initiatief om de bekendheid van sepsis te bevorderen en het navolgen van de richtlijnen betreffende de behandeling van sepsis te verbeteren. In 2002 werd door een initiatief van de Europese en Amerikaanse intensive care verenigingen en het Internationaal Sepsis Forum, de SSC opgericht. De SSC levert handvatten om de kwaliteit van zorg voor deze groep patiënten te meten en waar nodig te verbeteren. De missie van de SSC is om binnen 5 jaar de sterfte aan (ernstige) sepsis met 25% te verminderen.

De SSC heeft er voor gekozen om de belangrijkste diagnostische en therapeutische aanbevelingen te groeperen in 2 bundels: de 'resuscitatiebundel', bestaande uit diagnostische en therapeutische handelingen die binnen 6 uur uitgevoerd dienen te zijn, en de 'managementbundel' met therapeutische handelingen die binnen 24 uur voltooid dienen te zijn. Naast de oprichting van de SSC is in Nederland in 2007 het nationale veiligheidsmanagement systeem (VMS) ontwikkeld. Doel van het VMS is om binnen 5 jaar de onbedoelde en vermijdbare schade aan patiënten in Nederlandse ziekenhuizen met 50% te reduceren. Alle thema's die beschreven worden in het veiligheidsprogramma dienen aan het einde van 2012 in alle Nederlandse ziekenhuizen geïmplementeerd te zijn. Eén van de thema's van VMS is 'voorkomen van lijnsepsis en behandeling van ernstige sepsis', waarbij voor wat betreft de behandeling van ernstige sepsis gebruik gemaakt wordt van de SSC bundels.

In 2010 werden de eerste wereldwijde resultaten van de implementatie van de SSC bundels beschreven. In ***Hoofdstuk 5*** worden de Nederlandse resultaten van de implementatie van de SSC richtlijnen besproken en worden deze resultaten met de eerder beschreven internationale resultaten vergeleken.

Data van 863 patiënten uit vier verschillende Nederlandse ziekenhuizen

werden gebruikt voor nadere analyse. Deze data waren tevens onderdeel van de data die gebruikt waren voor de internationale analyses. Twee jaar na de implementatie van de SSC richtlijnen was er zowel internationaal als in Nederland een significante verbetering van de uitvoering van de resuscitatiebundel. Hoewel er internationaal ook een significante verbetering was van de uitvoering van de managementbundel, bleef de uitvoering van deze bundel in Nederland gelijk. De mortaliteit van patiënten in Nederland daalde in deze periode van 52% naar 35%, vergeleken met een daling van de mortaliteit van 37% naar 31% wereldwijd.

De implementatie van de SSC richtlijnen en de registratie betreffende het wel of niet naleven van deze richtlijnen heeft geleid tot een verbetering van het inzicht in de huidige kwaliteit van zorg voor patiënten met ernstige sepsis en septische shock in Nederlandse ziekenhuizen. Vergelijkbaar met andere landen worden, ondanks de uitvoering van diverse implementatiestrategieën, de SSC richtlijnen nog onvoldoende nageleefd.

Kennis van professionals

Het herkennen van de systemisch inflammatoir respons syndroom (SIRS) criteria is de eerste stap in het snel identificeren van patiënten met sepsis. Hoewel klinische verschijnselen zoals koorts, koude rillingen en een systolische bloeddruk <90 mmHg geassocieerd zijn met de aanwezigheid van een bacteriemie hebben eerdere studies aangetoond dat slechts ongeveer 30% van de artsen de SIRS criteria kan benoemen. Om het tijdstip van de start van de behandeling niet te vertragen is de scholing van zowel artsen als verpleegkundigen van wezenlijk belang.

Het korte-termijn en langere-termijn effect van een scholingsinterventie gericht op de herkenning en behandeling van patiënten met sepsis op de kennis van internisten in opleiding wordt beschreven in ***Hoofdstuk 6***. Door gebruikmaking van een door de onderzoeksgroep opgestelde schriftelijke vragenlijst werd de kennis over sepsis op drie verschillende momenten gemeten: direct voor een eenmalige scholing over de diagnostiek en behandeling van sepsis, 3 uur na de scholingsinterventie en 4-6 maanden na de scholingsinterventie. De vragenlijst bestond uit 10 meerkeuzevragen waarbij 5 vragen gericht waren op het herkennen van symptomen van sepsis en 5 vragen die gericht waren op de diagnostiek en behandeling van sepsis.

Bij de voormeting werd een gemiddelde score van 6,1 behaald, waarbij de score voor de herkenning van symptomen van sepsis significant lager was dan de diagnostiek en behandeling score (4,4 versus 8,0). Drie uur na de scholingsinterventie was er een significante verbetering van de gemiddelde score (8,2) en 4-6 maanden later bleef de score significant hoger (7,6) dan bij de voormeting. Vergelijking van de scores op basis van geslacht en ervaringsjaren leverde geen significante verschillen op.

Het geven van een eenmalige scholing aan internisten in opleiding, gericht

op de herkenning en behandeling van patiënten met sepsis, heeft geleid tot een verbetering van de kennis over de symptomen, diagnostiek en behandeling van deze patiëntengroep.

De rol van verpleegkundigen op de spoedeisende hulp

Een aanzienlijk deel van de patiënten met (ernstige) sepsis of septische shock wordt via de spoedeisende hulp van het ziekenhuis opgenomen. In dat geval komen de verpleegkundigen van de spoedeisende hulp vaak als eerste in contact met de patiënt en hebben zij een belangrijke rol in de herkenning van de symptomen van sepsis. Echter, in de aanwezige SSC richtlijnen wordt de rol van verpleegkundigen bij de herkenning van de symptomen van sepsis en het inzetten van de benodigde diagnostiek niet beschreven. Zodoende wordt er mogelijk onvoldoende gebruikt gemaakt van de meerwaarde die verpleegkundigen kunnen hebben in het snel identificeren en behandelen van patiënten met sepsis.

Hoofdstuk 7 beschrijft de studie waarbij het effect van de implementatie van een – in het bijzonder op verpleegkundigen toegespitst – sepsisprotocol op de spoedeisende hulp wordt gemeten. Het sepsisprotocol is ontwikkeld door een multidisciplinair team waarbij de SSC bundels de basis hebben gevormd. Het uiteindelijk sepsisprotocol bestaat uit een sepsis screeninglijst en een sepsis handelingenlijst. De screeninglijst ondersteunt de verpleegkundigen bij een snellere herkenning van patiënten met sepsis en de handelingenlijst beschrijft welke handelingen de verpleegkundigen binnen welke termijn dienen uit te voeren.

Bij 825 patiënten die op de spoedeisende hulp werden opgenomen vanwege sepsis werd gemeten of de handelingen die op de handelingenlijst beschreven zijn ook daadwerkelijk binnen de gestelde termijn werden uitgevoerd. De meting bestond uit de uitvoering van de complete bundel van 6 handelingen en het meten van de uitvoering van de 6 individuele bundelelementen. De resultaten van de voormeting (periode 1), de resultaten na introductie van het sepsisprotocol (periode 2) en de resultaten na het geven van scholing en feedback over eerder behaalde resultaten (periode 3) werden met elkaar vergeleken. De uitvoering van de complete bundel verbeterde van 3,5% in periode 1 naar 12,4% in periode 3. Na implementatie van het sepsisprotocol was er een significante verbetering van 4 van de 6 bundelelementen: het meten van lactaat (van 23% naar 80%), het maken van een röntgenfoto van de thorax (van 67% naar 83%), het afnemen van urine voor sediment en kweek (van 49% naar 67%) en de toediening van antibiotica binnen 3 uur na binnenkomst op de spoedeisende hulp (van 38% naar 56%). Deze studie laat zien dat de uitvoering van een bundel van handelingen binnen een vooraf vastgestelde termijn verbeterd kan worden door een relatief eenvoudige en goedkope implementatiemethode met als meest belangrijke

component het vergroten van de verantwoordelijkheid van verpleegkundigen in de herkenning en het op eigen initiatief inzetten van de benodigde diagnostiek door verpleegkundigen op de spoedeisende hulp.

Antimicrobiële behandeling

Eén van de aanbevelingen die beschreven wordt in de SSC resuscitatiebundel is de toediening van breedspectrumantibiotica binnen 3 uur na binnenkomst van een patiënt met sepsis op de spoedeisende hulp en de toediening van breedspectrumantibiotica binnen 1 uur na opname op een intensive care afdeling. Eerder gepubliceerde studies hebben aangetoond dat voor elk uur vertraging in de toediening van de juiste antibiotica bij patiënten met een septische shock, er een 7,5% stijging van de sterfte is.

Om het antibioticagebruik te structureren hebben veel ziekenhuizen op basis van de bestaande landelijke antibioticarichtlijnen en lokale resistentiepatronen hun eigen ziekenhuisbrede antibioticarichtlijnen ontwikkeld. Ondanks de aanwezigheid van deze richtlijnen is er een grote variatie in de naleving hiervan in de dagelijkse praktijk.

Eén van de grootste problemen ten gevolge van het niet goed naleven van de antibioticarichtlijnen is het ontstaan van resistentie. Om dit zo veel mogelijk te voorkomen is het noodzakelijk dat er een periodieke evaluatie plaatsvindt met betrekking tot het naleven van de aanwezige antibioticarichtlijnen in ieder ziekenhuis. De evaluatie van de naleving van de antibioticarichtlijnen bij patiënten met sepsis op de spoedeisende hulp van het UMC St Radboud wordt beschreven in ***Hoofdstuk 8***. Tevens wordt de *in vitro* gevoeligheid van de bacterie voor de in de antibioticarichtlijnen aanbevolen antibiotica beschreven.

In totaal werden 262 patiënten geïncludeerd waarbij 168 patiënten (61%) de in de antibioticarichtlijn voorgeschreven behandeling kregen voorgeschreven. Indien er afgeweken werd van de antibioticarichtlijn was de voorgeschreven antibiotische behandeling in 87% van de gevallen meer breedspectrum dan de in de antibioticarichtlijn aanbevolen antibiotica.

Bij 96 patiënten kon de *in vitro* gevoeligheid van de bacterie voor antibiotica worden bepaald. De gevoeligheid van de gevonden micro-organismen voor de voorgeschreven antibiotica in de groep patiënten waarbij werd afgeweken van de antibioticarichtlijn (n=28) was vergelijkbaar met de gevoeligheid voor de voorgeschreven antibiotica in de groep patiënten die behandeld werden volgens de in de richtlijn aanbevolen antibiotica (n=68). De conclusie van deze studie is dat alleen de aanwezigheid van antibioticarichtlijnen onvoldoende is voor een optimaal antibioticagebruik in ziekenhuizen. Het afwijken van de richtlijn is geassocieerd met een verbreding van de antibiotische behandeling, zonder dat dit op basis van de kweekuitslagen van nut is voor de patiënt.

Tot slot is in ***Hoofdstuk 9*** een Engelse samenvatting van dit proefschrift gegeven waarbij de belangrijkste bevindingen bediscussieerd worden. Aansluitend worden de belangrijkste conclusies van dit proefschrift en aanbevelingen voor de praktijk en nader onderzoek beschreven.

De belangrijkste conclusies van dit proefschrift zijn:

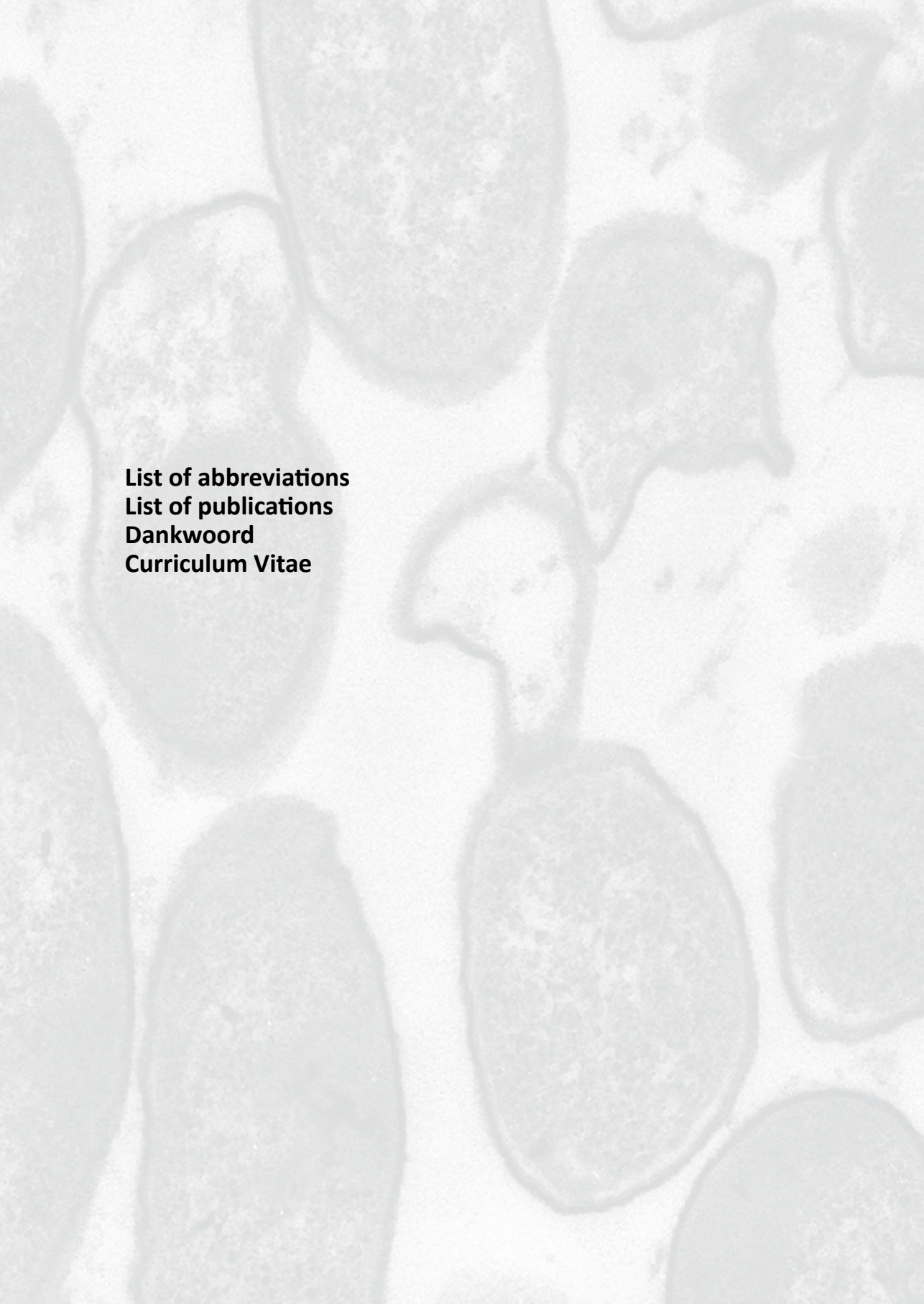
- Voor een optimale implementatie van de handhygiënerichtlijnen en het behoud van behaalde resultaten is een multidisciplinair handhygiëne verbeterprogramma inclusief educatie, feedback, reminders, activiteiten op het gebied van sociale beïnvloeding waaronder de aanstelling van rolmodellen en het verbeteren van faciliteiten cruciaal;
- Hoewel verpleegkundigen en artsen de handhygiënerichtlijnen beter opvolgen na de uitvoering van handhygiëne verbeterstrategieën, blijft verdere verbetering van handhygiëne bij zowel verpleegkundigen als artsen noodzakelijk;
- In vergelijking met een eenmalige bepaling van PCT levert de toevoeging van IL-6, LBP, CRP of klinische verschijnselen aan PCT of de bepaling van PCT gedurende 3 opeenvolgende dagen geen verdere verbetering op in de voorspelling van een bacteriemie bij patiënten met sepsis;
- De combinatie van CRP met LBP, PCT, IL-6, IL-18 of sTREM-1 heeft geen meerwaarde in de differentiatie tussen patiënten met een bacteriële lagere luchtweginfectie en patiënten met een virale lagere luchtweginfectie in vergelijking met de bepaling van CRP alleen;
- Door de registratie van de uitvoering van de sepsisbundels in de dagelijkse praktijk is er een beter inzicht verkregen in de huidige kwaliteit van zorg voor patiënten met ernstige sepsis en septische shock in de Nederlandse ziekenhuizen;
- Hoewel het opvolgen van de surviving sepsis campaign resuscitatiebundel significant verbeterd is na implementatie, blijft verdere verbetering van het opvolgen van de individuele adviezen in de resuscitatiebundel en het opvolgen van de adviezen beschreven in de managementbundel noodzakelijk;
- Het opvolgen van de sepsis resuscitatiebundel en managementbundel is geassocieerd met continue kwaliteitsverbetering in de zorg voor patiënten met sepsis en een daling van de mortaliteit ten gevolge van sepsis;
- Voor een vroege herkenning van patiënten met sepsis is de kennis van zorgprofessionals betreffende de diagnostiek en behandeling van sepsis van groot belang en deze kennis kan aantoonbaar en langdurig verbeterd worden door een korte scholingsinterventie;

- Door verpleegkundigen een grotere rol en verantwoordelijkheid te geven in de screening van patiënten met sepsis en het uitvoeren van de benodigde diagnostiek op de spoedeisende hulp worden patiënten met sepsis sneller herkend en behandeld;
- De aanwezigheid van landelijke en lokale antibioticarichtlijnen geeft nog geen garantie dat artsen zich ook aan deze richtlijnen houden;
- Het afwijken van de antibioticarichtlijnen leidt in het algemeen niet tot een betere antibiotische behandeling.

De belangrijkste aanbevelingen voor de praktijk en voor nader onderzoek zijn:

- Voor een verdere evaluatie en verbetering van handhygiëne is de ontwikkeling van nieuwe, op barrières gerichte implementatiestrategieën voor zowel verpleegkundigen als artsen noodzakelijk;
- Er dient meer onderzoek gedaan te worden naar voorkomende barrières bij de implementatie van handhygiënerichtlijnen;
- Het opvolgen van richtlijnen, inclusief die voor handhygiëne, dient geëvalueerd te worden tijdens het jaarlijkse functioneringsgesprek van iedere gezondheidszorgmedewerker;
- Het effect van de implementatie van de sepsisbundels op ligduur, mortaliteit en zorgprocessen dient in alle ziekenhuizen gemeten te worden;
- Om het succes van de implementatie van de sepsisbundels beter te kunnen begrijpen en om te weten welke implementatiestrategieën in het verleden het meest succesvol waren, is het noodzakelijk om inzicht te verkrijgen in de uitgevoerde implementatiestrategieën per ziekenhuis en dit te koppelen aan de behaalde effecten;
- Er dient meer onderzoek gedaan te worden naar voorkomende barrières bij de implementatie van de sepsisbundels;
- Om de kennis van artsen over sepsis en het gebruik van de sepsisrichtlijnen op de spoedeisende hulp te verbeteren, dient iedere nieuwe groep artsen in opleiding op de spoedeisende hulp geïnstrueerd te worden en dient sepsiseducatie standaard onderdeel te worden van het scholingsprogramma voor artsen in opleiding;
- Om vast te kunnen stellen of sepsisscholing zelf leidt tot een snellere herkenning en behandeling van sepsis op de spoedeisende hulp, is nader onderzoek naar het effect van scholing op klinische besluitvorming noodzakelijk;
- Om na te kunnen gaan of scholingsinterventies voor internisten in opleiding daadwerkelijk effectief zijn, dienen de effecten van verschillende scholingsinterventies regelmatig geëvalueerd te worden;

- Omdat een verpleegkundige in de meeste gevallen de eerste zorgmedewerker is die een patiënt op de spoedeisende hulp ziet, is het noodzakelijk dat verpleegkundigen een meer prominente rol krijgen in de herkenning en behandeling van patiënten met sepsis;
- Het effect van de implementatie van een sepsisprotocol op zowel spoedeisende hulp, verpleegafdelingen als intensive care afdelingen, inclusief intensivering van de rol van verpleegkundigen, dient in een toekomstige multicenter gerandomiseerde gecontroleerde studie geëvalueerd te worden;
- Voor een verdere verbetering van de vroegtijdige herkenning van patiënten met sepsis en het opvolgen van de op de surviving sepsis campaign gebaseerde richtlijnen is de uitvoering van aanvullende implementatie strategieën noodzakelijk;
- Om data met betrekking tot de uitvoering van de surviving sepsis campaign richtlijnen makkelijker te verkrijgen en te kunnen evalueren is de beschikbaarheid van een elektronisch registratiesysteem een absolute noodzakelijkheid;
- Om het opvolgen van de antibioticarichtlijnen te verbeteren dient een verbeterprogramma inclusief interventies op het niveau van zowel cultuur, context als gedrag ontwikkeld en uitgevoerd te worden;
- Om inadequaat en onnodig gebruik van antibiotica te reduceren dienen restrictieve strategieën onderdeel te zijn van een richtlijnverbeterprogramma.



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AUC	= area under the receiver operating characteristics curve
ED	= emergency department
CCMS	= central college of medical specialties
CI	= confidence interval
CRP	= C-reactive protein
ESBL	= extended-spectrum beta-lactamase
HAIs	= hospital-acquired infections
HH	= hand hygiene
ICU	= intensive care unit
IHI	= institute for health care improvement
IL	= interleukin
IQR	= interquartile range
LBP	= lipopolysaccharide (LPS)-binding protein
LOS	= length of stay
LRTI	= lower respiratory tract infection
NPV	= negative predictive value
OR	= odds ratio
PCT	= procalcitonin
PPV	= positive predictive value
ROC	= receiver operating characteristics
RODIN	= regional professional training for internal medicine
RUNMC	= Radboud university Nijmegen medical centre
SD	= standard deviation
SIRS	= systemic inflammatory response syndrome
SSC	= surviving sepsis campaign
(s)TREM-1	= (soluble) triggering receptor expressed on myeloid cells-1
UMC	= university medical centre
VMS	= safety management system

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2007

- **Tromp, M.** Tetanus. *Verpleegkundig Vademecum*, 19, 2007.
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Dankwoord

Wauw, wat ben ik veel mensen dank verschuldigd voor hun hulp en steun bij de totstandkoming van dit proefschrift! Ik kan onmogelijk de volgorde bepalen van wie hoe belangrijk was, want al deze bijzondere mensen hebben een essentiële bijdrage geleverd. Zonder begin geen einde, dus laat ik ook wat mijn dankwoord betreft maar gewoon bij het begin beginnen.

(Co) Promotoren

Professor P. Pickkers, beste Peter, in 2005 werd ik als net afgestudeerd verpleegkundig specialist gevraagd om lid te worden van de 'commissie patiëntenzorg' van het toenmalige Nijmeegs Universitair Centrum voor Infectieziekten (NUCI). Een van de doelen van deze commissie was het in kaart brengen en het – waar nodig – verbeteren van de kwaliteit van zorg voor verschillende patiëntencategorieën binnen de afdeling infectieziekten. Het eerste (met name door jou voorgestelde) verbeterproject werd 'de diagnostiek en behandeling van patiënten met sepsis'. Waar ik bij de eerste bijeenkomsten nog dacht dat er sprake zou zijn van een kortdurend project, bleek de werkelijkheid toch enigszins anders te zijn. Na onze eerste pilotstudie op de spoedeisende hulp werden jouw – en na wat meer ervaring ook mijn – plannen voor wat betreft het verbeteren van de zorg voor patiënten met sepsis alleen maar groter, waarbij je mij hebt meegenomen op een onbekende wetenschappelijke reis. Na alle inspanningen en het overwinnen van de nodige hobbels (soms bergen) blijkt de eindbestemming echt geweldig mooi te zijn. Ongelooflijk bedankt voor jouw kostbare tijd, voor de inbreng van (soms wat veel) nieuwe ideeën en overleg. Ook grote dank voor de zeer zinvolle feedback en het trekken van de kar. Ondanks – of dankzij? – de enorme inhoud van jouw mailbox is het jou een aantal keren gelukt om een door mij per ongeluk kwijtgeraakt bestand terug te vinden en mij weer toe te sturen. Zoals je zelf dan zei: 'Als je mij toch niet had…'. Inderdaad, dan was dit proefschrift nog lang geen feit geweest!

Professor B.J. Kullberg, beste Bart-Jan, gedurende de opleiding tot verpleegkundig specialist was jij mijn medisch mentor en zag jij de meerwaarde van deze nieuwe functie binnen de afdeling infectieziekten. Heel veel dank voor het mede ontwikkelen van de functie van verpleegkundig specialist infectieziekten, het vertrouwen in mijn kunnen, jouw steun in moeilijke tijden en de tijd die ik gekregen heb om mijn promotieonderzoek zo veel mogelijk in werktijd te kunnen uitvoeren. Ik realiseer me echt tot op de dag van vandaag dat dit heel uitzonderlijk is.

Professor T. van Achterberg, beste Theo, alweer 8 jaar geleden begeleidde jij mij bij mijn afstudeeronderzoek voor de opleiding Master of Arts in Advanced Nursing Practice. Wie had ooit gedacht dat deze opleiding het begin zou zijn van mijn onderzoekscarrière. De functie van verpleegkundig specialist bevindt zich op het overgangsgebied tussen verpleegkundige en medische zorg. Vandaar dat ik jouw begeleiding, naast die van medici, gedurende mijn promotietraject een vereiste vond. Heel veel dank voor jouw verpleegkundig wetenschappelijke bijdrage, feedback, jouw altijd positieve instelling, vertrouwen en de persoonlijke interesse.

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Ondanks het feit dat jij gedurende mijn promotietraject de rol van copromotor hebt vervuld, ben je inmiddels benoemd tot hoogleraar met als leeropdracht ‘kwaliteit van zorg voor infectie- en ontstekingsziekten’. Heel bijzonder om aan het einde van mijn promotietraject te kunnen zeggen dat ik begeleid ben door vier hoogleraren.

Paranimfen

Heel veel dank aan mijn paranimfen Chantal Bleeker - Rovers en Linda Linders - Evers. Al voordat dit promotietraject begon, hebben jullie mij met volle overgave gesteund en hebben jullie op een eigen manier een geweldige bijdrage geleverd aan de totstandkoming van dit proefschrift. Mijn dank hiervoor is eigenlijk niet in woorden uit te drukken!

Beste Chantal, heel erg bedankt voor het vertrouwen in mij en de tijd en energie die jij gestoken hebt in de ontwikkeling van de functie van verpleegkundig specialist infectieziekten en de totstandkoming van de artikelen in dit proefschrift. Hoewel niet officieel als zodanig benoemd ben jij voor mij gedurende het hele promotietraject ook mijn copromotor geweest. Ondanks je drukke agenda probeerde je altijd tijd vrij te maken voor het doorspitten van statussen en laboratoriumuitslagen, het lezen van mijn artikelen en het zetten van de spreekwoordelijke puntjes op de i. Naast het bespreken van werkgerelateerde zaken kon ik altijd bij jou terecht voor een persoonlijk gesprek (zeker ook in moeilijke tijden). Daarom ook op persoonlijk vlak heel veel dank voor jouw interesse, steun, begrip en zinvolle adviezen waarbij je soms terecht aangaf dat ik een pas op de plaats moest maken. Ik ben enorm blij en trots dat jij op deze bijzondere dag mijn paranimf wilt zijn.

En dan mijn beste vriendin Linda, lieve Lin, al sinds geruime tijd ben jij mijn hartsvriendin en hebben we 'lief en leed' met elkaar gedeeld. Belangrijke hoogtepunten die we samen hebben mogen delen waren de geboorte van Mick (2005), jouw huwelijk met Marco (2008), de geboorte van Anne (2010) en de geboorte van Thijmen en Julian begin dit jaar. Dieptepunten zijn er zeker ook geweest maar deze vallen, zeker bij een gebeurtenis als deze, in het niet bij alle gelukkige momenten. Ondanks onze drukke agenda's hebben we de afgelopen jaren regelmatig samen genoten van een weekendje weg, een dagje winkelen of heerlijk relaxen. Jij was altijd geïnteresseerd in mijn artikelen en je had er alle vertrouwen in dat het goed zou komen. Zie hier het resultaat! Het feit dat wij vertrouwen hielden in een goed einde, heeft er voor gezorgd dat het moment van de uitgave van mijn boekje nu toch is aangebroken en ik mijn proefschrift in het openbaar mag gaan verdedigen. Heel speciaal dat ook jij als paranimf naast mij wilt staan op deze bijzondere dag.

Medewerkers verpleegafdeling EOV

Anita van Rossum, beste Anita, heel veel dank dat ik de tijd en ruimte heb gekregen om een promotietraject af te leggen. Hoewel het doen van onderzoek soms ten koste ging van andere belangrijke werkzaamheden op de afdeling, heb ik mij altijd gesteund gevoeld door jou. We hebben de afgelopen jaren regelmatig

persoonlijke gesprekken gevoerd die voor mij zoveel meer hebben betekend dan een formeel gesprek met de hoofdverpleegkundige.

Dr. Han Repping-Wuts, hoewel je niet meer officieel werkzaam bent op verpleegafdeling EOV ben je nog steeds een belangrijk onderdeel van de afdeling reumatische ziekten en endocriene ziekten. Lieve Han, jij bent mijn grote voorbeeld voor wat betreft rust, structuur en doorzettingsvermogen. In die zin heb ik veel van jou geleerd en ben ik blij dat ik de eerste jaren van mijn promotietraject samen met jou een werkkamer heb mogen delen.

Physician assistant Michael Heijnen, verpleegkundig specialisten Rene Bakker en Anke Hendriks, seniorverpleegkundigen Maaike Eeren, Judith Hendriks en Hanneke Jansen en alle overige medewerkers van afdeling EOV, heel veel dank voor jullie interesse en steun gedurende het gehele promotietraject. Ondanks dat jullie mij de laatste jaren weinig op de afdeling hebben gezien, heb ik altijd het gevoel gehouden dat ik welkom ben. Na het afronden van mijn promotietraject hoop ik weer meer met jullie samen te werken.

Medewerkers afdeling spoedeisende hulp

Alle medewerkers van de spoedeisende hulp, ontzettend bedankt voor jullie gastvrijheid, het includeren van alle sepsispatiënten en het afnemen van extra bloedmonsters. Vanaf het begin zagen jullie de meerwaarde van de implementatie van het sepsisprotocol, hetgeen tot zulke goede resultaten heeft geleid. Het feit dat het sepsisprotocol nog steeds een begrip is op jullie afdeling is hiervoor tekenend.

In het bijzonder wil ik Lilian Peters bedanken. Beste Lilian, bij de introductie van het sepsisprotocol op de spoedeisende hulp fungeerde jij als rolmodel voor de afdeling. Dank daarvoor, dank voor jouw kritische blik en heel veel dank voor het, voornamelijk tijdens jouw nachtdiensten, opzoeken van de benodigde gegevens in E-care.

(Overige) medeauteurs

Professor van der Meer, beste Jos, ik wil je uiteraard heel hartelijk danken voor onze prettige samenwerking tijdens het handhygiëneproject maar vooral ook voor de samenwerking en jouw belangstelling buiten dit project om. Vooral heel veel dank voor het feit dat jij mij er in 2008 van hebt weten te overtuigen dat ik mijn functie als verpleegkundig specialist infectieziekten niet zou moeten opgeven voor een functie elders. Wat ben ik achteraf blij dat ik jouw advies heb opgevolgd. Hoewel ik jouw vertrek enorm betreur, ben ik er trots op dat ik tijdens jouw laatste jaar als medisch hoofd van de afdeling algemeen interne geneeskunde toch nog samen met jou een artikel heb mogen schrijven.

Drs. Anita Huis, hartelijk dank dat wij vanuit het project '*Clean Care is Safer Care'* hebben mogen aansluiten bij jouw ziekenhuisbrede handhygiëneproject *'Helping Hands'*. Door onze krachten te bundelen, hebben we de implementatiestrategieën op zowel verpleegkundigen als artsen kunnen loslaten en kunnen we ons handhygiëne artikel allebei gebruiken voor ons proefschrift!

Inge de Guchteneire, beste Inge, sinds 2009 vervulden we samen de functie van verpleegkundig specialist infectieziekten (jij destijds in opleiding). Zodoende was jouw betrokkenheid bij mijn promotieonderzoek en met name bij het project *'Clean Care is Safer Care'* groot. Heel veel dank voor onze prettige en gezellige samenwerking en jouw bijdrage als rolmodel tijdens het handhygiëne onderzoek. Hoewel ik jouw vertrek naar Universitair Longcentrum Dekkerswald volkomen begrijp vind ik het nog steeds erg jammer dat we zodoende geen directe collega's meer zijn.

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Dr. Hazra Biemond - Moeniralam, Drs. Simone Gielen - Wijffels, Drs. Geertjan Goekoop, Drs. Dave Tjan, physician assistant Christine Wallenborg en Dr. Arthur van Zanten. Jullie zijn een van de belangrijkste kartrekkers van de Nederlandse surviving sepsis campaign. Hartelijk dank voor de samenwerking en het vrijgeven van de Nederlandse surviving sepsis campaign data.

Drs. Daniëlle van den Berg, heel veel dank voor het verwerken van een heleboel data in SPSS. Heel bijzonder dat jij als – destijds – student geneeskunde een bijdrage hebt willen leveren aan mijn proefschrift.

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Tot slot, maar zeker niet het minst belangrijk, Professor George Borm, Drs. Benno Lansdorp en Dr. Mark van den Boogaard, super bedankt voor alle (in ieder geval voor mij) ingewikkelde analyses. Voor mij staat inmiddels vast dat analyseren nooit mijn favoriete bezigheid zal worden.

Manuscriptcommissie

Bij deze wil ik de leden van de manuscriptcommissie, Professor P. Verweij, Professor K. van Laarhoven en Professor P.J. van den Broek hartelijk danken voor het beoordelen van het manuscript.

Collega's polikliniek

Beste Marjolein Bosch, Karin Grintjes, Rolina Meijering en Bert Zomer, met jullie als kamergenoten heb ik volgens mij toch wel het leukste gedeelte van mijn promotietraject mogen delen, namelijk de afrondende fase. Hoewel ik in eerste instantie dacht dat ik het na het inleveren van het manuscript minder druk zou krijgen, hebben jullie mij de afgelopen maanden nog regelmatig horen zuchten en steunen. Ondanks dat was het vooral ook heel leuk om de totstandkoming van het uiteindelijke boekje en het regelen van het feest met jullie te kunnen delen. Ook jullie heel veel dank voor de prettige samenwerking, jullie luisterend oor en steun.

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Vormgever

Beste Theo Hafmans, bij deze wil ik jou heel hartelijk danken voor de geweldige samenwerking voor wat betreft de vormgeving van dit boekje. Heel bijzonder dat jij speciaal voor mij een *E-coli* bacterie hebt opgewerkt voor elektronenmicroscopie om er volgens prachtige foto's van te kunnen maken. Het eindresultaat van zowel de cover als het binnenwerk is echt geweldig!

Vrienden en familie

Lieve vriendinnen en vrienden, ik ben mij ervan bewust dat ik de afgelopen jaren vooral voor mijzelf en het afronden van dit proefschrift heb gekozen. Ondanks dat zijn vrienden net als sterren, je ziet ze niet altijd maar ze zijn er wel degelijk! Heel veel dank voor jullie interesse, begrip en luisterend oor tijdens de schaarse maar voor mij o zo waardevolle en ontspannende feestjes en avondjes uit.

Lieve (schoon-)ouders, zus, zwagers, en schoonzussen. Voor jullie was het wellicht soms moeilijk te bevatten waar ik al die tijd zo druk mee ben geweest. Hopelijk begrijpen jullie na de verdediging van mijn proefschrift waar ik mij, samen met een heleboel anderen, de afgelopen jaren mee bezig heb gehouden. Ik ben enorm trots en blij dat jullie deze bijzondere mijlpaal in mijn leven met mij kunnen en willen delen en ik heb zo'n vermoeden dat hier nog lang over nagepraat zal worden.

Lieve Mick, wat ben ik toch blij en dankbaar dat jij er bent! Door jou besef ik dat werk zeker niet het allerbelangrijkste is in het leven en geniet ik iedere dag van jouw vrolijkheid en kinderlogica.

Last but not least, dear sweetie, lieve Dennis, al voordat onze relatie serieuze vormen begon aan te nemen, ondersteunde jij mij bij het schrijven van de

artikelen ten behoeve van dit proefschrift. Na het behalen van een posterprijs organiseerden we ons eerste etentje samen. Dat was het begin van een geweldige tijd samen waarin je mij de ruimte hebt gegeven om aan dit proefschrift te kunnen werken. Jouw doorzettingsvermogen en motiverende instelling, zeker ook op de moeilijke momenten, hebben er absoluut toe bijgedragen dat mijn proefschrift nu een feit is.

De afgelopen twee jaar hebben we ons allebei op ons eigen project gestort: ik op de afronding van mijn proefschrift en jij op het plaatsen van de nieuwe badkamer. Dat we nu tegelijkertijd klaar zijn met ons project, kan toch geen toeval zijn. Ik hoop nog heel lang samen met jou te kunnen genieten van een warm bad. Dank je wel voor wie je bent!

Liefs, Mir

Curriculum Vitae

Mirjam Tromp werd geboren op 25 mei 1976 te Doetinchem. Na het behalen van haar MAVO-diploma aan het Dorenweerd College te Doorwerth (1996) volgde ze de opleiding HBO-Verpleegkunde aan de Hogeschool van Arnhem en Nijmegen (diploma 2000).

Haar verpleegkundige carrière startte zij als gediplomeerd verpleegkundige op de afdeling algemeen interne geneeskunde en longziekten (E10) van het UMC St Radboud. Haar aandachtsgebied was de zorg voor patiënten met HIV. Na de opening van een nieuwe verpleegafdeling binnen het toenmalige cluster inwendige specialismen werden de patiënten met infectieziekten niet langer primair op afdeling E10 opgenomen. Op dat moment werd nóg duidelijker dat de interesse voor patiënten met infectieziekten groot was. Zodoende volgde ze deze specifieke patiëntengroep en werkte zij sinds februari 2002 als gediplomeerd verpleegkundige op de afdeling algemeen interne geneeskunde en reumatische ziekten (EOV), alwaar haar aandachtsgebied '*HIV-zorg'* werd uitgebreid naar '*infectieziekten'*.

Om dit aandachtsgebied meer diepgang te geven startte zij in september 2002 met de opleiding Master of Arts in Advanced Nursing Practice (diploma 2004). Na afronding van deze opleiding nam ze deel aan diverse werkgroepen en verbeterprojecten. Zij was onder andere lid van de 'commissie patiëntenzorg' van het Nijmeegs Universitair Centrum voor Infectieziekten (NUCI), tegenwoordig Nijmegen Institute for Infection, Inflammation, and Immunity (N4i), waar in 2005 het project '*Verbeteren van de diagnostiek en behandeling van patiënten met sepsis'* startte. Daarnaast werd zij in 2009 projectleider van het twee jaar durende project *'Clean Care is Safer Care'*. Binnen deze twee projecten verrichtte zij in totaal 7 wetenschappelijke studies die geresulteerd hebben in dit proefschrift.

Mirjam Tromp woont in Elst (Gld), waar zij haar leven deelt met Dennis Brinke en haar zoon Mick (2005).