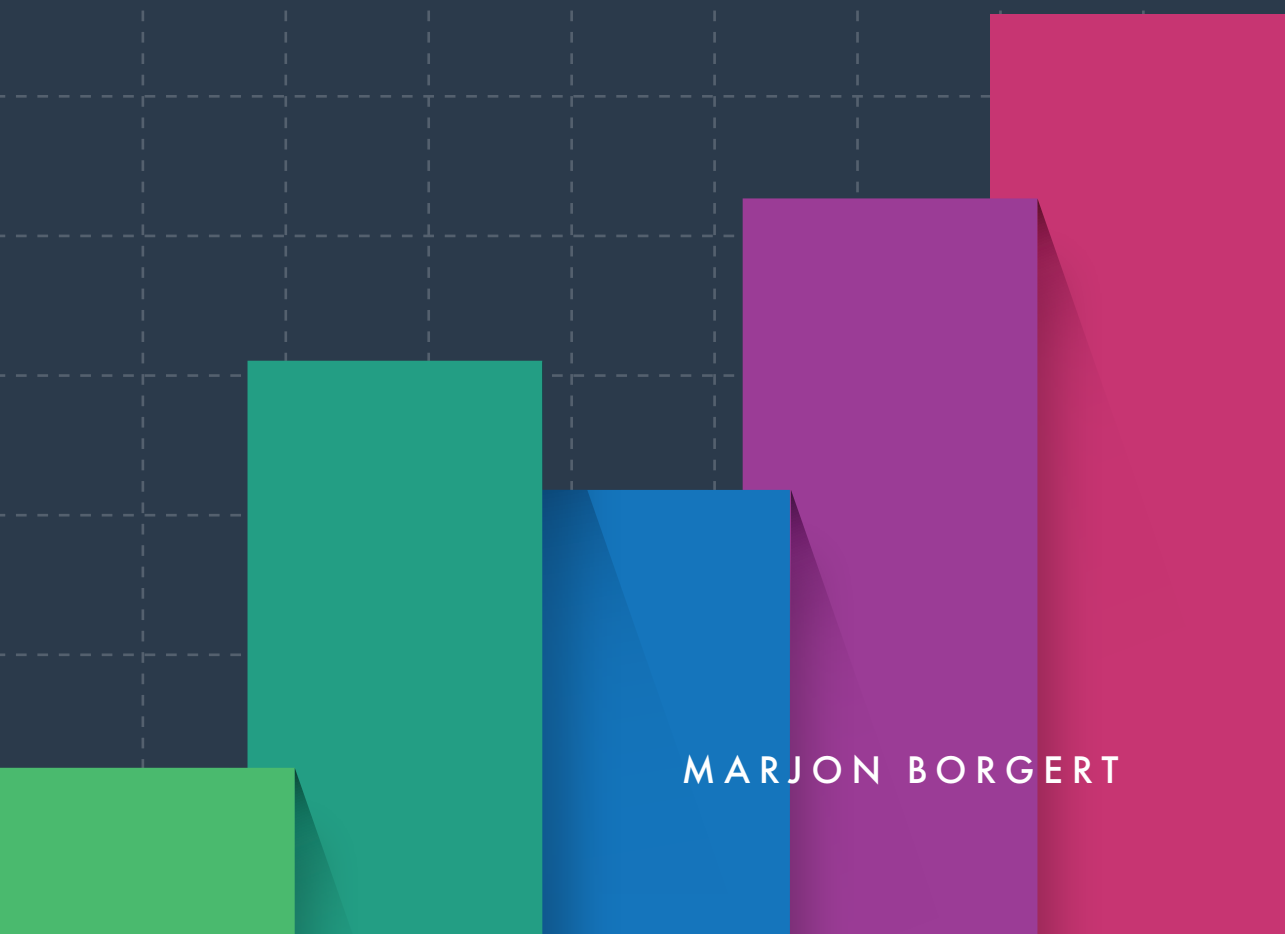
IMPROVING PATIENT SAFETY FOR THE CRITICALLY ILL

The challenges of implementation



MARJON BORGERT

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Cover design and layout by Design Your Thesis (www.designyourthesis.com)
Printed by Ridderprint (www.ridderprint.nl)
ISBN 978-94-6299-694-6

IMPROVING PATIENT SAFETY FOR THE CRITICALLY ILL
THE CHALLENGES OF IMPLEMENTATION

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit van Amsterdam
op gezag van de Rector Magnificus
prof. dr. ir. K.I.J. Maex
ten overstaan van een door het College voor Promoties ingestelde commissie,
in het openbaar te verdedigen in de Agnietenkapel
op vrijdag 3 november 2017, te 12.00 uur

door

Maria Johanna Borgert
geboren te Gramsbergen

PROMOTIECOMMISSIE

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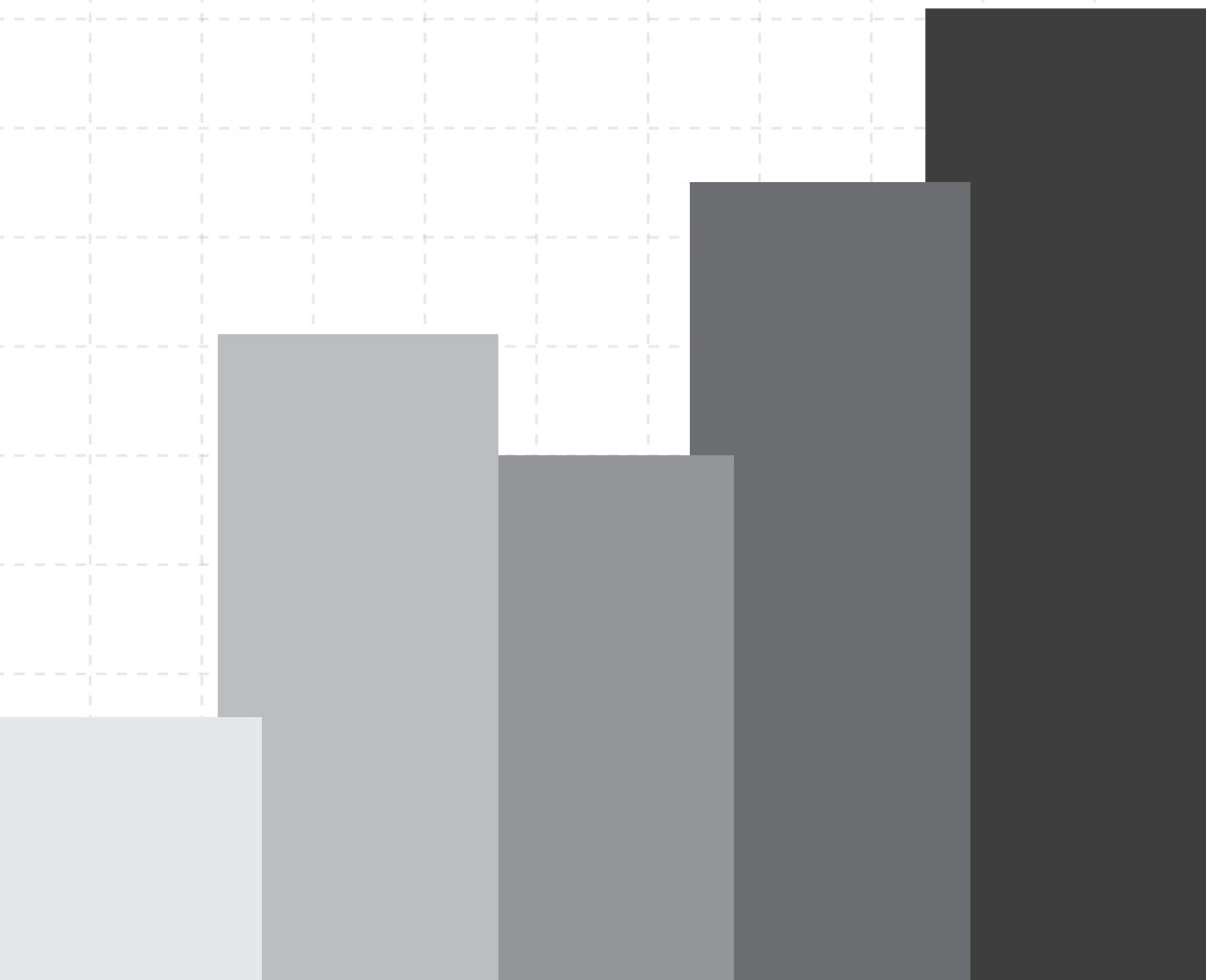
CONTENTS

Voor oom Koop en tante Truus



01

GENERAL INTRODUCTION AND OUTLINE OF THE THESIS

GENERAL INTRODUCTION

Intensive care

The intensive care unit (ICU) is a highly complex environment. This complexity is due to the multitude of technologies in use, the many different medications being administered, the complexity of illnesses being treated, and the wide range of ICU professionals who work together there, often under emergency circumstances. In such complex environments, adverse events are more likely to occur. Because the tolerance of critically ill patients to such events is low, patient safety is an important issue in the ICU.[1-3]

'To err is human'

In 1999, the Institute of Medicine (IOM) released its report 'To Err is Human: Building a Safer Health System'. Since then, the issue of patient safety has become increasingly important. This report stated that around 44,000 to 98,000 patients die in hospitals in the United States every year due to preventable medical errors.[4] The report has had an enormous impact on awareness of patient safety issues worldwide, and has led to an increase in the number of research projects being conducted on patient safety around the world.[5] Patient safety research applies outcomes of safety science to achieve reliable health care delivery systems; it also minimizes the incidence and impact of, and maximizes recovery from, adverse events.[6] Adverse events are injuries that occur as a result of health care delivery itself rather than the underlying disease[7], and are seen as a serious problem that must be prevented.

How defining patient safety has changed over time

Only a few decades ago, complications in hospitals were seen to be an inevitable consequence of medical interventions.[8] This has changed over the years, and some types of complications have come to be seen as unacceptable, and as potentially preventable adverse events. For example, hospital-acquired infections (HAIs) were once seen as unavoidable complications. Due to a better understanding of the mechanisms of infectious disease transmission and of how to prevent HAIs, we now see these infections as unacceptable complications.[9] Over the years, even more complications have become preventable - including falls, pressure ulcers, catheter-related urinary tract infections, and venous thromboembolism - and are now seen as unacceptable events. Due to the continuous improvement of medical interventions and surgical techniques and the growing concerns for patient safety, the number of unacceptable events might be even larger in future.[10] Vincent and Amalberti state that patient safety can be seen as a 'constantly moving target'.[10] According to Vincent, patient safety is therefore defined as

'the avoidance, prevention, and amelioration of adverse outcomes or injuries stemming from healthcare itself. It should address events that span the continuum of "errors" and "deviations" to accidents'.[11]

Learning from incidents

To improve patient safety, it is important to understand the causes of potentially preventable adverse events. Analysing adverse events and searching for interventions to prevent them is one way to gain insight into these causes. Progress has been made on the quality of patient safety research itself as well as on incident analyses. In the earlier days of patient safety research, incidents were viewed as a substandard performance by individual professionals, and inattentiveness, distractions, and low motivation were some of the reasons given for their occurrence.[10] Nowadays, though, incidents are seen more as problems resulting from organizational or system-wide factors.[12,13] Health care professionals are influenced by the work they are doing, the team they are part of, their working environment, and the organization they work for, which are known as system factors.[14] The actions of professionals are influenced by processes within the broader organization or within their local working environment. A slogan coined by Paul Batalden from the Institute for Healthcare Improvement (IHI) underlines this principle: 'Every system is perfectly designed to get the results it gets'.[15]

Quality chasm

Many patients come to harm because professionals do not consistently follow evidence-based recommendations or guidelines.[11] Guidelines aim to reduce variability in clinical care and to increase adherence to evidence-based interventions.[10] However, studies suggest that patients receive only about 50% of the recommended care, or undergo unnecessary or harmful treatments or investigations.[16,17] This problem actually starts with the slow uptake and dissemination of research findings from biomedical science in hospitals. Often, multiple studies have to be conducted before new findings become official recommendations for clinical practices.[18] One important reason for this is the external validity, generalization and applicability of new resarch findings.[19] Often, studies do not provide sufficient contextual information, which makes it hard to make judgements about the applicability of study results. Subsequent studies have shown that implementation of these recommendations lags even further behind. This means there is a large gap between the time new research findings become available and when they are actually incorporated into daily care practices. As a consequence, the clinical care many patients receive during this gap is not in line with the latest research

findings.[18] In the literature, this gap is called the 'quality chasm', and the IHI has captured it perfectly in a quote borrowed from the German poet Goethe: 'Knowing is not enough; we must apply. Willing is not enough; we must do'.[20]

Implementation of quality improvement interventions

Even though there might be strong evidence and high-quality clinical guidelines, it is a real challenge to actually implement new findings. This is especially true if this requires changes to behaviour, clinical practices, the organization, or how professionals collaborate.[17] To improve patient safety and the quality of care provided to critically ill patients, we need to understand those factors that facilitate or hamper successful implementation of evidence-based practices and guidelines.[21] According to Cabana *et al.,* implementation can be affected by multiple barriers related to professionals' knowledge, attitudes, and behaviour.[22] Examples from the literature show that the professionals themselves can form a barrier to implementation: sometimes they are not aware of clinical guidelines or are not familiar with evidence-based recommendations; they do not agree with the recommendations or the evidence; they believe the guideline is too difficult to use in their own hospital or that patient-related factors may interfere; or they are not motivated to change their practices.[23] However, patient-related factors, organizational factors, and economic factors have also been shown to be important barriers to implementation.[17,24] To select strategies for successful implementation, it is important to understand the barriers and facilitators to implementation.[25] Implementation science has therefore become more important over the years, especially for implementing quality improvement projects in hospitals. Implementation science can be defined as 'the scientific study of methods to promote the systematic uptake of research findings and other evidence-based practices into routine practice to improve the quality and effectiveness of health care'.[26,27]

Model for translating evidence into practice

Various models, frameworks, and theories have been developed to understand and explain why implementation of quality improvement initiatives succeeds or fails.[25,26] Pronovost *et al.* developed a useful model for translating research findings into daily practice in the ICU.[28] This model sets out the phases of the process of translating research into practice; it also includes how research findings are implemented. The model, which consists of four steps, can be used to guide the process of translating research into clinical practices, and is shown in Figure 1.

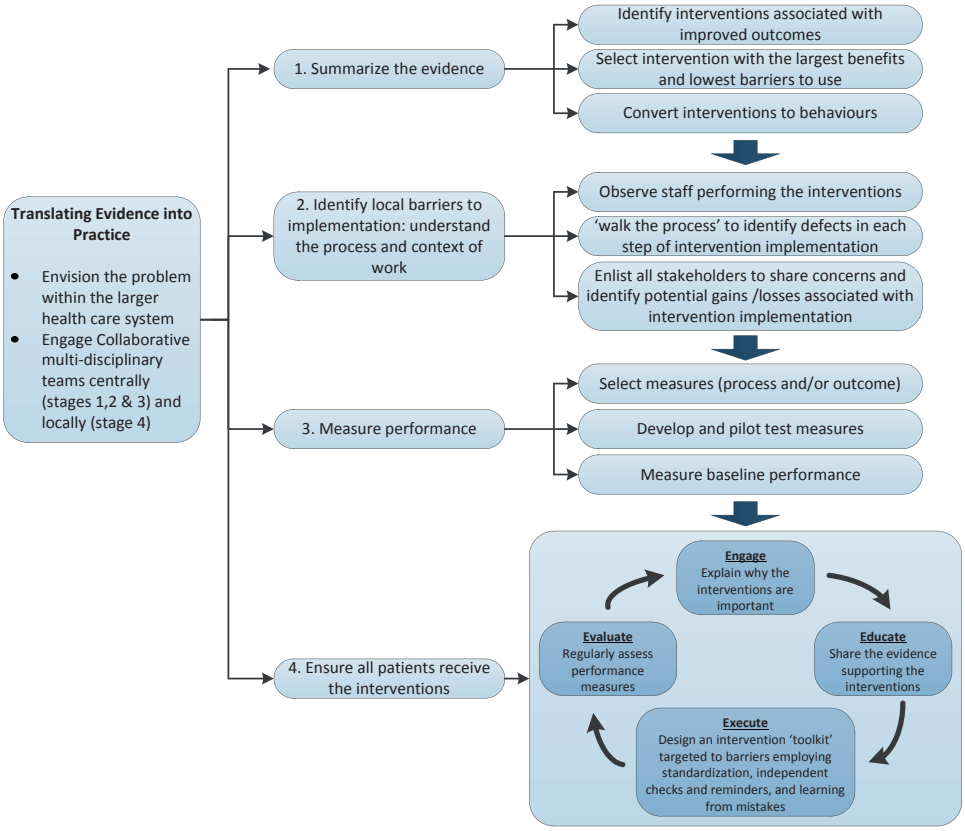


Figure 1. Model for translating evidence into practice.[28]

Pronovost *et al.* used this model to improve the reliability of care for patients with central venous catheters in the ICU.[28] This quality improvement project aimed to reduce the number of central line infections associated with central line insertions.[28] During the study period of 18 months, the overall central line infection rate was reduced by 66%. Despite this success, implementing evidence-based practices in the ICU remains a challenge on the whole.[17,25] Patient safety improvements show varying results.[25,29] In most cases, new evidence-based practices are introduced rapidly, with no structured implementation plan available for changing behaviour. Successful implementation usually depends on a systematic approach that has been thoroughly planned and analysed.[25]

AIM AND OUTLINE OF THIS THESIS

This thesis focuses on the implementation of strategies for improving patient safety and quality of care for critically ill patients by encouraging the uptake and implementation of best practices.

Part I focuses on improving patient safety for critically ill patients on nursing wards by implementing a rapid response system with support from the ICU. **Part II** focuses on improving patient safety for critically ill patients in the ICU by implementing evidence-based care bundles.

Part I. Improving patient safety for critically ill patients on nursing wards

Serious adverse events such as unplanned admission to an ICU, cardiac arrest, and unexpected death are often preceded by changes in vital sign observations.[30,31] In this respect, they are thus predictable.[30,31] However, hospital staff do not always recognize these signs in time, or do not act on them in an adequate or timely fashion.[32] Failure to recognize or respond adequately to the deteriorating patient can lead to a delay in treatment, which can subsequently lead to serious adverse events such as cardiopulmonary resuscitation or even death.[32-34] Rapid response systems (RRSs) are developed to improve care for the deteriorating patient. RRSs have 'afferent' (criteria for detecting deterioration) and 'efferent' (responsive) arms.[35] The afferent arm is concerned with recognizing the patient's condition prior to deterioration using a 'track-and-trigger system', such as the modified early warning score (MEWS).[36] The efferent arm is designed to trigger response by the rapid response team (RRT).[35] This team generally consists of ICU physicians and ICU nurses, and is designed to respond within 10 minutes for evaluation, triage, and treatment of patients who clinically deteriorate on a nursing ward and to prevent them from suffering a serious adverse event.[37]

Part I consists of the following two chapters. **Chapter 2** describes the effects of different MEWS implementation strategies on nursing wards. Nursing wards were randomized to measure the MEWS either three times daily or on indication (i.e. if one or more vital signs were abnormal). In this quasi-experiment, we studied the effects of protocolized measurement (i.e. three times daily) of the MEWS versus measurement on indication. In **Chapter 3**, we retrospectively analyse the 'false arrests' to determine the 'level of urgency' of these false arrests to find scope for improving efficiency within emergency care.

Part II. Improving patient safety for critically ill patients in the ICU.

The IHI developed the concept of care bundles to enhance the reliability of care and to improve the quality of care.[38,39] A care bundle is a structured way of improving care processes and patient outcomes. Bundles consist of a small set of three to five evidence-based interventions for clinical processes or patient populations. The strength of bundling a small set of interventions is that the evidence-based care will be applied uniformly to every eligible patient. This may result in better patient outcomes than when the interventions are implemented individually.[38-41]

Part II focuses on the development and implementation of evidence-based care bundles for ICU patients, and consists of the following five chapters. In **Chapter 4**, we use a systematic literature review to identify methods other than the IHI approach for supporting the development of new evidence-based care bundles for the ICU. **Chapter 5** describes enteral nutrition delivery in the ICU. To find ways of improving quality of care, it is important to identify patients at risk of malnutrition. In this study, which was conducted over a period of three years, we assessed the extent to which ICU patients received their daily enteral nutritional intake during ICU admission. This study could form the basis for developing strategies for supporting ICU staff in providing adequate enteral nutrition, thereby minimizing the risk of malnutrition. In **Chapter 6**, we determine common strategies for implementing care bundles in the ICU and assess the effects of these strategies on the quality of the implementation of these bundles. **Chapter 7** describes the implementation of a transfusion care bundle for the delivery of red blood cells (RBC). In this implementation study, which had a quasi-experimental comparative study design, we investigated the difference in the effect on transfusion bundle compliance between monthly team-level audit and feedback (A&F) versus monthly team-level A&F plus timely individual A&F. In **Chapter 8** we quantify the true effect of the transfusion bundle by assessing, per transfusion, whether the decision to transfuse was based on a lower pre-transfusion haemoglobin (Hb) level than the patient's individual preset Hb threshold. The objective of this study was to investigate whether the application of the transfusion bundle would reduce the number of inappropriate RBC transfusions in an ICU setting. The final two chapters include the general discussion and summaries in both English and Dutch **(Chapters 9 and 10).**

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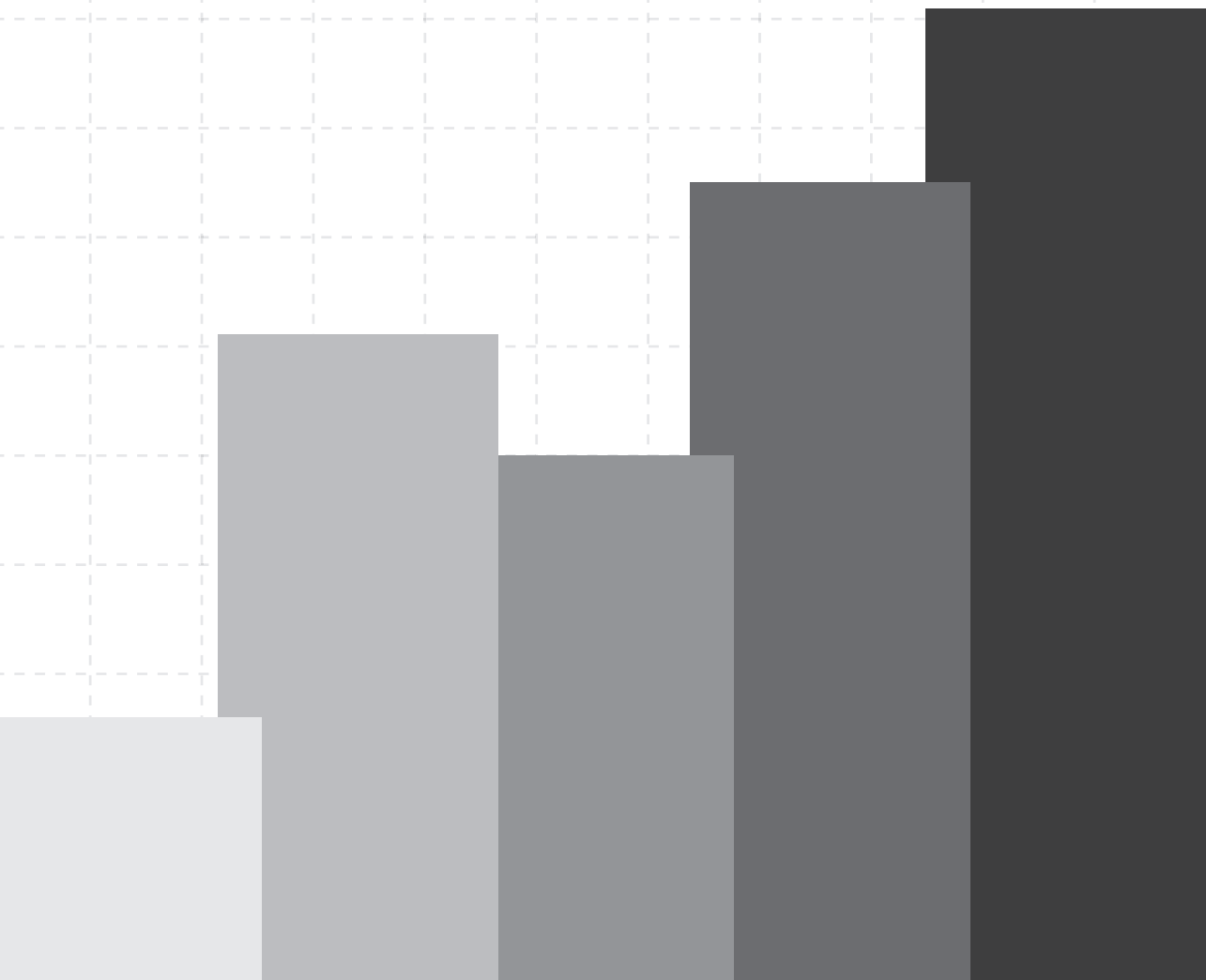
PART I

IMPROVING PATIENT SAFETY FOR CRITICALLY ILL PATIENTS ON NURSING WARDS



02

STANDARDIZED MEASUREMENT OF THE MODIFIED EARLY WARNING SCORE RESULTS IN ENHANCED IMPLEMENTATION OF A RAPID RESPONSE SYSTEM: A QUASI-EXPERIMENTAL STUDY

Jeroen Ludikhuize, Marjon Borgert, Jan Binnekade, Christian Subbe, Dave Dongelmans and Astrid Goossens

Resuscitation 2014;85:676-682.

ABSTRACT

Objectives. To study the effect of protocolized measurement (three times daily) of the Modified Early Warning Score (MEWS) versus measurement on indication on the degree of implementation of the Rapid Response System (RRS).

Methods. A quasi-experimental study was conducted in a university hospital in Amsterdam between September and November 2011. Patients who were admitted for at least one over-night stay were included. Wards were randomized to measure the MEWS three times daily ('protocolized') versus measuring the MEWS 'when clinically indicated' in the control group. At the end of each month, for an entire seven-day week, all vital signs recorded for patients were registered. The outcomes were categorized into process measures including the degree of implementation and compliance to set monitoring standards and secondly, outcomes such as the degree of delay in physician notification and Rapid Response Team (RRT) activation in patients with raised MEWS (MEWS ≥ 3).

Results. MEWS calculations from vital signs occurred in 70% (2513/3585) on the protocolized wards versus 2% (65/3013) in the control group. Compliance with the protocolized regime was presents in 68% (819/1205), compliance in the control group was present in 4% (47/1232) of the measurements. There were 90 calls to primary physicians on the protocolized and 9 calls on the control wards. Additionally on protocolized wards, there were twice as much RRT calls per admission.

Conclusions. Vital signs and MEWS determination three times daily, results in better detection of physiological abnormalities and more reliable activations of the RRT.

INTRODUCTION

Rapid Response Systems (RRS) have been implemented without unequivocal evidence regarding their effectiveness.[1,2] The goal of RRS is to identify clinical deteriorating patients in hospitals to prevent cardiopulmonary arrests, unplanned admissions to the Intensive Care Unit (ICU) and unexpected deaths.[3] Up to 80% of patients have vital signs abnormalities in the 24 hours prior to adverse events (AE).[4-6] Presence of suboptimal care and lack of clinical urgency are suggested as significant contributors.[7,8] To aid in the detection process of patients at risk for AE, Track and Trigger Systems have been developed.[9] One commonly used is the Modified Early Warning Score (MEWS), whereby nurses allocate points to the measurement of vital signs resulting in a summary score.[10,11] Upon reaching a predefined threshold, either the primary physician and/or a Rapid Response Team (RRT) is activated. In general the RRT consists of an ICU physician and nurse who respond within 10 minutes after activation.[12,13] This system combined with educational and organizational components is called a RRS.[14] The MERIT trial measured the effect of a RRS but was unable to show a significant clinical benefit.[15] Post hoc analyses identified a high rate of afferent limb failure, i.e. failure to respond to patients with signs of deterioration.[16] Although the face-validity of RRS is high, universal spread and acceptance of the system is hampered by the lack of robust evidence.[17] Current research is focused on afferent limb failure and causes for the delay in identifying deteriorating patients in hospitals where these systems are already implemented.[8,18] It is clear that monitoring of patients on general wards is not uniform in nature and unreliable even in hours prior to AE.[19] Even after major surgery, measurements of vital signs might be incomplete or absent,[20] while evidence is present that increased monitoring is associated with improved outcome.[21,22] In the Netherlands the implementation of a RRS has recently been dictated by the Health Care Inspectorate. We studied the effect of a protocolized measurement (three times daily) of the MEWS versus measurement on indication on the degree of implementation of the RRS.

METHODS

Study design

A quasi-experimental study was conducted from the 1st of September to the 31st of November 2011 in a University Hospital in Amsterdam, the Netherlands. We implemented a RRS on 18 adult general wards. Ten wards were randomized to the protocolized arm to measure the MEWS minimal three times daily and eight to the control arm, i.e. MEWS measurements when clinically indicated. Randomization was performed after stratification according to surgical or medical ward. Patients with at least one overnight stay were included.

Components of RRS

Staff on the intervention (protocol) wards performed a full set of vital signs including a MEWS at least three times daily. Staff on the control wards performed vital signs when judged to be clinically indicated. In both groups, the RRS algorithm (Fig. 1) stipulated that upon reaching a MEWS of 3 points or more ('critical MEWS'), the patients' physician should be notified by the nurse. In accordance with the 'two-tiered' Dutch protocol the patients' primary physicians were instructed to attend to their patients within 30 minutes, perform an assessment and initiate treatment. The physicians' intervention could include activation of the RRT. If the patient did not improve after the primary intervention or if the physician was unable to assess the patient, the RRT had to be notified. The RRT operated 24/7 and consisted of an ICU physician and nurse who attended the patient within 10 minutes after notification.

Implementation process

Implementation of the RRS started in June 2011. Per ward three nurses were trained. Using a 'training the trainers' concept, these nurses educated their colleagues from June until August 2011. There were separate sessions for physicians during hand-over meetings. The RRS algorithm was distributed on pocket cards and advertised with posters, emails to staff and on the local website. From the 1st of September, the RRS was officially in use.

Definitions

Clinically indicated measurement of the MEWS was defined as when regular vital sign measurements led to a MEWS-sub score of 1 or more, this required the complete set of measurements to be calculated (Supplementary File 1). MEWS-sub scores refer to the MEWS applied to a single vital sign. The term 'MEWS' is used for the summation of all (available) sub scores. A MEWS of three or more was defined as a 'critical score'.[10,11]

'Retrospectively calculated MEWS' represent the MEWS calculated by the researchers based on the actual set (irrespective of completeness) of vital signs measured. 'Complete set of measurements' relates to the measurement of eight MEWS parameters and the MEWS summary score. Cardiopulmonary arrest was defined as an event in which respiratory and/or cardiopulmonary activity was absent and for which the cardiopulmonary arrest team was called and initiated cardiopulmonary resuscitation which included pharmacological, fluid, or mechanical resuscitation.[23] An unplanned ICU admission was defined as an admission that could not have been deferred without risk for at least 12 hours.[24] APACHE IV (Acute Physiology and Chronic Health Evaluation) scores indicate illness severity for those admitted to the ICU, whereby higher scores correspond to more severe disease and higher risks of death.[25]

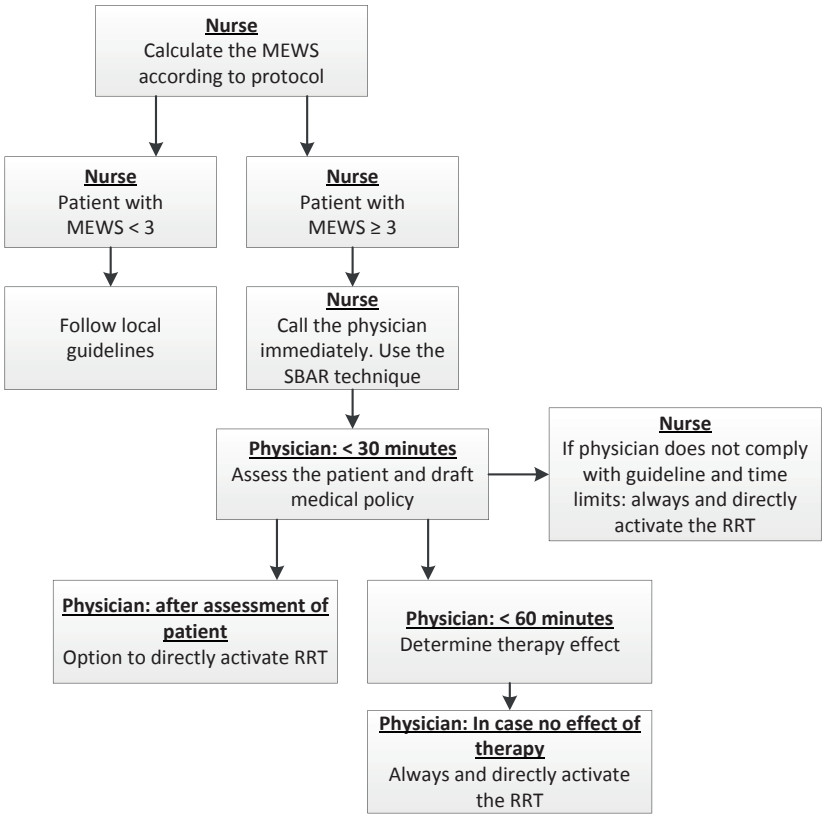


Figure 1. Algorithm for RRT activation which displays the protocol of handling critical MEWS values including all subsequent actions which either nurse or physician has to undertake together with set time limits.

Data collection

Two types of data were collected during a study period of three months: 1) all vital signs were recorded during a seven-day period at the end of each study month; 2) all AEs (i.e. cardiopulmonary arrests and unplanned ICU admissions) and the RRT activations were recorded during the whole three study months. MEWS was recorded on paper-based charts supported by a flowchart for RRT activation (Fig. 1). Measurements were excluded from data analysis when: 1) taken on non-participating wards e.g. delivery rooms; 2) taken during palliative care; 3) taken on days while the patient was significantly absent from the ward e.g. due to surgery; 4) predefined alterations on four protocolized wards were present (Supplementary File 2) which defined alternate frequency of measurement of MEWS; 5) deviations from the MEWS threshold (or sub scores) defined by the primary physician were recorded (Supplementary File 2). The presence of delay in notifying the physician was determined by measuring the time between the first critical MEWS (nurse documented and/or retrospectively determined) and the notification of the physician (Fig. 2). Dates and times at which the physician was notified including the critical MEWS were used and all subsequent first occurrences for these parameters were located. Patients were excluded when thresholds were uncertain (specific vital signs and/or MEWS) or if the physician raised the threshold for calling, e.g. MEWS of 5 instead of 3.

Data analysis and statistics

We applied an intention-to-treat analysis. Consequently, patients who were transferred to a different ward were analyzed in the original study arm (n=21). Continuous variables that were normally distributed were expressed as means with standard deviations and not normally distributed variables as medians and inter-quartile ranges (IQR). To test two independent groups of not normally distributed continuous variables, the Mann-Whitney U test was used. Categorical variables were expressed as percentages, numerators and denominators and were compared with the Chi-square test or Fisher's exact test or when appropriate as Relative Risk. Statistical uncertainty was expressed by 95% confidence intervals as appropriate, and statistical significance was defined at < 0.05. All data were entered into a Microsoft Access database and the analyses were performed using SPSS version 19.0 (Chicago, Illinois, USA) and confidence interval analysis software version 2.2.0 (University of Southampton, UK).

Ethics

This study conforms to the provision of the Declaration of Helsinki in 1975 (revised in 2008).[26] Given the observational nature of the study the hospital medical ethics committee waived the need for informed consent.

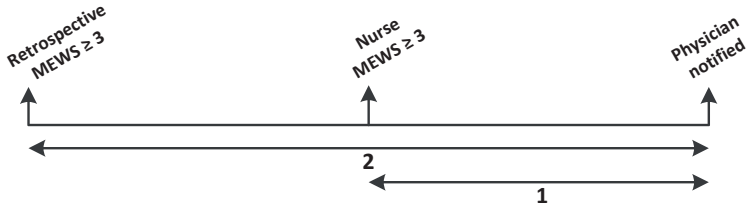


Figure 2. Time spans 'presence of delay'.

Time span 1, reflects the presence of delay between a registered critical MEWS by the nurse and the notification of the physician. According to the protocol, the physician should be notified immediately. Time span 2, reflects the theoretical 'window of recognition'. This is based upon registered vital signs and a retrospectively calculated critical MEWS. Thus, the critical MEWS could be derived by nurses and indicates the first moment at which the patient should be identified according to their vital signs.

RESULTS

Demographics

Due to logistical issues, the haematology/oncology unit, randomized as a control ward, dropped out of the study. According to the exclusion criteria 5752 measurements were excluded from analysis. In total, 372 patients were included on the protocolized wards (3585 measurements) and 432 patients (3013 measurements) on the control wards (Table 1). Of the patients 49% (394/804) were male; the mean age was 56.7 years (SD 17.7) and 1% (11/804) of the patients died during their hospital stay.

Table 1. Demographics of patients who were hospitalized during the seven-day period at the end of each of the three study months.

	Protocolized wards	Control wards
Patients during the three study weeks, % (n/N)	46 (372/804)	54 (432/804)
Age in years, mean (SD)	55.0 (17.7)	58.3 (17.6)
Gender (male), % (n/N)	56 (207/372)	43 (187/432)
LOHS[a] (days), median (IQR)	10 (6 - 20)	8 (5 - 10)
Died during hospital stay, % (n/N)	2 (7/372)	1 (4/432)

[a] LOHS, length of hospital stay

Compliance with protocol and degree of implementation

Compliance with the MEWS and RRS protocol is described in Table 2. Nurses calculated a MEWS in 70% (2513/3585) of the measurements on protocol wards and in 2% (65/3013) on control wards. Compliance of vital sign measurements three times per day on the protocol wards was achieved in 68% (819/1205). The median number of measurements per day was 3 (IQR 2-3) on protocol wards and 2 (IQR 1-2) on control wards. On control wards, retrospective review of vital signs indicated abnormal observations warranting the need for calculation of a MEWS according to the protocol in 41% (1232/2977) of all measurements. In only 4% (47/1232) of the measurements, the score was actually determined. A critical MEWS was recorded by nurses in 9% (338/3585) on the protocolized versus 1% (35/3013) on the control wards. Comparing the actually documented MEWS with the retrospective MEWS calculations, a critical MEWS was identified in 11% (381/3585) on the protocolized versus 7% (217/3013) on the control wards indicating the presence of calculation errors. In 43% (1552/3585) of measurements on protocol wards, the complete set of vital signs including MEWS was measured compared to 1% (31/3013) on control wards. In the majority of the measurements taken on control wards, the 'routine' set consisted of temperature, blood pressure, and heart rate. A 'perfect' measurement of all vital signs, including MEWS without calculation errors, was present in 14% (483/3585) of protocolized measurements versus 0.3% (8/3013) of control measurements.

Delay in notification of the physician

The presence of delay was analyzed in 99 patients (Table 3). In 49% (28/57) of the patients in the protocol arm and 50% (2/4) in the control arm, delays were present in identifying deterioration. When critical MEWS were measured by nurses on protocolized wards, a delay of 20 hours (IQR 5.5-54.0) was observed between the first registered critical MEWS and the notification of the physician, versus 44 hours on control wards, (P=0.79). When analyzing the delay using the retrospectively calculated critical MEWS, the presence of delay was 16.5 hours (IQR 6.0-40.5) on protocolized wards versus 23.5 hours (IQR 23.5-23.5) on control wards, (P=0.79).

Table 2. Description of compliance to the RRS protocol.

	Measurements on protocolized wards (N=3585)	Measurements on control wards (N= 3013)	95% CI of % difference	*P*-value[e]
Demographics of measurements				
Number of MEWS registered by nurse[a], % (n/N)	70 (2513/3585)	2 (65/3013)	67.9 (66.3 to 70.0)	< 0.001
Critical MEWS registered by nurse, % (n/N)	9 (338/3585)	1 (35/3013)	8.3 (7.3 to 9.3)	< 0.001
Retrospectively calculated MEWS[b], median (IQR)	0 (0 - 1)	0 (0 - 1)	-	-
Retrospectively calculated critical MEWS, % (n/N)	11 (381/3585)	7 (217/3013)	3.4 (2.0 to 4.8)	< 0.001
Compliance to measurement regime				
Days present on which MEWS could have been measured 3 or more times per day[c], % (n/N)	44 (1205/2763)	56 (1558/2763)	-12.8 (-15.4 to -10.2)	< 0.001
Compliance of measurements taken ≥ 3 times per day, % (n/N)	68 (819/1205)	-	-	-
Measurements with retrospectively calculated MEWS ≥ 1, % (n/N)	59 (1745/2977)	41 (1232/2977)	17.2 (14.8 to 19.7)	< 0.001
Compliance of MEWS registered by nurse if retrospective MEWS ≥ 1, % (n/N)	-	4 (47/1232)	-	-
Completeness and errors in measurements of all 9 parameters during single measurement				
No missing parameters, % (n/N)	43 (1552/3585)	1 (31/3013)	42.3 (40.6 to 44.0)	< 0.001
1 missing parameter, % (n/N)	11 (391/3585)	1 (21/3013)	10.2 (9.2 to 11.3)	< 0.001
2 missing parameters, % (n/N)	5 (174/3585)	1 (19/3013)	4.2 (3.5 to 5.0)	< 0.001
3 or more missing parameters, % (n/N)	41 (1468/3585)	98 (2942/3013)	-56.7 (-58.4 to -55.0)	< 0.001
Errors in calculation[d]				
No errors, % (n/N)	20 (713/3585)	10 (309/3013)	9.6 (7.9 to 11.3)	< 0.001
1 error, % (n/N)	35 (1270/3585)	6 (175/3013)	29.6 (27.8 to 31.4)	< 0.001
2 errors, % (n/N)	14 (508/3585)	7 (203/3013)	7.4 (6.0 to 8.9)	< 0.001
3 or more errors, % (n/N)	31 (1094/3585)	77 (2326/3013)	-46.7 (-48.8 to -44.5)	< 0.001

Due to rounding, percentages do not always add up to 100%.

[a] This parameter describes if a nurse has registered a MEWS in the nursing chart, irrespective of correct calculation and/or based upon a complete set of measurements.

[b] Retrospective calculation of the MEWS is performed by the researchers by calculation of the sub scores based upon the registered vital signs and subsequent determination of the MEWS according to the vital signs registered (irrespective of complete set presence).

[c] The total number of nursing days per patient were calculated and cross checked if three or more measurements (irrespective of completeness and correctness) had taken place on the protocolized wards.

[d] For this parameter, allocation of the sub scores (for each individual vital sign) including MEWS was calculated. Of note, errors were defined as all vital signs missing as well as miscalculated and/or not recorded sub scores and MEWS.

[e] Chi-square test

Table 3. 'Presence of delay' between critical MEWS calculation and notification of physicians.

	Patients on protocolized wards (N = 90)	Patients on control wards (N = 9)	Relative Risk (95% CI)	*P*-value[c]
'Presence of delay'[a] when a critical MEWS was:				
Registered by a nurse or was retrospectively calculated, % (n/N)[b]	49 (28/57)	50 (2/4)	0.98 (0.36 to 2.71)	0.97
Registered by a nurse, % (n/N)[b]	22 (15/69)	20 (1/5)	1.09 (0.18 to 6.64)	0.93
Retrospectively calculated, % (n/N)[b]	39 (22/57)	50 (2/4)	0.77 (0.28 to 2.17)	0.65

[a] 'Presence of delay' is the time between a critical MEWS measurement and the notification of the physician.
[b] The 'presence of delay' could not be determined in case one of the following deviations from the RRS-protocol was found:
1) in case the critical MEWS calculated by the nurse and/or retrospectively calculated critical MEWS were absent, or;
2) one or both of these critical MEWS were present after primary notification of the physician, or;
3) the notified critical MEWS registered by the nurse turned out to be based upon a miscalculation.
[c] Fisher's exact test

AE incidence, RRT activations and ICU admissions

During the three-month study period 64 AE occurred of which 95% (61/64) were unplanned ICU admissions and 5% (3/64) cardiopulmonary arrests. In September the AE incidence on protocol wards was 13.4/1000 hospital admissions which reduced to 8.5/1000 in November (95% CI: -0.004 to 0.014). The AE incidence in the control arm also dropped in the same period from 9.1/1000 to 6.5/1000 (95% CI: -0.006 to 0.012) (Fig. 3). The total number of RRT activations in the protocolized arm (62/84) was significantly higher compared to the control arm (22/84) (X^2=8.79, df=1, $P < 0.003$). The number of RRT activations on protocolized wards increased from 11.8/1000 to 19.6/1000. The number of activations on control wards was unchanged with 8.0/1000 in September to 9.8/1000 in October and 6.5/1000 in November. The APACHE IV score of patients admitted to the ICU in both arms showed no statistically significant difference. APACHE IV scores in protocolized and control wards in September were 64 (IQR 58-82) and 63 (IQR 54-97) and in November 61, (IQR 47-83) and 73, (IQR 54-108). Following a RRT activation, patients from protocolized wards were taken less often to the ICU in November (26% (6/23)) compared to September (67%, (10/15)). On control wards a slight decrease was observed in November (50% (3/6)) versus September (57% (4/7)).

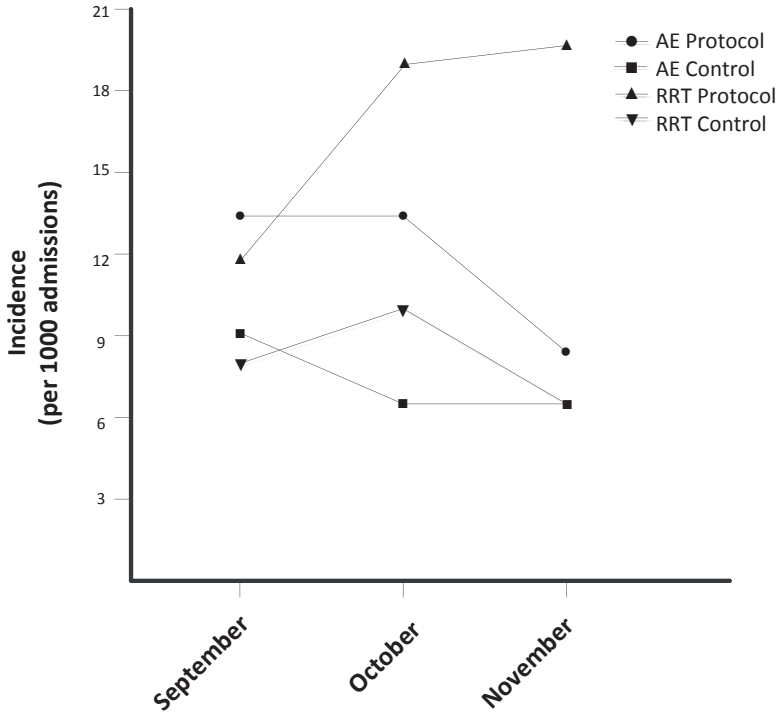


Figure 3. Incidence of AE and RRT activations per 1000 hospital admissions during the whole three study months.

DISCUSSION

Applying a protocol in which nurses have to measure the MEWS at least three times daily leads to better compliance and more reliable activation of the patients' own physician or the RRT compared to leaving frequency of measurement up to nurses themselves. Therefore, imposing regular measurements of the MEWS could actually lead to enhanced patient safety.

In this study, a multi parameter system was used to ensure more comprehensive measurements of vital signs and thus a greater chance in detecting deterioration. In theory the approach of a structured monitoring plan could also be applied to single parameter systems but their more extreme trigger points might lead to late alerts for physiological deterioration.[27]

To our knowledge, only one study has shown insight in the degree of implementation of the RRS protocol. Shearer *et al.* explored the causes of the lack of compliance to the RRS protocol using a mixed-method design.[28] In our study, we also give insight in the degree of implementation by describing the level of compliance of the MEWS measurements and the activations of the primary physician and/or RRT. Until now, data on effectiveness of RRS shows conflicting outcomes.[1,2] Effectiveness of any kind of intervention depends on the degree of implementation. The number of RRT activations has been directly linked to a decrease in incidence of AE[16]. However, effectiveness of RRS depends on more than only the dose of RRT.[14] Afferent limb failure and delayed detection of deteriorating patients is associated with worse clinical outcome.[29] Obviously, effectiveness also depends on compliance with the protocol,[30] and the degree of monitoring on wards,[20,31] both of which are in many studies not reported.[3] To date no trials have linked the reliability of measuring vital signs and MEWS to RRS performance. We show an improvement on protocolized wards, though reasons for the almost complete failure to calculate MEWS on control wards are not clear. Miscalculations of the MEWS[32], and incomplete 'routine sets' of observations in which respiratory rate is often not incorporated, may provide part of the explanation.[19] To which extend these factors and errors influence individual patient outcome, remains unknown. Despite the intense nature of the implementation process, unfamiliarity with the protocol may still have been present in our study. It is more likely though that there is a knowledge deficit regarding recognition of abnormal vital signs.[33,34]

Early admission to the ICU is directly correlated with improved survival.[35] It is imperative that escalation of care and early notification of responders is without any delay. In our study, no delay in notification of the physician prior a RRT call was found in 51% (29/57) of protocol versus in 50% (2/4) of the patients on control wards. It should however be noted that on control wards delays were difficult to interpret due to omissions in the recording of measurements in vital signs. Therefore, comparisons between both study arms regarding the presence of delay are fraught with difficulty.

Although this study was not designed to analyze the effect on clinical outcomes, we did observe an interesting trend in a decrease of AE. Protocol wards and to a lesser extent control wards, showed increased utilization of the RRT, better compliance with the MEWS protocol and a decrease in AE. This may mirror the presence of a dose/response relationship between the dose of RRT calls and improved clinical outcomes found by others.[16] It is possible that observed differences between groups are influenced due to the so called Hawthorne effect. Since nurses from control wards might have been informed about the intervention. This in our opinion could have led to an underestimation of the observed differences. The fact that patients assessed by the RRT on protocolized wards

were able to stay on the ward more frequently in November compared to September (70% versus 27%), may substantiate this claim and could reflect earlier detection. A major strength of this study is the completeness of data acquisition from nursing charts during the weeks of measurement and thus the ability to review the actually provided care. As this study depends on records kept by nurses, some information bias may be present. However, this cohort represents all admitted patients and not a selection of patients that experienced an AE. This enables a realistic description of the alertness of nursing staff beyond the few hours preceding an AE.

An important limitation of this study is the single centre setting which possibly limits its external validity.[36] The exclusion of measurements in which the patient was absent from the ward for a significant part of the day, may have resulted in an underestimation of our findings since hypothetically speaking, a patient may have received an intervention due to clinical deterioration. Also the fact that we started collecting data shortly after having introduced the RRS may have led to an underestimation of our results since one can question if the RRS was already most effective at that point in time. Ideally, the implementation phase should have been longer; time and money constrains led to the decision for a three-month period. Another limitation is that measurement of vital signs, three times daily, without MEWS calculation might also lead to increased awareness of deteriorating patients. Finally, since stratification of wards was only for medical/surgical specialty and not for other possibly influencing factors such as severity of illness, our findings regarding clinical effectiveness have to be weighted accordingly.

The findings of our study have implications for future work and might favour changing to electronic medical record keeping. Recent evidence from the UK shows better completeness of vitals signs and scores with an electronic vital sign assessment chart.[37] Partial automation of responses and standard operating procedures as used in the VITAL care study may offer new opportunities to improve problems in the current system.[38] Opportunities to detect deterioration depend in many cases on recording vital signs. Automated systems will allow an even greater frequency, thus potentially further reducing the number of 'missed opportunities' due to lack of measurements. In order to understand conflicting scientific evidence of RRS processes measurements need to go beyond RRT activation rates to understand why clinical outcomes improve in some studies but not in others. Institutions with a RRS should describe local algorithms for measurements of vital signs and monitor compliance in order to understand the level of performance of their RRT.

CONCLUSIONS

Recording complete sets of vital signs and MEWS three times daily results in better detection of physiological abnormalities, a significant increase in call-out rates and a more reliable activation of the RRT, and are thus increasing opportunities to avoid AE.

Acknowledgements

We would like to thank the nursing and medical staff from the Academic Medical Center in Amsterdam for participating in this study. We also wish to thank and acknowledge RN Hanna van der Pol for collaboration and data collection.

Conflict of interest statement

Dr. C. Subbe consulted for and received honoraria from Philips. On behalf of the remaining authors, the corresponding author states that there is no conflict of interest.

Funding

This study was funded by an internal AMC fund for quality improvement.

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Supplementary File 1

The Modified Early Warning Score (MEWS).

MEWS score	3	2	1	0	1	2	3
Heart rate		<40	40-50	51-100	101-110	111-130	>130
Systolic blood pressure	<70	70-80	81-100	101-200		>200	
Respiratory rate		<9		9-14	15-20	21-30	>30
Temperature		<35.1	35.1-36.5	36.6-37.5	>37.5		
AVPU score				A (Alert)	V (response to Voice)	P (reacting to Pain)	U (Unresponsive)
Worried about patient's condition: 1 point							
Urine production below 75 mL during previous 4 hours: 1 point							
Saturation below 90% despite adequate oxygen therapy: 3 points							

Upon reaching 3 or more points → call resident in charge
The MEWS instrument was implemented as a tool that ward staff can use to identify the patient at risk of deterioration. The described method was adapted from Subbe *et al.*[11]

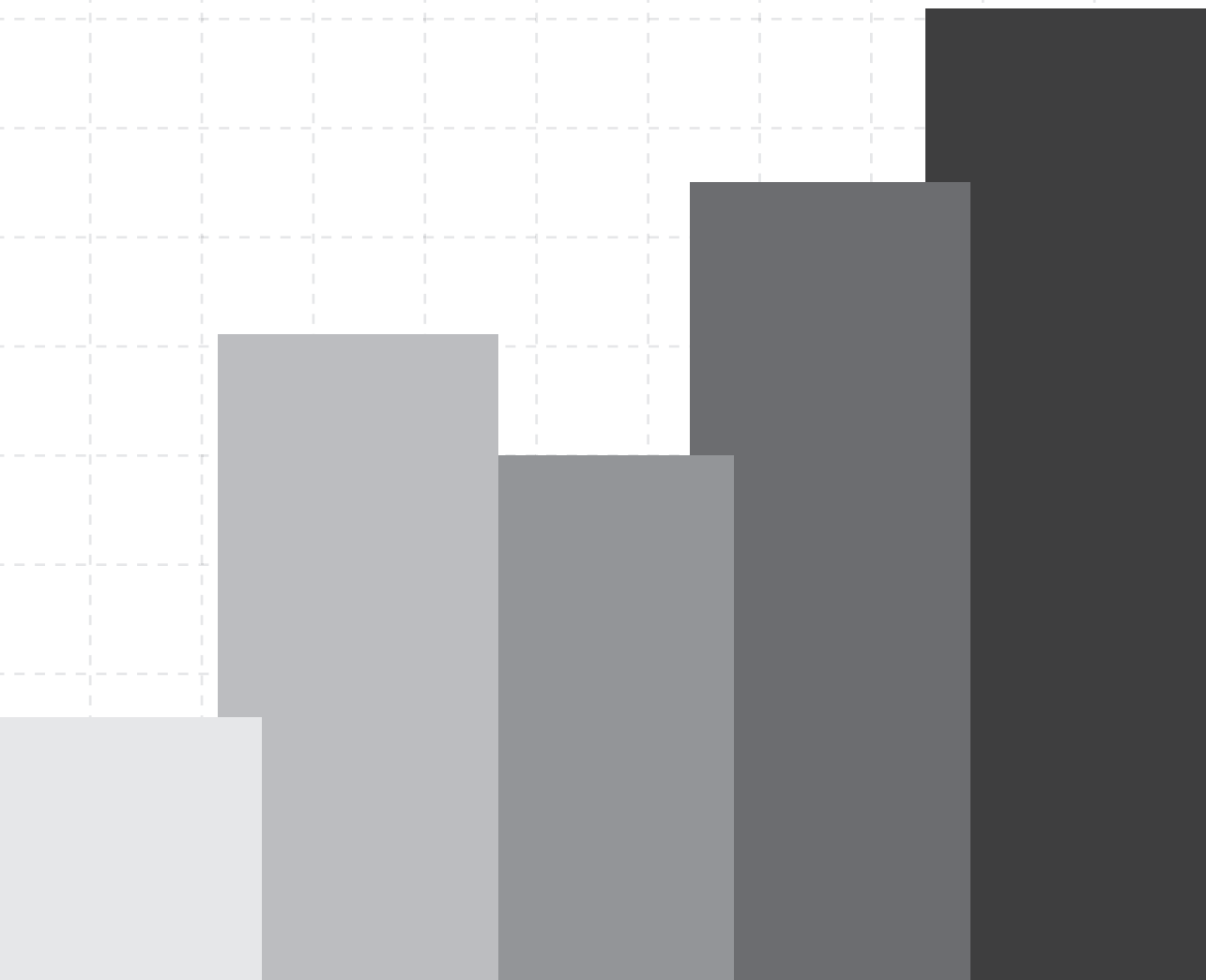
Supplementary File 2

Description of included general wards.

Specialty/ward	Surgery (Yes/No)	Study arm	Pre-defined alteration of protocol, if applicable	Exclusion of patients
Pulmonology	No	Protocolized		Patients admitted for sleep apnoea registration.
Kidney diseases	No	Protocolized		All patients admitted for sleep apnoea registration, fluid deprivation tests for diabetes insipidus, synacthen tests or research patients in general.
Cardiology	No	Clinically indicated		
Internal medicine/ infectious diseases	No	Clinically indicated		
Internal medicine/ Rheumatology	No	Protocolized		
Internal Medicine/Gastro-intestinal diseases	No	Protocolized		
Abdominal surgery	Yes	Protocolized	After 'moments at risk': MEWS measured three times daily for subsequent five days after which the MEWS is determined as clinically indicated unless patient encountered a new moment at risk.	
General/oncology surgery and mouth/jaw surgery	Yes	Protocolized	Identical as previous ward 'abdominal surgery'.	
Urology and short-stay surgery	Yes	Protocolized		All patients other than those admitted for: radical cystectomy (Bricker) and cystectomy with orthotopic bladder construction, laparoscopic and open radical nephrectomy and laparoscopic and open radical prostatectomy including according to Millin.

Specialty/ward	Surgery (Yes/No)	Study arm	Pre-defined alteration of protocol, if applicable	Exclusion of patients
Cardiothoracic surgery	Yes	Clinically indicated		
Orthopaedics	Yes	Clinically indicated		
Trauma surgery	Yes	Protocolized	After 'moments at risk': MEWS measured three times daily for subsequent three days. After three days as clinically indicated unless patient encountered a new moment at risk.	
Vascular surgery and plastic surgery	Yes	Protocolized		All patients other than those admitted for: all post-ICU patients irrespective of primary diagnosis, all aneurysm of the aorta, surgery for stenosis of the carotid arteries and thrombolytic therapy.
Ear, Nose and Throat/ Ophthalmology/ Dermatology	Yes (two out of three are surgery)	Clinically indicated		
Neurology	No	Clinically indicated		
Neurosurgery	Yes	Clinically indicated		
Maternity and delivery ward	No	Protocolized	All surgery patients, MEWS three times daily. Remainder as clinically indicated.	
Gynaecology	Yes	Clinically indicated		All patients staying one night admitted for chemotherapy only.

A description of the 18 included study wards is shown. Primarily, all patients admitted for at least one night are eligible for inclusion. The specialties on the wards are described including whether the ward was primarily denoted as being a surgery type based ward. For ear, nose and throat, ophthalmology and dermatology, the ward was also denoted as surgery because two out of three are primary surgery based. Four wards indicated that some alterations were applicable for patients admitted to these wards. These primarily indicated that not throughout the entire admission, MEWS was to be determined three times daily. Five wards also defined patient groups specifically for in- or exclusion. 'Moments at risk' are defined as the period (specifically defined per specialty/general ward) after admission to the hospital, after receiving surgery and after discharge from ICU/high dependency wards.



03

EMERGENCY CARE WITHIN HOSPITALS: CAN IT BE DONE MORE EFFICIENTLY?

Marjon Borgert, Astrid Goossens, Rob Adams, Jan Binnekade and Dave Dongelmans

British Journal of Nursing 2015:820-824.

ABSTRACT

Objectives. Cardiac Arrest Teams (CATs) are frequently activated by nurses when patients experience 'false arrests' (FAs). In those cases activation of the Rapid Response Team (RRT) might be more efficient. We determined the level of urgency of FAs to find a scope for improvement in efficiency within emergency care.

Methods. CAT-activations for FAs in a university hospital from September 2009 to 2012 were retrospectively analysed and classified as urgent or less-urgent.

Results. In 26% (107/405) the CAT was activated for FAs. Calls were classified as urgent in 43% (46/107). Less urgent calls comprised 57% (61/107) of the FAs, difference 14% (95%CI: 1% to 26%).

Conclusions. A significant part of the CAT-activations for FAs were less urgent and an RRT-activation might be more efficient. To minimise the CAT-activations for FAs, nurses need to recognise early patients who clinically deteriorate. Therefore, nurses should use the Modified Early Warning Score correctly.

INTRODUCTION

Increasing economic restraints and awareness about patient safety mean hospitals are encouraged to evaluate their care processes.[1] This should lead to a more efficient healthcare delivery and an improvement of the quality of care. The process of activating teams that are 24/7 on standby in case of medical emergencies, i.e. the traditional Cardiac Arrest Teams (CATs) and the more recently introduced Rapid Response Teams (RRTs), could potentially managed more efficiently.

Approximately 80% of patients have vital signs abnormalities in the 24 hours prior to Adverse Events (AEs), i.e. cardiac arrests, unplanned intensive care unit admissions and unexpected death.[2,3] These abnormalities could be detected in an early stage, by measuring the vital signs frequently. To aid in this detection process the Modified Early Warning Score (MEWS) has been developed. This is a tool whereby nurses allocate points to the measurement of vital signs resulting in a summary score.[4,5] When reaching a predefined threshold nurses should act by either calling the doctor on duty or emergency teams.

In the Netherlands there are differences in organisation between the emergency teams. The CAT, with an average of four members, is responsible for immediate response for patients suffering from cardiac arrests.[3] The RRT, with generally two members responds within 10 minutes for evaluation, triage and treatment of patients who clinically deteriorate to prevent them from suffering an AE.[2,3,6,7] CATs are focussed on cardiopulmonary resuscitation or unexpected life-threatening medical emergencies. They intervene according to strict advanced resuscitation protocols[8], while RRTs have specific expertise in care for clinically deteriorating patients before the occurrence of cardiac arrests.[3] The most common reasons for calling RRTs are hypoxia, hypotension, altered conscious state, tachycardia or oliguria.[9]

To monitor CAT performances and outcomes, hospitals are registering CAT activations according to the international Utstein guideline.[10] In a substantial number, CATs are activated while patients do not suffer from cardiac arrests. These activations are called 'false arrests' (FAs).[11-14] For these calls basic or advanced life-support is not needed[10] and immediate response of the larger CAT may not be necessary. More importantly, previous studies have shown that most patients with FAs have signs of clinical deterioration that are commonly seen prior to cardiac arrests.[13] CATs are frequently activated for FAs, proportions ranging from 8% to 30%.[11-13] Nevertheless, the characteristics of these calls are hardly ever reported in detail and little information is available about their medical urgencies. It is suggested that the RRT would be an appropriate and more efficient team

to respond to these calls.[15] If health professionals would know the level of urgency of FAs, this information could be used as a first step to assess the potential to reorganise both emergency teams to achieve greater efficiency. The aim of this study was to assess what proportion of the CAT activations in a Dutch university hospital within a 3-year period were classified as FAs and what percentage of these FAs were classed as urgent or less-urgent in order to find a scope for improvement in efficiency within the emergency care. Therefore, we addressed the following research questions: 1) what proportion of the CAT activations within a 3-year period were classified as FAs? 2) What percentage of these FAs were classed as urgent or less-urgent at the moment the nurses activated the CAT?

METHODS

Ethics

The study was approved by the Medical Ethics Committee of the Academic Medical Center of Amsterdam, the Netherlands. This study conforms to the provision of the Declaration of Helsinki in 1975 and revised in 2008. The Medical Ethics Committee waived the need for informed consent.

Design and setting

A retrospective study was conducted in a university hospital in Amsterdam. All registered FAs that occurred between September 2009 and September 2012 were retrospectively analysed.

Inclusion and exclusion criteria

Registered CAT activations for FAs for adult patients (≥ 18 years) who collapsed in hospital, i.e. on nursing wards or interventions rooms, were included in this study. In our hospital the RRT can only be activated for patients who are admitted to the hospital and so calls from the outpatients department, emergency rooms, or public areas were excluded from analyses. No information was registered for the cancelled calls and these were excluded from analysis.

Cardiac Arrest Team (CAT)

In our hospital, the CAT is available 24/7 and consists of a resident, and a nurse from the cardiology department and a resident and a nurse from the anaesthesiology department. The CAT-members are formally trained and certified in all aspects of advanced life support and they intervene according to strict resuscitation guidelines.[8]

The CAT is responsible for patients who suffer from cardiac arrests or with an unexpected or suspected life-threatening medical emergency. The CAT attends to the patient within 2 minutes after activation.

Rapid Response Team (RRT)

The RRT is part of a system; the Rapid Response System (RRS). The RRS aims to detect and treat deteriorating patients on general wards and to prevent them from suffering an AE.[2,3] The first step of the RRS protocol is the detection of deteriorating patients. A commonly used instrument to detect these patients by measuring vital signs is the MEWS.[4,5] The Dutch MEWS incorporates eight vital signs or parameters (Table 1). Each parameter has a standardised range of cut-off points. Predefined weighted trigger scores should be allocated to each recorded parameter. Nurses should record all 8 parameters for a correct completion of the MEWS. According to the two-tiered Dutch system, the RRS-protocol dictates that when reaching a predefined threshold, the nurse has to notify the physician on duty on the ward. The physician must assess the patient within 30 minutes and could either initiate treatment or activate the RRT instantly.[6] In case the clinical condition is not improving or if the physician is not able to assess the patient, it is the nurse who must activate the RRT. The RRT consist of an ICU fellow and ICU nurse and is 24/7 available. They attend to the patient within 10 minutes of activation.

Training in emergency care

Nurses are trained in Basic Life Support (BLS), which includes training in: 1) recognizing cardiac arrests; 2) call for help and activate the CAT; 3) acting as a first responder and start resuscitation. Nurses are required to follow the BLS retraining every 3 years. In September 2011 the RRS protocol was implemented in our hospital. All nurses and physicians on the wards were trained in measuring the MEWS and in activating the RRT. New nursing employees are trained in the RRS protocol on the nursing wards by senior nurses specialised in quality improvement.

Table 1. The Modified Early Warning Score (MEWS)[4]

MEWS score	3	2	1	0	1	2	3
Respiratory rate		<9		9-14	15-20	21-30	>30
Saturation with adequate oxygen therapy	< 90						
Heart rate		<40	40-50	51-100	101-110	111-130	>130
Systolic blood pressure	<70	70-80	81-100	101-200		>200	
AVPU score				A (Alert)	V (response to Voice)	P (reacting to Pain)	U (Unresponsive)
Temperature		<35.1	35.1-36.5	36.6-37.5	>37.5		
Urine production below 75 mL during previous 4 hours: 1 point							
Worried about patient's condition: 1 point							
Upon reaching 3 or more points → call resident in charge							

CAT registrations

All CAT activations are real-time registered in an electronic database 'Advanced Life Support Information System' according to the Utstein guidelines.[10] Data belonging to the AE (i.e. patient characteristics, first observed symptoms, location of collapse, cause of the AE, clinical outcomes) are recorded at the bedside by a nurse who participates in the CAT.

Classifying observations

The symptoms that were used to determine the level of urgency of the FAs were systolic blood pressure, Glasgow Coma Score (GCS) and respiratory status. The vital signs are directly recorded in standard categories in the database (Table 2). The data was registered and stored in the electronic database and the calls categorised as 'urgent' or 'less urgent'. Calls were classified as *urgent* when at least one of the following observations was registered: 1) Systolic blood pressure levels between 50 and 75 mmHg or not palpable[16,17], or 2) GCS < 9 [18], or 3) assumed apnoea or gasping.[8,19] Calls were classified as *less urgent* when all of the following observations were present: 1) Palpable systolic blood pressure or levels ≥ 76 mmHg[16,17], and 2) GCS ≥ 9 [18] and 3) breathing normally or with effort.[8,19]

Table 2. Classifications of the false arrests

	Urgent false arrests All the observed symptoms are present[a]	**Less urgent false arrests** At least one of the observed symptoms are present[a]
Systolic blood pressure	pressure levels between 50-75 mmHg or not palpable	palpable systolic blood pressure or levels ≥ 76 mmHg
GCS[b]	GCS < 9	GCS ≥ 9
Respiratory pattern	assumed apnoea or gasping	breathing normally or with effort

[a] Symptoms observed by hospital staff while activating the CAT
[b] GCS: Glasgow Coma Scale

Statistical analysis

Continuous normally distributed variables were expressed by their mean and standard deviation or when not normally distributed as medians and their interquartile range (IQR). Categorical variables were expressed as percentages, numerators and denominators. Differences between groups were tested by using the Student's t-test and if continuous data was not normally distributed the Mann-Whitney *U* test was used. Categorical variables were compared with the chi-square test or Fisher's exact tests when appropriate. Statistical significance was considered to be at $p < 0.05$. Statistical uncertainty was expressed as 95% Confidence Intervals (CI). Data analysis was performed with IBM SPSS version 20, inc., Chicago, IL.

RESULTS

Within the 3-year study period 405 CAT-activations were registered. In 74% (298/405) of these activations, the patients suffered from true cardiac arrests according to the Utstein guidelines. In 26% (107/405) the CAT was activated for FAs (Fig. 1). After analysing the CAT-activations for FAs, we found that 43% (46/107) of the FAs were urgent calls because of the severity of the observed symptoms. Less urgent calls were present in 57% (61/107) of the FAs (Fig. 1), difference 14% (95% CI: 1% to 26%). The median age of patients with an urgent FA was 67 years (IQR 50-76) and in the less urgent group a median age of 62 years (IQR 45-71) was found, $p=0.085$ (Table 3). The median time the CAT spent at urgent calls was 27 minutes (IQR 13-41) versus 20 minutes (IQR 10-30) at less urgent calls, $p=0.072$.

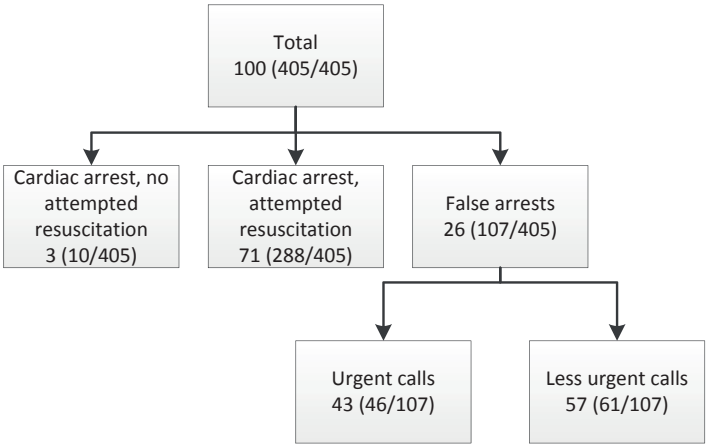


Figure 1. Classification of the CAT activations and false arrests, (% (n/N)).

Table 3. Demographics

	Urgent false arrests	**Less urgent false arrests**	***P-value***
Age in years, median (IQR)	67 (50-76)	62 (45-71)	0.085[a]
Sex, male, % (n/N)	44 (20/46)	66 (40/61)	0.023[b]
Died during hospital admission, % (n/N)	13 (6/46)	8 (5/61)	0.414[b]

[a] Mann-Witney U test
[b] Chi-square test
IQR: interquartile range

DISCUSSION

This study shows that in 26% of the calls, the CAT was activated for FAs. These findings are comparable with previous studies about FAs.[11-13] Nearly 60% of the FAs identified were classified as 'less urgent calls'. Immediate attendance of the larger CAT might not be required for the less urgent calls and the smaller RRT could be activated instead. RRTs have fewer team members than CATs, thus fewer emergency team members are mobilized. RRTs are especially developed to intervene in an earlier stage of clinical deterioration.[3,7]

Although, the majority of the patients with FAs seem to have non-urgent symptoms, it is noteworthy to mention that these symptoms often exist prior to cardiac arrests.[20-22] Therefore, even these less urgent calls must be taken seriously.[11] This indicates the importance of following the complete RRS protocol. It starts by measuring the vital signs and MEWS frequently to detect patients who are at risk for clinical deterioration. When reaching a predefined threshold nurses should act on this by either calling the primary physician or RRT. By measuring the MEWS nurses will have a clear guideline on how to act when patients clinically deteriorate and who to call. The remaining FAs were classified as 'urgent calls', because at least one serious clinical symptom was observed.[8,19,20] Despite the urgency of these calls, these are still defined as FAs according to the Utstein guidelines. Nevertheless, given the severity of the symptoms, immediate response of an emergency team is required. Since the CAT attends to patients within 2 minutes, the CAT is the most suitable team to activate for urgent FAs.

Opportunities for enhancement

Although this study was not designed to consider efficiency or potential improvements, the results could still be used to enhance emergency care. Previous studies have shown that cardiac arrests are not unpredictable events. More than 80% of the patients have identifiable signs of physical deterioration in the hours prior to cardiac arrests.[20,21,23] However, incomplete vital sign or MEWS measurements often exists.[24-26] It is known that the respiratory rate, in particular, is often not recorded.[24,27] This is in spite of the fact that there is evidence that an abnormal respiratory rate is an important predictor of serious AEs.[27,28] Nurses do not always recognise symptoms of physical deterioration and this can lead to delayed care.[29,30] This is also associated with decreased survival from in-hospital cardiac arrests[29] and lower survival rates.[30] Protocols are available for activating emergency teams. However, protocols are often not followed completely.[25,26,31] Education could help with implementation.[25,32] Measuring the MEWS more often could also help. Standardized measurements of the MEWS 3 times daily significantly improves the correct measurement of the MEWS, i.e. recording of all 8 MEWS parameters.[24]

The Utstein guideline was developed in order to monitor CAT performances and the effects on patient outcomes.[10] By collecting and reviewing performance data the quality of emergency care can be improved and risks can be reduced. A guideline in the Utstein format for standardising RRT calls, performances and calling criteria is available[33], although not widely used in the literature. Another point emerging from this discussion is the possibility of making one of the teams redundant by either merging the teams or rearranging the team compositions. Originally, the RRT superseded the traditional CAT[34] and responded to all types of in-hospital emergency care including cardiac arrests. The

benefit of one emergency team being operational is that there is no uncertainty about which team to call. However, several disadvantages have been described as well. For instance, barriers exist to call a large attending team for clinically deteriorating patients who might not be seriously ill, but for whom the team must be called according to the predefined calling criteria.[35] Moreover, inexperienced staffs sometimes feel anxious about seeking help and calling this team.[35] This also results in patients receiving delayed care.

Limitations

The present study has some limitations. We analysed the CAT activations for FAs retrospectively. The data was, however, real-time registered in the database. Another limitation is that the data is from a single medical centre and the results may not be generalizable to other hospitals. Another limitation is that in our hospital two emergency teams are operational. The composition and call procedures of emergency teams varies highly between hospitals, which has consequences for the generalisability of our results. By excluding the out-patient department, emergency rooms and public areas in the data-analysis, the total number of patients with FAs for whom the CAT was activated might be an underestimation of the results. Finally, analysis of the RRT calls was not possible due to lack of a predefined system of classifying RRT calls in the hospital.

Future research

Future research is needed in order to find effective strategies for implementing the MEWS on nursing wards and to improve the sustainable adoption of the MEWS. Computerised decision support could play a role especially as we are moving towards systems in which all vital signs are monitored continuously by using a wireless patient monitoring system.[36] Use of qualitative research methods are needed to provide data on why and how the implementation succeeded or not as well as to explore nurses' perceptions and experiences of using the MEWS and related protocols.[37] Using a qualitative approach would allow exploration around measuring the MEWS, barriers to activate the emergency teams or to identify external environment factors, such as busyness of wards. Furthermore, research should focus on how emergency teams could be optimised by either merging or rearranging the composition of both teams to achieve both financial and qualitative benefits.

CONCLUSIONS

Since nurses are almost continuously present on the ward while caring for their patients, they are responsible for the early detection of clinical deterioration of patients. Nurses are also the first to be confronted with the majority of collapsed patients. Hence, nurses play an important role in the activation of the emergency teams. Our results show that when nurses activated the CAT, a significant part of the FAs were less urgent. In those cases activation of the RRT might be more efficient. In order to avoid cardiac arrests and thus potentially minimise the CAT activations for FAs, nurses should early recognise and respond to patients who clinically deteriorate. In our view, it is therefore imperative that nurses should use the MEWS correctly. When completing the MEWS nurses have a clear guideline on how to act when patients clinically deteriorate and who to call. Future research should focus on finding strategies to implement the MEWS successfully and how the organisation of the emergency teams could be optimised to achieve both financial and qualitative benefits.

Competing interest

The authors declare that they have no competing interests.

Funding

No funding

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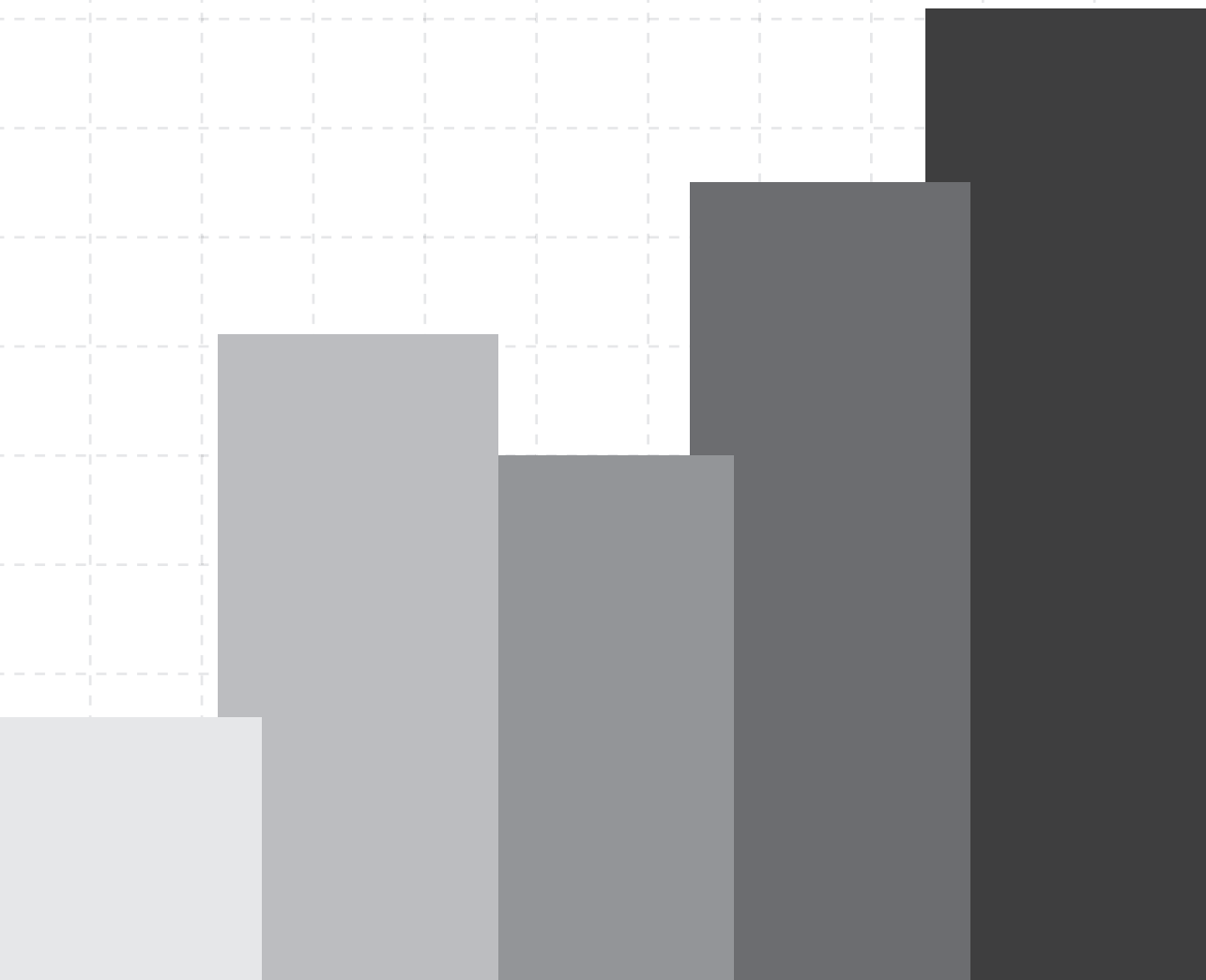
PART II

IMPROVING PATIENT SAFETY FOR CRITICALLY ILL PATIENTS IN THE ICU



04

A FLOWCHART FOR BUILDING EVIDENCE-BASED CARE BUNDLES IN INTENSIVE CARE: BASED ON A SYSTEMATIC REVIEW

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Int J Qual Health Care 2017;1;29:163-175.

ABSTRACT

Purpose. The Institute for Healthcare Improvement is the founder of the care bundled approach and described the methods used on how to develop care bundles. However, other useful methods are published as well. In this systematic review, we identified what different methods were used to design evidence-based care bundles in intensive care units. The results were used to build a comprehensive flowchart to guide through the care bundle design process.

Data sources. Electronic databases were searched for eligible studies in PubMed, EMBASE and CINAHL from January 2001 to August 2014.

Study selection. There were no restrictions on the types of study design eligible for inclusion. Methodological quality was assessed by using the Downs and Black checklist or Appraisal of Guidelines, REsearch and Evaluation II.

Data extraction. Data extraction were independently performed by two reviewers.

Results of data synthesis. A total of 4665 records were screened and 18 studies were finally included. The complete process of designing bundles was reported in 33% (6/18). In 50% (9/18) one of the process steps was described. A narrative report was written about care bundles in general in 17% (3/18). We built a comprehensive flowchart to visualize and structure the process of designing care bundles.

Conclusions. We identified useful methods for designing evidence-based care bundles. We built a comprehensive flowchart to provide an overview of the methods used to design care bundles so that others could choose their own applicable method. It guides through all necessary steps in the process of designing care bundles.

INTRODUCTION

Guidelines are developed in order to standardize care processes to improve the quality of care. However, it is known that guidelines are often not followed completely and therefore patients do not receive the care they need.[1] In 2001, the Institute for Healthcare Improvement (IHI) developed the concept of care bundles.[2] Care bundles aim to enhance the reliability of care and to improve clinical outcomes by bundling a small set of interventions together.[2]

The IHI defined criteria for evidence-based care bundles. For example, care bundles consist of three to a maximum of five evidence-based interventions, or so called 'elements', for a clinical process or patient population. The elements should be applied together in every eligible patient. The completion of an element could only be answered with 'yes' or 'no'. Compliance should be measured by using the all-or-none approach. This means that the bundle should be counted as completed only in case all included bundle elements are performed. The strength of bundling a small set of elements is to ensure that evidence-based care will be uniformly applied together in every eligible patient so that patients receive reliable care.[2-4]

Care bundles are widely applied tools in intensive care units (ICUs). They are frequently introduced as components of quality improvement initiatives.[5,6] The earliest developed care bundles, i.e. the central line bundle and ventilator bundle, are nowadays generally accepted in ICUs.[5] The effectiveness of these bundles has led to the development of more care bundles for other care processes or patient populations, such as the sepsis care bundle[7] or the urinary tract infection bundle (UTI).[8]

The IHI described the process on how they developed the central line bundle and ventilator bundle.[3,4] Their reports were descriptive in nature. They described the main steps of the bundle design process as well as the particular methods they have used within each process step. For instance, the first step they described was to identify certain processes at risk for ICU patients or that contributed to great harm.[2-4] This was done by systematically reviewing the literature.[9] Throughout the bundle development process other methods were used by the IHI. However, the methods used by the IHI may not always be applicable to all ICUs and in every situation. For example, use of systemic reviews is not for all ICUs a useful method to identify risks when the results are not valid due to the heterogeneity of data or due to the low quality of the included studies. In the literature, other useful methods to design care bundles have been published as well, such as a Root Cause Analysis (RCA) to identify risks or the use of a weighing and scoring technique for selecting bundle elements.[10,11] We wanted to identify what methods were

available that could also support the development of new bundles for the ICU besides the IHI approach. Therefore, we conducted a systematic review. The primary objective was to identify what different methodologies were used in the literature to design new evidence-based ICU care bundles. Based on the results, we built a comprehensive flowchart to provide an overview of the methods used so that others could choose their own desired method and to guide through the necessary steps of the development of new evidence-based care bundles for the ICU.

MATERIALS & METHODS

Design

A systematic review was conducted to identify methods for designing new care bundles for adult ICUs. The protocol for this study was not registered.

Selection criteria

We included studies that described the different methods within the whole care bundle design process in adult ICUs or the methods described in just certain parts of the design process. Studies were also included in case one or more IHI methods were used. Studies of any design were included and published in the English language.

Search strategy

A systematic search was performed in the electronic databases PubMed, EMBASE and CINAHL from the year care bundles were designed in January 2001 to August 2014. Furthermore, the reference lists of the full-text articles were screened. The search was designed for maximal retrieval, with no limitation of language or types of study design to be identified. The complete list of search terms and strategy of PubMed can be found in Supplementary File 1.

Study selection

The screening of the titles and abstract was conducted in two parts. At first, one author (M.B.) roughly screened all titles and abstracts. Studies were excluded when: (i) the language was not in English; (ii) the bundle was designed for pediatric departments or non-ICU departments or (iii) care bundles were not the subject of the study. Secondly, the titles and abstracts of the remaining articles were again screened. Two authors independently screened the titles and abstracts (M.B.,D.D.). In case of discrepancies, we reached consensus through discussion. A third reviewer was involved in case of disagreement. Full-text studies were reviewed and selected by two authors

independently. Studies were included in the analyses in case a description was given of the methodologies used on how to develop care bundles on ICUs for adult patients. Consensus was reached by discussion and a third author was involved in case of disagreement.

Data extraction

We extracted the following data from the identified studies: author, publication year, research design, setting, type of care bundle, methods used to develop the care bundle. Data extraction was independently performed by two authors (M.B.,D.D.). In case of discrepancies, consensus was reached by discussion. A third author was involved in case of disagreement.

Quality assessment

Given the diversity in study designs of the selected articles, we used two different tools for assessing the quality of the studies. For studies that primarily described the development of a care bundle, we used the Appraisal of Guidelines, REsearch and Evaluation II (AGREE II) instrument.[12,13] This instrument is designed for assessing the process of guideline development and how well this process is described.[13] To categorize the study quality we used the following cut-off points: excellent: (90-100); good (70-89); fair (50-69; poor (≤49).[13]

The checklist of Downs and Black was used for studies that primarily assessed clinical outcomes by using non-randomized study designs.[14] Checklist item number 27 about sample size calculation was simplified to a score of 0 (no sample size calculation) or 1 (sample size calculation reported). The following cut-off points have been reported to categorize studies by quality: excellent (26–28); good (20–25); fair (15–19) and poor (≤ 14).[15,16] Quality assessments were conducted by two reviewers independently. Disagreement between the reviewers was resolved through discussion. A third reviewer was involved in case of disagreement.

Flowchart

Based on the IHI methods as well as on the results of the systematic review we built a comprehensive flowchart for designing new care bundles. The flowchart contains the main process steps that should be followed. Each step contains methods that can be used for that particular part of the bundle design process. The development of the flowchart will be explained in the next paragraphs.

Expert team

For the development of the flowchart, a multidisciplinary expert team was created. The team consisted of two senior researchers (J.B.,F.P.), an intensivist/senior researcher (D.D.) and a junior researcher (M.B.). The junior researcher provided all the information for the consensus meetings. Two senior researchers (J.B.,F.P.) were former ICU nurses who are now involved in quality and patient safety initiatives on the ICU. The intensivist/senior researcher (D.D.) is experienced and trained in quality and safety in healthcare. This multidisciplinary team has a wide experience in the ICU care processes and was familiar with the conditions or requirements of care bundles.

Development process

The IHI was the founder of the care bundled approach. They described the methods they used to develop the central line bundle and ventilator bundle.[2-5] Their reports were more descriptive in nature.[2-5] These IHI reports formed the basis to structure the flowchart. We analyzed the IHI methods on how they have developed the central line bundle and ventilator bundle.[2,5] We analyzed their process in two ways. At first, we converted their descriptive reports into main process steps. For example, the IHI started the bundle development process by identifying problems by using the results of a systematic review. Therefore, this first main process step was labelled as: 'identify problems/risks'. Subsequently, the main steps were identified for the whole bundle development process. All steps were structured in a flowchart. Secondly, we selected the specific methods the IHI used for designing the central line bundle or ventilator bundle. For example, the IHI started the bundle development process by identifying problems by using the results of a systematic review. We incorporated the method of a systematic review in process step one: 'identify problems/risks'. Additionally, the methods identified by the literature search were incorporated in one of the main process steps of the flowchart.

Consensus meetings

We used consensus meetings with the expert team to analyze the IHI reports. At first, we identified the main process steps. Secondly, we built the flowchart and thirdly, we selected the methods and placed it in one of the process steps. Two meetings were arranged for defining the main process steps and to build the flowchart and two for filling in the specific methodologies per process step of the flowchart. Differences between the members were discussed until 100% consensus was reached. The meetings were highly structured by using the nominal group technique.[18] This is a structured meeting with experts about a certain issue and consists of two rounds in which the experts rate, discuss and rerate topics or issues.[17]

RESULTS

In total, 4665 articles were identified for possible inclusion through the initial search (Fig. 1). After screening titles and abstract, 107 full-text articles were reviewed. A final set of 18 articles met the inclusion criteria and were included in this study.

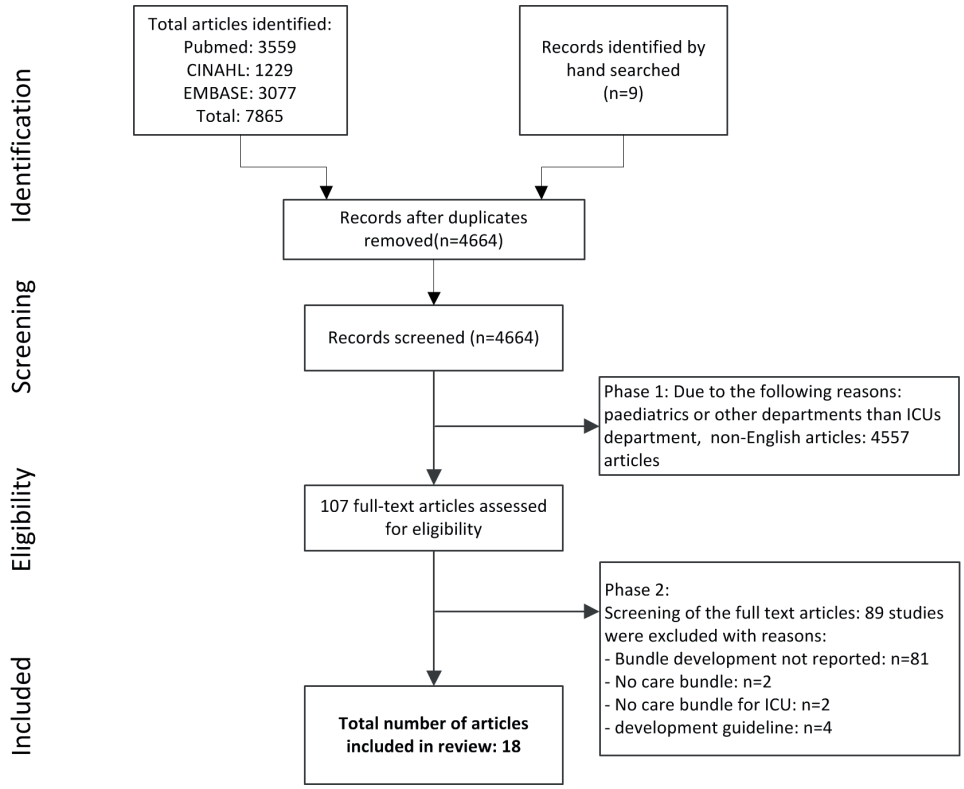

Figure 1. Flowchart of the study selection procedure

Study characteristics

The development of the ventilator bundle was reported in 17% (3/18) and for central line placement as well as for prescribing antibiotics in 11% (2/18). The remaining studies reported the methods used for the following bundles: sepsis; cerebral ventricular drainage; ventriculostomy placement; palliative care; thirst intensity and thirst distress (Table 1). In 33% (6/18), the whole bundle design process was reported. In 50% (9/18),

only one method for one process step was reported, i.e. conducting a literature review to identify risks in step 1.[31] In 89% (16/18), a literature review was used as a method to design bundles. In 75% (12/16) of these studies, a review was only used for identifying problems. In 12,5% (2/16), a review was used to underpin elements with evidence. In 12,5% (2/16), a bundle development process was described in general and that systematic reviews could be used to find evidence for the bundle elements. In 17% (3/18), a narrative report was written about bundles in general. Quality improvements were described in 39% (7/18), methodological studies in 17% (3/18), before and after designs in 11% (2/18). The remaining designs were one randomized trial, one case series and one observational study.

Table 1. Study characteristics

Author/ year of publication/ country	Design	Study period	Study outcomes	ICU	Type of bundle	Aim of the bundle	Methods used in the care bundle design process
Hocking[17], 2013, New Zealand	Before and After study	Oct 2007-Apr 2011	Central line associated bacteraemia rate	General	Central line High risk patient bundle	Reduce infections In the high risk population	1) Analysis of the implementation data of the CLABSI insertion bundle and maintenance bundle: the data highlighted a group of patients who were continuing to get a CLABSI despite good compliance in both the insertion and maintenance bundle. 2) Search for literature for adding elements in the high risk bundle.
Berenholtz[19], 2007, USA	Description of bundle methodology	NR	Develop a preliminary set of quality measures for ICU patients with sepsis	ICU in general	Sepsis care bundle	Improve outcomes for patients with sepsis	1) Identify evidence based elements that improves outcomes: establish goals of the initiative and discuss potential quality measures 2) Review of the literature 3) Review the literature synthesis: the panel had to list their own recommendations for domains of sepsis care that should be evaluated as a potential quality measure. All measures were discussed in the panel until complete agreement was achieved. 4) Using the GRADE approach to evaluate the quality of the evidence and to balance the potential benefits and harms for each potential measure. 5) Writing the design specification for each measure or explicit definitions. Consensus in the panel was achieved through an iterative process.
Berenholtz[20], 2004, USA	Quality improve-ment	Mar 4-Apr 29, 2002	Percentage of ventilator days per week when patients received the bundle elements	Surgical	Ventilator bundle	Reduce infections	1) Qualitative review of the ICU quality indicators: a) Systematic review: identify interventions that improves patient outcomes in the ICU. b) Potential measures were evaluated based on the impact, feasibility, variability and the strength of the evidence to support each measure and to categorize each measure as outcome, process, access or complication measures 2) Four measures retrieved from the search were selected that were associated with improved outcomes in patients receiving mechanical ventilation. 3) These four core measures were grouped into a bundle: the ventilator bundle

Table 1. (continued)

Author/ year of publication/ country	Design	Study period	Study outcomes	ICU	Type of bundle	Aim of the bundle	Methods used in the care bundle design process
Chatzi[21], 2014, Greece	Clinical prospective case series	2007-2012	Prevalence and outcome of external cerebral ventricular drainage-associated ventriculitis	General	Bundle of external cerebral ventricular drainage associated ventriculitis	Reduce infections	1) Assess clinical and microbiological patient data 2) Study the risk factors which are associated with ventriculitis 3) Literature review: the bundle was based on published data, adjusted on local protocols and setting.
Cooke[22], 2007, UK	Narrative report	NR	Propose of an antibiotic care bundle for prescribing antibiotics	NR	Antibiotic bundle	To select antibiotics to cure the patient, reducing risks of side effects and the risk of resistance and C. difficile.	1) Review of the literature 2) Selected elements were based on the IHI criteria (elements are evidence based)
Fulbrook[23] ,2003, UK	Narrative report/review	NR	Explain what contributes a care bundle and describe how it can be implemented	NR	Care bundle in general	General: improve clinical effectiveness	1) identify a critical care theme 2) identify a cluster of interventions/practices within the same theme 3) Undertake literature searches, related to each of the interventions/ practices, to identify all relevant research 4) extract the research literature 5) Categorize the available research according to its quality 6) Delete any intervention/practice from your list that do not have an adequate evidence base to refer to 7) On the basis of analyze research evidence, develop evidence based interventions/practices.

Table 1. (continued)

Author/ year of publication/ country	Design	Study period	Study outcomes	ICU	Type of bundle	Aim of the bundle	Methods used in the care bundle design process
Pulcini[24], 2008, UK	Quality improvement	NR	Develop and test a set of process measures	NR	'Day 3 bundle'	Assess and improve the reassessment of inpatient empirical antibiotic prescriptions around day 3.	1) Literature search: selection of key process measures by one reviewer 2) selection of 3 to 5 measures thought to be valid and easy to collect.
Khalid[11], 2013, Saudi Arabia	Quality improvement	2009-2012	CLABSI rates	Medical-surgical ICU	Central line bundle	CLABSI reduction in developing countries	1) identify problems with a RCA 2) a flowchart was developed to identify the steps in the process and discover the potential weak links in the process. 3) all aspects of central line insertion and maintenance were analyzed and depicted in a flowchart 4) by using the flowchart: improvement plans and strategic interventions were developed.
Kollef[25], 2011, USA	Narrative report/review	NR	Prevention of nosocomial pneumonia	ICU in general	VAP prevention bundle	Prevention of VAP	1) Using the SMART approach: - **S**pecific interventions: a) identify bundle elements likely to be successful b) review evidence in support of proposed bundle elements c) consult with experts d) do not become sold on any single bundle element without evidence that it actually works - **M**easurable outcomes: a) use clinically relevant criteria to define outcome (e.g. VAP) b) demonstrated ability to accurately measure outcome of interest c) be aware of reporting biases, especially when using b/a or time series methods - **A**chievable program a) develop prevention strategy according to availability of local resources b) Target one problem or outcome at a time c) Start with a smaller problem to refine the local approach then apply to larger problems

Table 1. (continued)

Author/ year of publication/ country	Design	Study period	Study outcomes	ICU	Type of bundle	Aim of the bundle	Methods used in the care bundle design process
							- **R**elevant a) Target problems that have direct clinical significance and consequences to patient care b) ensure that updated information is employed in the development of the prevention program c) update prevention program over time - **T**ime-Bound a) use discrete time periods for the implementation of the various phases b) have a cut-off time at which to determine the success or failure of the prevention program c) have specific time periods over which the prevention program will be re-evaluated to determine whether it needs updating or efforts to re-establish compliance with its components.
Kubilay[26], 2013, USA	Quality improvement	Q4 2006-Q1 2012	Infection rates	Neuro ICU	Ventricu-lostomy placement bundle	Decrease the ventricular catheter associated in-fection rate	1) Define the problem 2) FMEA was used to identify failure modes and solutions and to implement change and track results. 3) Broad literature review to outline evidence-based best practices.
Nelson[27], 2006, USA	Quality improvement	2003-2004	Create a palliative care bundle	ICUs in general	Palliative care bundle	Improving comfort and communi-cation in palliative care	1) Describe the problem 2) Review of the literature 3) Identify processes that were associated with desirable outcomes 4) Consensus about the candidate list of indicators 5) Specify and define the quality measures 6) Pilot test the quality measures

Table 1. (continued)

Author/ year of publication/ country	Design	Study period	Study outcomes	ICU	Type of bundle	Aim of the bundle	Methods used in the care bundle design process
Puntillo[28], 2014, USA	RCT	NR	Thirst intensity thirst distress	Medical-Surgical, neurologic cardio-vascular ICU	Intervention bundle for thirst intensity thirst distress and dry mouth	Reduce thirst intensity and thirst distress.	1) Identify problem, 2) Evaluating prior research to find interventions to relieve thirst or dry mouth 3) Combining the single interventions into a bundle 4) Test the new care bundle
Rello[27], 2010	Description of bundle methodology	NR	Developing a comprehensive care bundle	ICUs in general	Ventilator-Associated Pneumonia care bundle	Reduce the incidence of VAP	1) Findings of a previous review of hospital acquired pneumonia and VAP guidelines across Europe were used to produce a comprehensive list of interventions. 2) The MCDA (Multi-criteria decision analysis) method was used to develop the bundle. MCDA is a weighting and scoring technique that supports decision making when numerous and conflicting evaluations are being assessed.
Rello[29], 2011	Description of bundle methodology	NR	Developing a comprehensive care bundle	ICUs in general	VAP care bundle: VAP diagnoses bundle and VAP treatment bundle	Promote guideline compliance	1) Findings of a previous review of hospital acquired pneumonia and VAP guidelines across Europe were used to produce a comprehensive list of interventions. 2) The MCDA (Multi-criteria decision analysis) method was used to develop the bundle. MCDA is a weighting and scoring technique that supports decision making when numerous and conflicting evaluations are being assessed.
Romero[30], 2013, Chile	Before and After study	Mar'09-Jul'11	Medication errors	Medical-Surgical ICU	Preventive Interventions Program bundle (PIP-bundle): interventions on medication errors	Reduce medication errors	1) Each bundle intervention was selected based on the types and causes of medication errors during the baseline period. 2) A multidisciplinary team systematically evaluated every stage of medication use to identify the causes of medication errors.

Table 1. (continued)

Author/ year of publication/ country	Design	Study period	Study outcomes	ICU	Type of bundle	Aim of the bundle	Methods used in the care bundle design process
Titsworth [31], 2012, USA	Observational study	Aug'08 – Dec'10	Catheter-associated urinary tract infections	Neuro ICU	Urinary Tract Infections (UTI) prevention bundle	Reduce the incidence of catheter-associated UTI	1) Review of the literature
Álvarez[32], 2014, Spain	Quality improvement	NR	Description of the methods applied to identify the recommendations to be included in the zero-VAP bundle and to accomplish implementation	ICUs in general	"zero-VAP" bundle	Reduction of the national VAP incidence rate by 25% and to less than 9 episodes per 1000 days of mechanical ventilation	1) Define the objectives of the bundle 2) Selection of VAP prevention measures derived from the literature 3) Classification of the interventions as "functional", "mechanical" or ""pharmacological". 4) Evaluation of the measures by teams with at least 2 members of the national Task Force team by using GRADE 5) Quantitative assessment by 11 members of the panel considering: 1) quality of the evidence, 2) its safety, 3) its feasibility in Spanish ICUs. 6) Finally, feasibility and cost criteria were applied based on which groups of 7 basic mandatory and 3 highly recommended measures were generated.
Harnage[33], 2007, USA	Quality improvement	Jan'06-Mar'07	Infection rates	Medical, surgical, Trauma, Neurologic ICU	Central line bundle	Reduce Catheter Related Blood Stream Infections	1) Reviewing and updating the current practices and procedures. 2) Review of the literature 3) Compare the current policies and procedures with the literature. 4) Determine if the policies and procedures matched the evolution of available products 5) meetings with product representatives for the multitude of products used in the placement and care of central venous catheters. 6) Bundle selection was based on available research, CDC recommendations, new product technology, changes required by the nurse and ease of use by the end user.

NR: None Reported; ICUs: Intensive cares; CLABSI: Central Line Associated Bloodstream Infection; VAP: Ventilator Associated Pneumonia; UTI: Urinary Tract Infections; MCDA: Multi-criteria decision analysis; FMEA: Failure Mode Evaluation and Analysis; GRADE: Grading of Recommendations, Assessment, Development and Evaluation; RCT: Randomized Clinical Trial; CDC Centers for Disease Control and Prevention.

Quality assessment

For nine studies the checklist of Downs and Black was used. In 56% (5/9), studies scored between 15-19 points and were classified as 'fair'. One study scored 24 points and was classified as 'good'.[28] Studies were classified as 'poor' quality in 33% (3/9) (Supplementary File 2, Table 1). In six studies the AGREE II was used. Quality scores were calculated per domain[13] (Supplementary File 2, Table 2). For Domain 1, all six studies were classified as 'good', which means that the scope and purpose of the bundle were clearly explained. Six studies were classified as 'fair' for Domain 2, i.e. stakeholder involvement and for Domain 4, i.e. clarity of presentation. For three studies it was not possible to assess their quality, because narrative reports were written about care bundles in general and no assessment tools were available.

Flowchart for bundle design

The expert team created a flowchart containing all process steps to design new care bundles. The outline of the flowchart is shown in Figure 2. Three evaluations were added to the flowchart. These moments can be used to assess if the bundle conditions are met or to identify risks or problems prospectively.[2]

Reported methods for bundle design

The methods identified by the review were placed in either one of the main process steps. Table 2 shows all methods per process step. The table is complementary to Figure 2. In four process steps no other methods than the IHI methods were found.

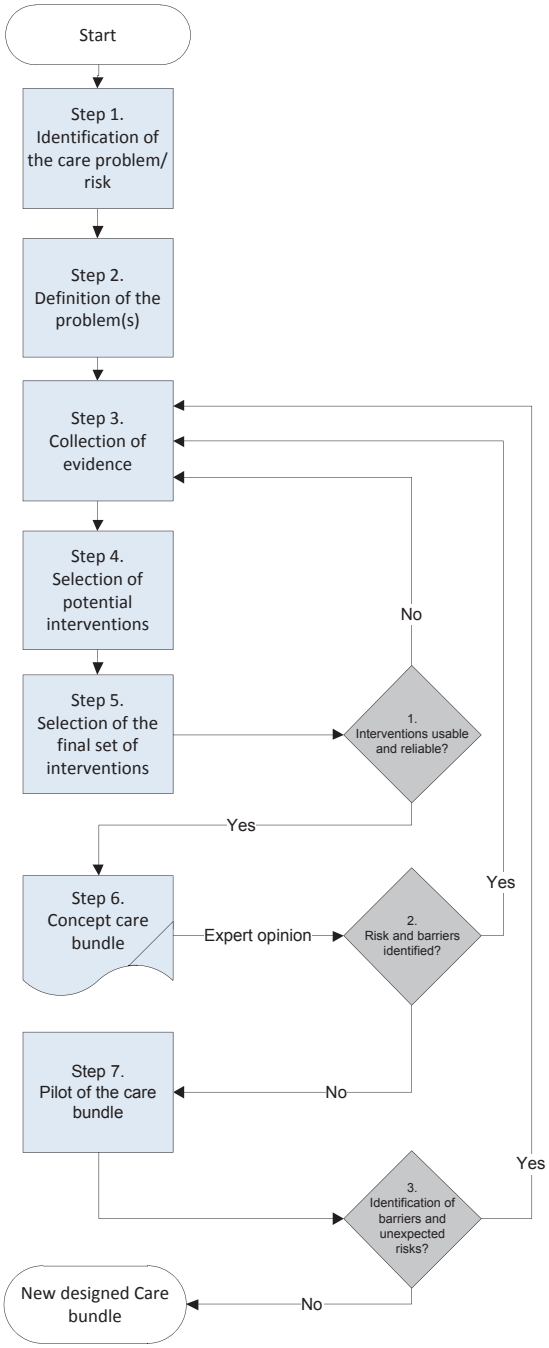

Figure 2. Outline of the comprehensive flowchart for designing new care bundles

Table 2. Process steps to design evidence-based care bundles

Process steps		Reported methods of the IHI	Additional reported methods
Step 1.	Identify problems or risks in a specific patient population or intervention that contributes to great harm and/or high costs.	Systematic reviews[2,10,19,20,23,29,33] Adverse Event Trigger Tool.[2]	Analysing own clinical patient data[18,21,30]; Root Cause Analyses[11]; Failure Mode Evaluation and Analysis (FMEA)[26]
Step 2.	The identified care problems or risks should be clearly defined.	Comprehensive literature search strategy[2]	No additional methods reported
Step 3.	Conduct a literature search to collect relevant evidence for the problems or risks and to find related elements.	Collect evidence from the international electronic databases and from the distillation from (inter)national clinical guidelines[2,19,20,23,26-28,32,33]	No additional methods reported
Step 4.	Select potential relevant and feasible elements from the literature search.	Select those elements that were described in the literature and were associated with the identified problem[2,10,18,19-33] or from local or (inter)national clinical guidelines[10,21,29]	Selected elements by analysing the medication errors[30]
Step 5.	Select a final set of maximally five elements	Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach to evaluate the quality of the evidence of the elements.[19,24,32]	Weighing and scoring technique to select the most suitable, reliable or most appropriate key elements[10,29,32]; Root Cause Analyses[11]; FMEA[26]; Through discussion sessions or consensus meetings with experts or hospital staff.[19,23,25,27]
Step 6.	Create the care bundle in draft form.	Create the bundle in draft form and check if the IHI bundle requirements are met.[2,22,24]	No additional methods reported
Step 7.	Pilot test the care bundle in order to assess the reliability.	The pilot should be performed in a small sample of patients to identify (potential) risks or barriers for implementation. It is important to monitor the performance of all bundle elements to identify potential problems or risks and to evaluate if the care bundle is feasible, comprehensive, effective and easy to use[2,25,27,28]	No additional methods reported

DISCUSSION

The results of our systematic review show that besides the IHI approach various additional methods exist to design care bundles. Most included studies reported only one part of the design process (67%, 12/18), while in 33% (6/18) the whole process was described. Given the diversity in the methods used for designing care bundles, it might be suggested that the original IHI methods may not always be applicable to all ICUs and in every situation. For example, Romero *et al.* selected a set of elements by using the results of their analysis on medication errors. The potential elements were based on the types and causes of medication errors that were reported during their baseline period.[30] To prevent these errors, a care bundle was created based on these types and causes of medication errors. In this case, the IHI method for identifying risks might not have given the best results for this ICU. Moreover, Khalid *et al.* used a RCA for identifying risks.[11] They show that this is an effective tool to clearly identify the local risks and discover the potential weak links in the process. They show that the results of a RCA could form a perfect basis to design new care bundles. Furthermore, we identified studies in which different types of bundles were developed. Besides the well-known central line bundle and ventilator bundle, other care bundles were described in the literature such as the bundle for prescribing antibiotics[22], ventriculostomy placement[26] or for the bundle in palliative care.[27]

The first step in the bundle design process is to identify (potential) problems or risks.[2] The IHI used the adverse event trigger tool for this step.[34] Besides this tool, we identified additional risks assessment tools, such as a RCA[11] or FMEA.[26] These can be highly effective in the bundle design process due to their focus on local problems or risks.[11,26] This is important for designing care bundles because the included bundle elements should be a generally accepted practice in order to deliver reliable care.[2-4] Rello *et al.* used the Multi-Criteria Decision Analysis (MCDA) to design the ventilator bundle. They showed that this method is highly structured and efficient to use in the bundle design process.[10,29] Another example is the use of a systematic review. The IHI used this method for designing the ventilator bundle.[4] Systematic reviews were also reported in the literature to underpin evidence for the bundle elements in step 3 of the development process.

It is important that care bundles meet the IHI criteria. One of the criteria is that bundle elements must be supported by level 1 evidence.[2-4] However, robust evidence of care processes in relation to patient outcomes is often not available.[35,36] Therefore, evidence could also consist of clinical practice guidelines or other peer-reviewed synthesis of the evidence or studies published in a peer-reviewed journal.[35,36] Even though care bundles

aim to improve quality of care, the possibility exists that bundled elements have unexpected negative effects on other care processes. This issue is not well described in the literature but should not be neglected. Therefore, moments for evaluations were incorporated in the bundle design process intended to identify unexpected risks (Fig. 2).

Strengths and weaknesses

To our knowledge, this is the first study that reported about the different methodologies used in literature to develop new evidence-based care bundles. Our systematic review has several limitations. A description of the bundle development process is not often reported in detail nor described in abstracts. Therefore, we might have missed some relevant articles. We searched for bundles that were developed for ICUs, while methods used in other hospital areas might be relevant and valid as well. However, the first developed bundles of the IHI were also designed for adult ICUs. Furthermore, the complexity in ICU care is not comparable with other hospital wards. We screened the titles and abstracts of the articles in two steps. During the first, step one author screened all titles and abstracts. However, predetermined unambiguously clear exclusion criteria were applied. In case there was any uncertainty, the study was included for the second step in this screening process. In the second step the titles and abstract were screened by two authors independently as recommended in the PRISMA-statement.[37] The quality assessment of the articles were conducted by two persons independently. However, the interrater reliability was not calculated. Although the outline of the flowchart is based on the IHI approach, the order of the process phases and incorporating the methodologies in each process phase was conducted by opinions of the expert group. However, we have used a validated consensus method to overcome this issue. By combining both IHI and additional methods, we created a flowchart on how to develop new evidence-based ICU care bundles. We only searched for studies that described the methods used for bundle development and we incorporated these methods into the flowchart (Fig. 2). However, other methods might also be applicable that were not identified in our literature search. For instance, in step 1 (Fig. 2) other risk assessment tools might be effective instead, such as a BowTie analyses[38] or using the analysis from incident reporting systems[39,40] or 'lean management'.[41]

CONCLUSIONS

In this systematic review, we identified useful methods to design new evidence-based care bundles for ICUs, besides the original IHI methods. The results were used to build a generic comprehensive flowchart for designing new evidence-based care bundles. The flowchart provides a detailed view of all process steps of the bundle development process. The flowchart can be used as a useful tool to guide through all necessary steps in the process of designing care bundles. Further research is needed to validate the process steps of the flowchart.

Competing interest

The authors declare that they have no competing interests.

Funding

There is no funding to report for this publication

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Supplementary File 1

Search strategy PubMed

((“Intensive Care Units”[Mesh] OR Intensive Care* OR ICU OR critical care OR “Critical Care”[Mesh]) AND (bundle* OR care bundle* OR evidence based*[tiab] OR “evidence-based practice”[MeSH] OR “Evidence-Based Medicine”[Mesh]) AND (development*[tiab] OR invent*[tiab] OR create*[tiab] OR method[tiab] OR methods[tiab] OR methodolog*[tiab] OR design*[tiab])) Filters: Publication date from 2002/01/01 to 2014/07/31

Supplementary File 2

Quality assessments

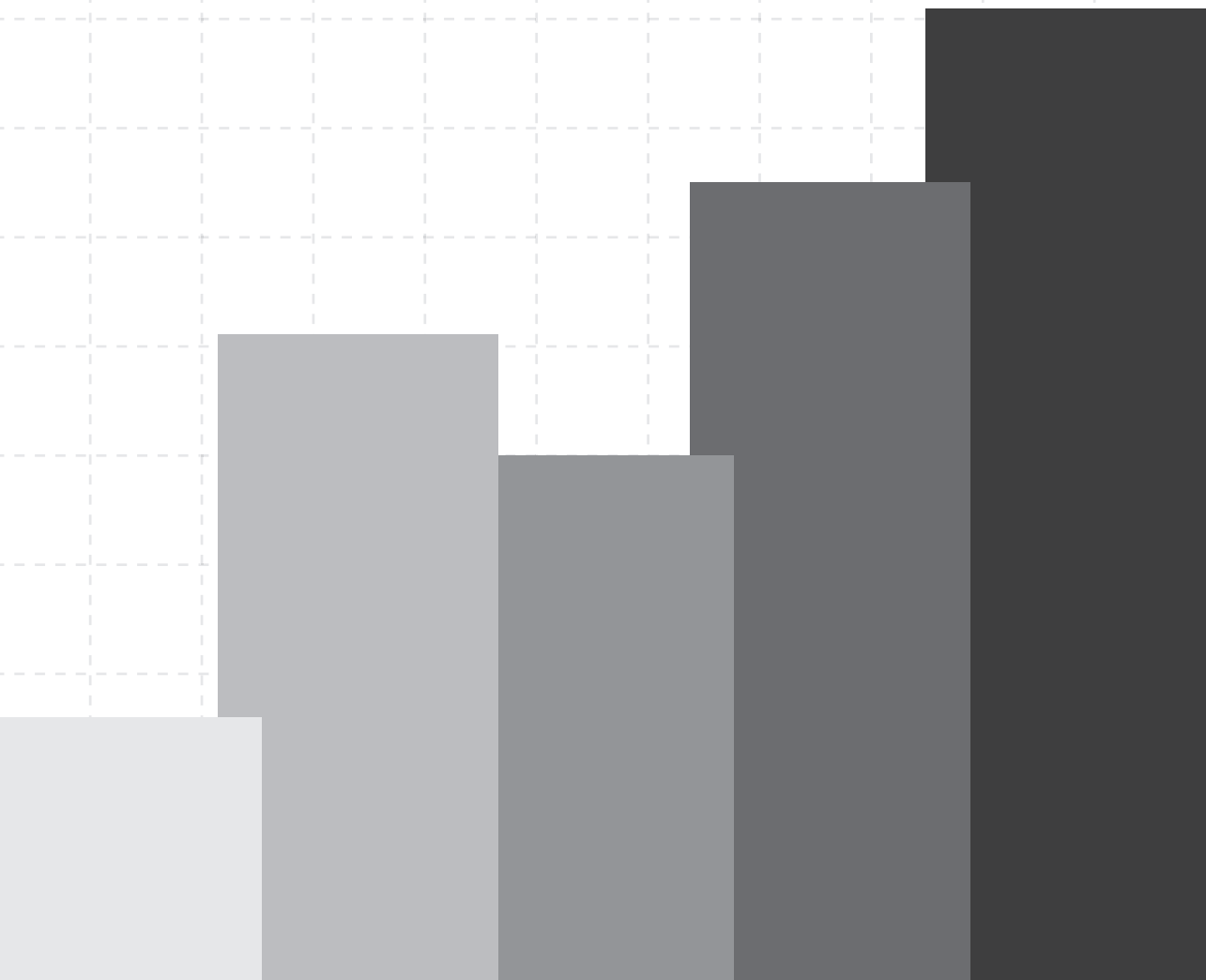
Table 1. Quality assessments by using the checklist of Downs and Black[15]

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	Total score
Harnage, 2007	1	1	0	1	0	0	0	0	1	0	1	0	1	0	0	0	1	0	0	0	1	1	0	0	0	1	0	10
Berenholtz, 2004	1	1	0	1	1	1	1	0	1	1	1	1	1	0	0	1	1	1	1	1	1	1	0	0	0	1	0	19
Khalid, 2013	1	1	0	1	0	1	1	0	1	1	1	0	1	0	0	0	1	1	1	1	0	1	0	0	0	1	0	15
Kubilay, 2013	1	1	1	1	0	1	0	0	1	0	1	0	1	0	0	0	1	1	1	1	0	1	0	0	0	1	0	14
Romero, 2013	1	1	1	1	0	1	1	0	1	1	1	0	1	0	0	0	1	1	1	1	0	1	0	0	0	1	0	16
Puntillo, 2014	1	1	1	1	0	1	1	0	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	24
Titsworth, 2012	1	1	1	1	0	0	0	0	1	1	1	0	1	0	0	0	1	1	1	1	0	1	0	0	0	1	0	14
Chatzi, 2014	1	1	1	1	0	1	1	0	1	1	1	1	1	0	0	0	1	1	1	1	1	1	0	0	0	1	0	18
Hocking, 2012	1	1	1	1	0	0	1	0	1	1	1	1	1	0	0	0	1	1	1	1	1	1	0	0	0	1	0	17

Table 2. Quality assessments by using AGREE II[14]

	Domain 1 Scope and purpose				**Domain 2** Stakeholder involvement				**Domain 3** Rigour of development									**Domain 4** Clarity of presentation				**Domain 5** Applicability					**Domain 6** Editorial independence		
	1	2	3	DS	4	5	6	DS	7	8	9	10	11	12	13	14	DS	15	16	17	DS	18	19	20	21	DS	22	23	**DS**
Álvarez, 2014	5	6	6	**77**	3	2	5	**61**	4	2	1	1	1	4	1	1	**15**	4	4	6	**61**	2	6	4	5	**54**	6	6	**75**
Rello, 2010	6	6	6	**83**	6	4	2	**50**	7	5	5	6	6	4	1	1	**56**	5	4	6	**67**	2	4	4	5	**46**	5	6	**67**
Rello, 2011	6	6	6	**83**	6	4	2	**50**	7	5	5	6	6	4	1	1	**56**	5	4	6	**67**	2	4	4	5	**46**	5	6	**67**
Berenholtz, 2007	6	6	4	**72**	6	4	2	**50**	6	6	6	5	6	6	1	5	**69**	5	4	6	**67**	4	7	4	6	**60**	6	6	**75**
Nelson, 2006	6	6	4	**72**	6	4	2	**50**	6	5	4	4	6	5	6	1	**60**	5	4	6	**67**	2	6	4	6	**58**	5	6	**67**
Pulcini, 2008	6	6	4	**72**	6	4	2	**50**	3	3	2	2	4	2	2	2	**25**	5	4	6	**67**	2	5	4	6	**54**	5	6	**67**

DS = Domain score in percentages



05

IDENTIFYING POTENTIAL RISK FACTORS IN THE DELIVERY OF ENTERAL NUTRITION IN CRITICALLY ILL PATIENTS - ARGUMENTS FOR INTRODUCING A NUTRITIONAL CARE BUNDLE

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Margreeth Vroom, Astrid Goossens and Dave Dongelmans

Submitted

ABSTRACT

Background. Malnutrition is a serious problem in critically ill patients. Identifying patients who are at risk of malnutrition is important in order to find ways of improving the quality of care. This study might form the basis to develop strategies to support intensive care unit (ICU) staff to provide adequate enteral nutrition (EN) and to minimize the risks for malnutrition in critically ill patients.

Methods. This retrospective observational study was conducted in a university hospital in Amsterdam, the Netherlands. Patients admitted to the ICU from January 2012 to December 2014 were included. Ideal calorie intake is calculated as 25 Kcal/kg/day. Ideal protein intake as 1.2 to 1.5 g/kg/day. Multilinear regression was used to describe the factors of success of EN intake.

Results. Overall, patients received 65% of the ideal protein intake and 66% of the ideal caloric intake. The daily success of EN intake has a median of >90%. The multilinear analyses showed that the nasoduodenal-, nasojejunal- and percutaneous endoscopic gastrostomy (PEG) feeding tubes achieved a significant better intake than nasogastric tubes.

Conclusion. The delivery of EN in critically ill patients was moderate to high in the majority of the patients. However, a substantial part of the EN delivery was still suboptimal during admission and needs to be improved. This implies a strong argument to support ICU staff in the adequate delivery of EN. This could be facilitated by a nutritional care bundle to support guideline uptake and thereby improve the delivery of EN.

INTRODUCTION

Malnutrition is a serious problem in critically ill patients. It is associated with increased morbidity and mortality and leads to higher costs of the healthcare system.[1,2] Due to the hypermetabolic response in critically ill patients the energy expenditure is increased.[3] But, feeding critically ill patients can be challenging since patients suffer from gastrointestinal intolerance, due to impaired gastrointestinal motility, digestion or absorption in more than 60%.[3,4] This, in combination with an increased energy expenditure leads to malnutrition.[3] Around 30 to 50% of critically ill patients admitted to intensive cares (ICUs) do not receive their daily protein and energy intake.[5,6]

An important therapy to prevent malnutrition in critically ill patients is Enteral Nutrition (EN).[7] This is usually administered through a nasogastric tube. An early start of EN within 24-48 hours following ICU admission has been advocated to enhance an adequate EN intake.[7] EN has several physiological benefits in the preservations of gut integrity and prevents the increase in intestinal permeability.[7,8] Adequate delivery of EN has positive effects on relevant clinical outcomes, such as the ICU and hospital length of stay, ventilator-free days, wound healing and nosocomial infections.[9,10]

Despite the positive effects of adequate EN, discrepancies exist between the actual intake and optimal EN intake.[2,3,6] Guidelines have been developed to enhance the adequate delivery of EN in critically ill patients. However, poor adherence to the EN guideline still exists.[11] Cahill et al. showed that only 60% of the patients were adequately fed during their ICU admission.[6] Multiple factors negatively affecting the delivery of EN in critically ill patients could be determined. For instance, delayed placement of feeding tubes and subsequent delayed administration of EN, interruptions in EN due to patient transports for advanced diagnostics and procedures outside the ICU. Another contributing factor is the existence of nutrition intolerance, causing for instance abdominal distension, vomiting, constipating or diarrhea.[2,5,12,13]

The delivery of care, such as the delivery of EN, consists of a complex series of interactions between physicians, nurses, patients and medical interventions.[14] Monitoring and systematically analyzing these interactions can be helpful in identifying those areas where optimal care is potentially at risk. The identification of those potential risks is important in finding opportunities in improving the quality of care.[14] We do not exactly know to what extent patients are at risk in receiving adequate EN therapy, nor which patient categories or areas might even be at higher risk. If we could determine if patients are at risk for malnutrition, quality improvement strategies could be used to enhance the EN intake. In this study we aim to assess to what extent patients receive their daily

EN intake during ICU admission in a large cohort of ICU patients. In addition we aim to identify subgroups of patients or areas within the EN practices where the daily EN intake is inadequate. This study might form the basis to develop strategies to support ICU staff to provide adequate EN, thereby minimizing the risk for malnutrition.

MATERIALS & METHODS

Setting

This retrospective observational study was conducted in an ICU for adult patients in a university hospital in Amsterdam, the Netherlands. The ICU is a closed-format department and has 28-beds with a mixed surgical and medical patient population. Patients are under the direct care of the medical ICU team. The nurse-to-patient ratio is 1:1 or 1:2, depending on the patients' severity of illness.

Protocol for enteral nutritional feeding

Our EN protocol is aimed at the early and continuous administration of EN (Supplementary File 1). The protocol includes instructions on when to start EN, directions to achieve the daily EN targets and directions to manage gastric retention. According to the EN protocol, patients' individual EN requirements are reviewed on a daily basis by the intensivist. These requirements are adjusted according to changes in the clinical conditions of the patient and on the nutritional intake of the previous days. Additionally, twice a week an intensivist, who is an expert in nutritional support, together with a dietician, are monitoring the nutritional conditions of every admitted patient. The EN delivery starts as soon as possible after ICU admission in patients whose length of ICU stay is expected to be more than 24 hours with the exception of surgical patients. These patients do not receive nutrition on the day of surgery or on the first day of ICU admission.

Data collection

Adult patients (≥ 18 years) admitted to the ICU from January 2012 to December 2014 were included in this study. Each bed is equipped with an electronic Patients Data Management System (PDMS) (Metavision, Ite medical Tiel), in which patient data is prospectively collected. Medical and nutritional data were extracted from this database. Data from patients with EN were used from admission until discharge from the ICU or with a maximum of 30 days. Other data we collected are age, gender, body length, last known body weight before hospital admission ICU and hospital length of stay, referral specialty in the ICU and Apache II.

Analysis

Descriptive statistics were used to summarize the baseline patient and feeding characteristics. Continuous variables that were normally distributed were expressed as means with standard deviations and not normally distributed variables as medians and inter-quartile ranges (IQR). To test two independent groups of not normally distributed continuous variables, the Mann-Whitney U test was used. Categorical variables were expressed as percentages, numerators and denominators and were compared with the Chi-square test or Fisher's exact test. Statistical uncertainty was expressed by 95% confidence intervals as appropriate, and statistical significance was defined at a *P* value of < 0.05. Adequate EN intake is defined as the real EN intake at least equal to the ideal EN volume/calorie/protein intake or more. Ideal calorie intake is calculated as 25Kcal/kg last known body weight before hospital admission/day[7], success of calorie intake as percentage of ideal realized calorie intake. Ideal protein intake is calculated as 1.2 to 1.5 g/kg/last known body weight before hospital admission/day[7,15], likewise success of protein intake as percentage of ideal realized protein intake. Patients with a body mass index of > 27-30 were excluded for analysis. To describe the factors of success or failure of feeding intake we used a multilinear regression model. We calculated the total feeding intake during ICU stay in terms of calorie as well as protein intake. We divided this number by the total duration of ICU stay (in hours) as a single outcome measure for overall success of feeding. In the multilinear regression model we included all patients that have been enterally fed during their ICU stay. As candidate predictors we selected age, gender, apache II score, type of admission (medical/surgical) planned admission (yes/no), mechanical ventilation (yes/no), type of feeding tube (nasoduodenal, nasojejunal, percutaneous endoscopic gastrostomy (PEG), naso-gastric tubes). The goal of the analysis by this prediction model was to find the most valid subset of available predictors and the corresponding best fitting regression model for describing the relationship between average EN intake of protein and calories during ICU stay and the predictors. A multiple linear regression model was used with forward selection (by hand) of predictors. Analyses were performed using R (version: 3.3.1; R Foundation for Statistical Computing, Vienna, Austria).

Ethical statement

The study was approved by the Medical Ethics Committee of the Academic Medical Center of Amsterdam, the Netherlands and the need for informed consent was waived.

RESULTS

Demographics

A total of 6862 patients were admitted to the ICU from 2012 to 2014. Table 1 shows the differences between the patients who received enteral nutrition and who were not. Sixty five percent of the patients (4456/6862) received other forms of intake than EN,70% (3115/4456) of these patients, mostly elective admitted were discharged from the ICU within 48 hours after admission. In 34% (2355/6862) patients received EN during ICU admission. Patients who received EN were longer admitted to the ICU and were more severely ill than patients who did not receive EN.

Table 1. Patient demographics

	Enterally fed patients	**Non-enterally fed patients**	**95% CI, *P*-value**
Total number of ICU patients	2355	4456	
Age, mean (sd)	61.3 (15.6)	60.7 (16.9)	-1.46 to 0.15, *P* 0.1086
Gender, Male, % (n/N)	60% (1413/2353)	62% (2778/4455)	*P* 0.0063
Planned admission, % (n/N)	18% (422/2355)	45% (1982/4456)	-0.29 to -0.24, *P* <0.001
Apache II, mean (sd)	19.52 (7.39)	14.70 (6.34)	-5.1743 to -4.4707, *P* <0.001
ICU LOS in hours, median (IQR)	95.0 (45-214)	32.0 (20-63)	*P* <0.001
Died in ICU, % (n/N)	28% (659/2355)	8% (359/4456)	*P* <0.001

Feeding tube locations

In Table 2 the feeding tube locations are shown for the delivery of EN. In the vast majority of patients a nasogastric tube was used (87%, 2037/2355). The median hours fed by using a nasogastric tube remained stable over the years. From 2012 to 2014 the median hours fed by a nasojejunal feeding tube decreased from 128 hours (IQR 43 to 336) to 19 hours (IQR (3 to 45) respectively, *P*-value <0.001.

Table 2. Feeding tubes for enteral nutrition

Patients with:	2012	2013	2014	*P*-value[b]
Nasogastric tube[a]	729	687	621	
- Median (IQR) hrs. fed	63 (19 to 175)	67 (20 to 188)	79 (27 to 214)	0.9
- Median (IQR) hrs. ICU-LOS	96 (51 to 207)	104 (48 to 233)	117 (57 to 265)	<0.0001
Nasoduodenal tube	19	22	21	
- Median (IQR) hrs. fed	24 (15 to 44)	83 (35 to 246)	65 (47 to 115)	0.02
- Median (IQR) hrs. ICU-LOS	23 (17 to 47)	92 (38 to 167)	126 (63 to 154)	0.03
Nasojejunal tube	22	25	11	
- Median (IQR) hrs. fed	128 (43 to 336)	29 (7 to 113)	19 (3 to 45)	0.001
- Median (IQR) hrs. ICU-LOS	127 (34 to 228)	44 (23 to 121)	25 (21 to 71)	0.01
PEG tube	9	27	20	
- Median (IQR) hrs. fed	82 (33 to 158)	29 (13 to 132)	146 (31 to 238)	0.2
- Median (IQR) hrs. ICU-LOS	69 (44 to 161)	46 (29 to 148)	235 (62 to372)	0.4

[a] Nasogastric tubes used for enteral nutrition
PEG: percutaneous endoscopic gastrostomy
[b] Kruskall Wallis test

Adequacy of enteral nutritional intake

During the first days of admission, the adequacy of mean percentage calorie and protein intake was 22% (413/1878) on day one and increased to 82% (675/823) on day five, difference 60%, 95% CI: -0.63 to -0.57, *P*-value <0.001. Figure 1 shows a wide variation in the delivery of EN. The success of daily EN intake of proteins has a median of more than 90% during ICU admission, except for the first five days of admission (Fig. 1). Furthermore, EN was initiated within 24-48 hours following admission. The differences between the actual and ideal intake was calculated for calories and protein per type of feeding tube over the years (Table 3 and 4). Each type of feeding tube showed an overall moderate EN delivery of calories and proteins. The mean percentage of adequate calories using the nasogastric feeding tube remained the same over the years, 66% (481/729) in 2012 to 67% (416/621) in 2014, difference %, 95% CI: -0.06 to 0.042, *P*-value 0.74. The same applies to the delivery of protein when using the gastric feeding tube. The mean percentage of ideal protein intake by using 1.2 g/kg/day was 64.6% and 55.8% by using 1.5 g/kg/day as an individual target. In ICU patients individual targets are often based on 1.2 g/kg/day.[7,15]

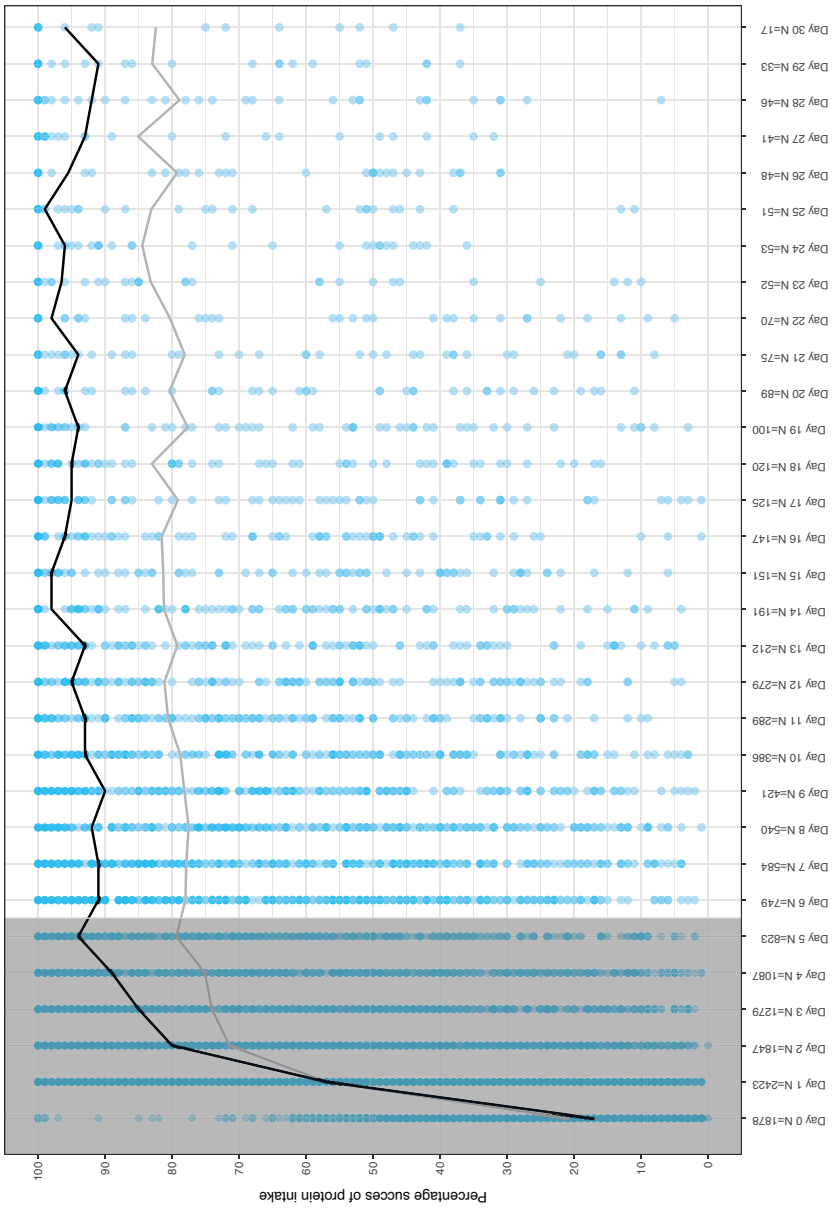

Fig. 1. Plot of the median for the adequacy of protein intake of 1.2g/kg/day for ICU patients.
Each dot represents one patient receiving EN. Black line represent the median percentage of success of protein intake. Grey line represent the mean percentage of success of protein intake.

Table 3. Kcal intake as percentage from the ideal intake

Year	Feeding tube	25 Kcal/kg	
		mean	95% CI
2012	Nasoduodenal tube	71	(60 to 82)
2012	Nasojejunal tube	71	(66 to 76)
2012	Nasogastric tube	66	(65 to 67)
2012	PEG tube	68	(57 to 79)
2013	Nasoduodenal tube	67	(60 to 74)
2013	Nasojejunal tube	69	(61 to 77)
2013	Nasogastric tube	66	(65 to 67)
2013	PEG tube	72	(65 to 79)
2014	Nasoduodenal tube	68	(60 to 76)
2014	Nasojejunal tube	47	(32 to 62)
2014	Nasogastric tube	67	(66 to 68)
2014	PEG tube	61	(53 to 69)

Table 4. Protein intake as percentage from the ideal protein intake

Year	Feeding tube	1.2g/kg		1.5g/kg	
		mean	95% CI	mean	95% CI
2012	Nasoduodenal tube	69	(58 to 80)	62	(51 to 73)
2012	Nasojejunal tube	72	(67 to 77)	64	(59 to 69)
2012	Nasogastric tube	68	(67 to 69)	57	(56 to 58)
2012	PEG tube	66	(55 to 77)	55	(45 to 65)
2013	Nasoduodenal tube	68	(61 to 75)	59	(53 to 65)
2013	Nasojejunal tube	69	(61 to 77)	64	(56 to 72)
2013	Nasogastric tube	68	(67 to 69)	58	(57 to 59)
2013	PEG tube	55	(49 to 61)	48	(42 to 54)
2014	Nasoduodenal tube	66	(58 to 74)	56	(49 to 63)
2014	Nasojejunal tube	47	(33 to 61)	38	(26 to 50)
2014	Nasogastric tube	69	(68 to 70	59	(58 to 60)
2014	PEG tube	59	(51 to 67)	49	(42 to 56)

Multilinear regression analysis for average EN intake

The multilinear analyses showed that the nasoduodenal-, nasojejunal- and PEG feeding tubes were significant better performers in terms of intake per hour than nasogastric tubes (Table 5). For a unit change in medical admissions there was a 5.10-point increase in average EN intake per hour (beta: 5.10, *P*-value <0.001). Planned admission had an adverse effect on EN intake (beta: -7.59, *P*-value <0.001). Age and Apache II score were not associated with an average EN intake per hour. The model accounted for 7.1% of the variance in average hourly EN intake.

Table 5. Multiple linear regression model for average volume feeding intake per hour during ICU stay[a]

	β	Se	β 95% CI	*P* value
Nasoduodenal tube[b]	8.69	3.26	2.29 to 15.08	0.008
Nasojejunal tube[b]	13.33	2.97	7.51 to 19.14	<0.0001
PEG tube[b]	7.89	3.40	1.23 to 14.56	0.020
Gender (male)	2.87	0.90	1.12 to 4.63	0.001
Apache II	0.12	1.26	-0.01 to 0.24	0.068
Mechanical ventilation (yes/no)	2.49	1.26	0.02 to 4.96	0.048
Planned admission (yes/no)	-7.59	1.34	-10.21 to -4.96	<0.0001
Admission type (medical/surgical)	5.10	1.06	3.02 to 7.19	<0.0001

Adjusted R^2: 0.071
[a] Total intake per patient divided by total hours IC stay
[b] Compared with reference Nasogastric tube

DISCUSSION

In the present study we retrospectively observed that overall patients received 65% of the ideal protein intake and 66% of the ideal caloric intake by EN during ICU admission. This is a higher intake than previous studies described.[5,6,12,16,17] Binnekade *et al.* showed that approximately 50% of the patients received the prescribed amount of EN intake.[5] In a prospective observational study of Cahill *et al.* it was shown that there is a poor adherence to the EN guideline resulting in a calorie and protein intake of nearly 60%.[6] However, close to ideal caloric and protein intake by EN is associated with improved clinical outcomes.[9] Furthermore, we showed that the median level of adequate EN intake was high, more than 90% per day. Targets of 80% are used in literature as an indicator for high performance in EN delivery practices.[6,18] In our study, the majority of

the patients received their daily protein targets of more than 80%. Our cohort, however, showed a wide variation in the delivery of EN intake as shown in Figure 1. Approximately 30% of the enterally fed patients still received inadequate EN, i.e. values below 80%. This indicates that there is room for further improvement in the delivery of EN.

During the first days of admission the actual calorie and protein EN intake was low. This was to be expected since in our EN protocol the first five days are used to build-up to patients' ideal EN intake. Furthermore, our results show that EN was initiated within 24-48 hours following admission. The early initiation of EN within the first 24-48 hours following ICU admission is strongly recommended in EN guidelines.[7] Observational studies have shown that patients who received an early start of EN had lower morbidity and lower mortality rates than patients who did not.[18]

The results from our model explained 7% of the average EN intake per hour, and may be accounted for a large variance in EN intake. This study was, however, not performed as an attempt to identify factors that contribute to a success or failure of EN intake; rather to describe the daily EN intake in critically ill patients and to determine groups of patients or areas where the daily EN intake might be inadequate while controlling for covariates. The model showed, however, that nasoduodenal-, nasojejunal- and PEG feeding tubes were factors for improved success of feeding compared to the nasogastric feeding tube. This can be explained by the fact that patients who fail to be fed by nasogastric tubes are in most cases fed by post pyloric feeding tubes.[19] Furthermore the model shows that medical patients were associated with a 5.10-point increase in average EN intake per hour (beta 5.10, *P*-value < 0.001) and a decrease in planned admissions (beta -7.59, *P*-value < 0.001). It may suggest that medical patients are associated with better EN intake than surgical patients. Other studies showed similar findings.[2,20] Dover et al. showed that surgical patients received less EN intake compared to medical patients. While patient undergoing cardiovascular and gastrointestinal surgery are even at higher risk of receiving inadequate nutrition.[20] It is suggested that there might be a delay in initiating EN due to the hemodynamic instability in these patients. Hemodynamic instability might be a barrier for some physicians to start the feeding protocol.[20] In our model we did not account for the different types of surgery.

It is known that using nurse-driven EN protocols or advice from dieticians is associated with improved feeding practices on ICUs.[21] This may have contributed to the moderate to high levels of EN delivery in our ICU. However, we showed that a substantial part of the EN delivery is still suboptimal and needs to be improved. In our view this implies a strong argument for the development of a nutritional care bundle to support guideline uptake and thereby improve the delivery of EN.[7,22] Care bundles are designed

by the Institute for Healthcare Improvement (IHI).[23] It is a practical tool to improve the performance of evidence based interventions. Care bundles aim to improve the reliability of care processes by grouping a small set of evidence based interventions together. All interventions should be performed together for every eligible patient to ensure patients receive the care they need.[23] Care bundles monitor professionals' bundle performance over time. Subsequent, the effect of the bundle could then be measured by using predefined outcome measures, i.e. quality indicators.[23,24] The quality indicator reflects a change as a result of the implementation of the care bundle. There is evidence that higher bundle compliance rates are associated with improved outcomes.[25]

In this observational study we retrospectively analyzed the EN delivery in critically ill patients. We observed if patients or groups of patients were at risk of malnutrition and considered whether there was room for improvement. Identifying problems or potential risks within care processes is the beginning of the bundle design process according to the IHI.[23] Multiple steps follow to design an evidence based care bundle.[23,26] This process is described in detail by the IHI.[23] Further research is needed to develop and validate a care bundle for the delivery of EN. Furthermore, research should focus on determining factors to enhance the implementation and sustainability of this care bundle. By continuously monitoring the effect of the care bundle on the predefined quality indicators changes in the performance of professionals can be detected. This provides valuable information on the EN delivery in critically ill patients.

Limitations

Our study has several limitations. We analyzed the data from a single center hospital, which can affect the generalizability of the results. We retrospective analyzed the data and therefore risk of bias could exist. We used a selected set of factors to describe the adequacy of EN intake. Other important factors affecting adequate EN delivery described in the literature are interruptions due to (re)intubation/extubation, fasting for interventions, patient transports, intestinal intolerance, diagnostic tests and problems with feeding tubes.[2,27] In our study we were not able to assess the influence of these factors on malnutrition. Furthermore, we were not able to identify other interfering factors for the adequate delivery of EN such as barriers in knowledge or organization.[28] Given the nature of our study, we did not find patients with a feeding prescription and a zero EN intake.

CONCLUSIONS

The delivery of enteral nutrition in critically ill patients was moderate to high in the majority of the patients in our ICU. However, a substantial part of the EN delivery was still suboptimal and needs to be improved. This implies a strong argument to support ICU staff in the adequate delivery of EN. In our view a nutritional care bundle to support guideline uptake and thereby improve the delivery of EN could facilitate this.

Competing interest

The authors declare that they have no competing interests.

Funding

There is no funding to report for this publication.

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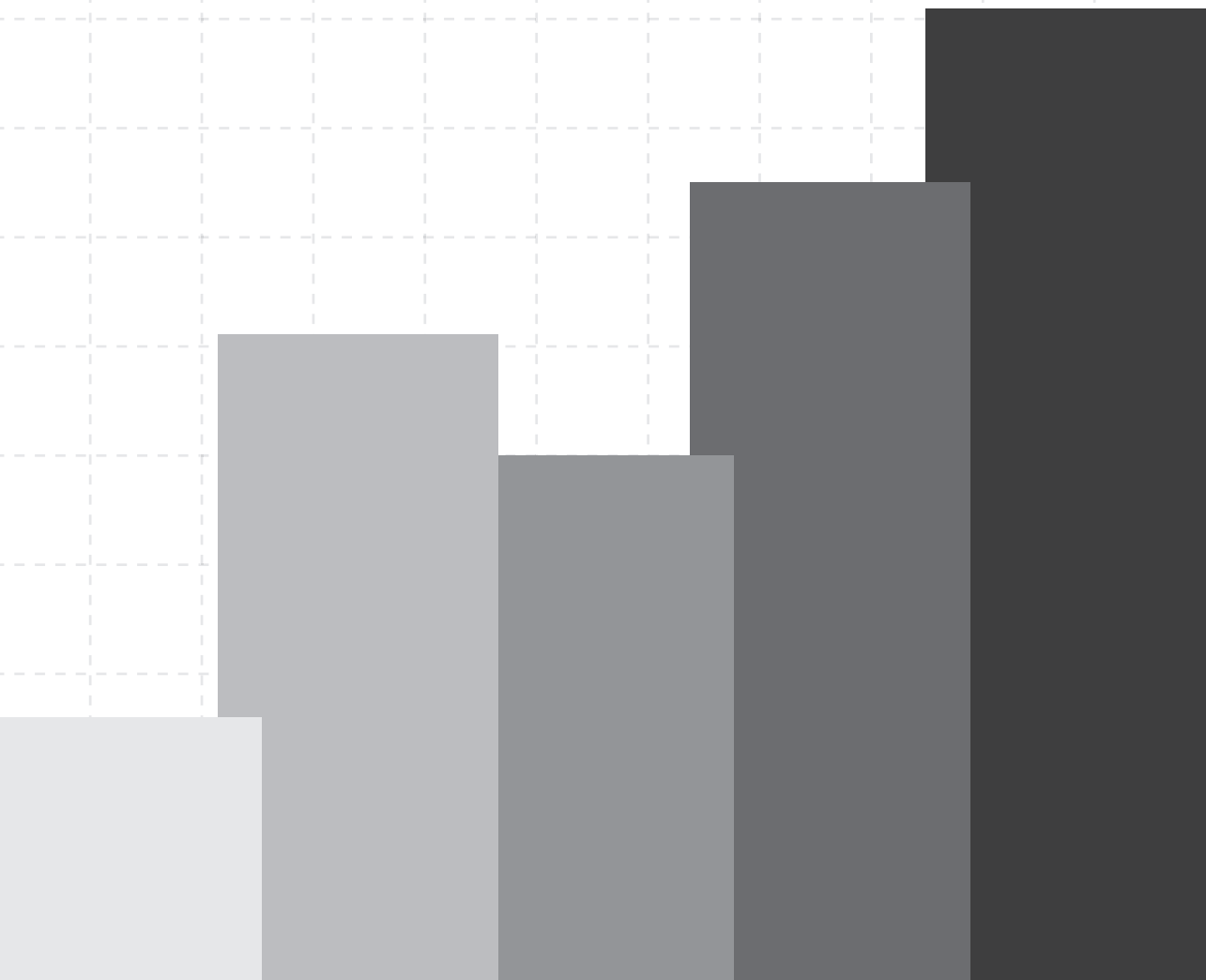

06

WHAT ARE EFFECTIVE STRATEGIES FOR THE IMPLEMENTATION OF CARE BUNDLES IN ICUS: A SYSTEMATIC REVIEW

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Implementation Science 2015; 10:119.

ABSTRACT

Background. Care bundles have proven to be effective in improving clinical outcomes. It is not known which strategies are the most effective to implement care bundles. A systematic review was conducted to determine the strategies used to implement care bundles in adult intensive care units and to assess the effects of these strategies when implementing bundles.

Methods. The databases MEDLINE/PubMed, OVID/EMBASE, CINAHL and CENTRAL were searched for eligible studies until January 31, 2015. Studies with (non)randomized designs on central line, ventilator or sepsis bundles were included if implementation strategies and bundle compliance were reported. Methodological quality was assessed by using the Downs and Black checklist. Data extraction and quality assessments were independently performed by two reviewers.

Results. In total, 1533 records were screened and 47 studies were finally included. In 49% pre/post designs were used, 38% prospective cohorts, and the remaining studies used retrospective designs (6%), interrupted time series (4%) and longitudinal designs (2%). The methodological quality was classified as 'fair' in 77%, and the remaining as 'good' (13%) and 'poor' (11%). The most frequently used strategies were education (86%), reminders (71%) and audit and feedback (63%). Our results show that compliance is influenced by multiple factors, i.e. types and numbers of elements varied and different compliance measurements were reported. Furthermore, compliance was calculated within different time frames. Also, detailed information about compliance, such as numerators and denominators, was not reported. Therefore, recalculation of consistent monthly compliance levels was not possible.

Conclusions. The three most frequently used strategies were education, reminders and audit and feedback. We conclude that the heterogeneity among the included studies was high due to the variety in study designs, number and types of elements and types of compliance measurements. Due to the heterogeneity of the data and the poor quality of the studies, conclusions about which strategy results in the highest levels of bundle compliance could not be determined. We strongly recommend that studies in quality improvement should be reported in a formalised way in order to be able to compare research findings. It is imperative that authors follow the standards for quality improvement reporting excellence (SQUIRE) guidelines whenever they report quality improvement studies.

INTRODUCTION

Because of the aging population the number of patients with chronic illnesses and comorbidities increases.[1] More complex medical care is needed for these patients when admitted to hospitals[1] of which the critically ill are admitted to the intensive care units (ICUs). To provide comprehensive care according to the best available evidence and to decrease the variation in daily care, clinical guidelines and protocols are developed.[2] Despite the efforts made in implementation, the adherence to guidelines and protocols is often poor[3], which negatively influences the quality of care.[3,4]

In order to encourage the adherence to clinical guidelines and to improve care processes, the Institute for Healthcare Improvement (IHI) has developed the concept of 'care bundles'.[4-6] Initially, care bundles were introduced to reorganize the structure and organization of care processes within the ICU departments. For example, the central line bundle was developed to reduce bloodstream infections.[5,7] Care bundles are designed around specific elements of patient care and consist of three to five key interventions, the so called 'elements'.[4] These elements are either evidence based or are already generally accepted in ICUs and in national guidelines. The strength of a care bundle is that all elements must be performed in every eligible patient, unless medically contraindicated, using the all-or-none (AON) approach.[4-6,8]

The bundled approach has already proven to be effective in improving clinical outcomes.[7,9,10] In accordance with the model of Donabedian, high levels of bundle compliance should be achieved to improve clinical outcomes.[11] For instance, Resar *et al.* have shown that ICUs with the highest levels of bundle compliance had the highest rate of infection reduction.[12] Pronovost *et al.* demonstrated that the implementation of the central line bundle resulted in a large reduction in infection rates (up to 66%) during the study period of 18 months.[9] Positive results can be obtained when improving the reliability of care processes to ensure patients receive all evidence-based interventions needed. This also includes the improvement of the organizational culture, i.e. the context in which care is delivered.[13] The IHI recommends achieving more than 95% reliability.[4] Care bundles formed part of multiple patient safety initiatives in hospitals and ICUs worldwide and are nowadays widely accepted on ICUs.

Various strategies were described in the literature to encourage the implementation of care bundles on ICUs.[14,15] Single strategies as well as multifaceted approaches, e.g. the combination of at least two strategies, were commonly used.[9,16] It is not known which strategies were used to implement care bundles nor which ones are the most effective. Therefore, we conducted a systematic review to determine the strategies

used to implement care bundles in adult ICU settings and to assess the effects of these strategies when implementing care bundles. We addressed the following questions: which strategies were used to implement the three most used care bundles, i.e. central line, ventilator and sepsis bundle, on adult ICUs and which implementation strategy or strategies lead to the highest levels of compliance?

METHODS

Study design

A systematic review was conducted to determine the strategies used to implement care bundles in adult ICU settings and to assess the effects of these strategies when implementing care bundles. The protocol for the systematic review was not registered.

Selection criteria

We included studies of any design which implemented one of the three mostly used care bundles, i.e. central line, ventilator or sepsis bundle, on ICUs for adult patients. Studies were only included if a description of the implementation strategy was given, and if the level of compliance of the whole bundle or either compliance for each bundle element was reported separately. Studies written in non-English language were excluded. Protocols, abstracts, letters, commentaries or editorials were also not eligible.

Search strategy

Systematic and comprehensive searches were developed with a clinical librarian and designed for optimal retrieval. The electronic databases MEDLINE/PubMed, OVID EMBASE, CINAHL and CENTRAL were searched for literature until January 31, 2015. The complete list of search terms and strategy of MEDLINE/PubMed can be found in Supplementary File 1. Additionally, the reference lists of included articles were checked.

Inclusion of relevant studies

Two reviewers independently selected the studies (MB/DD or MB/AG). In case of discrepancies in study selections we reached consensus through discussion. A third reviewer (DD or AG) was involved in case of disagreement. Studies were selected if they reported about: 1) central line, ventilator or sepsis bundle; 2) implementation strategies used; and if 3) compliance levels for the whole care bundle was reported or for each bundle intervention separately. Two criteria for selecting studies, i.e. compliance rates and implementation strategies, were not (clearly) reported in abstracts, while these criteria could be well described in the full text. Therefore, if there was uncertainty

whether a study reported about one of these two inclusion criteria, it was selected for full-text screening. Full-text articles were thoroughly reviewed and studies were included if all three selection criteria were clearly described.

Data extraction

Data extraction was performed by using a pre-defined data-abstraction sheet. The following data were extracted: author, publication year, research design, setting, participants, i.e. bundle users such as nurses or physicians, type of care bundle, implementation strategies, bundle elements, compliance rates and the type of compliance measurements. Two reviewers performed data extraction independently. In case of discrepancies, consensus was reached by discussion. A third reviewer was consulted in case consensus could not be reached.

Quality assessment

A great variety exists in quality assessment tools for non-randomized studies. A valid checklist to assess the quality is currently lacking.[17] However, Downs and Black designed a checklist to evaluate the methodological quality of studies with both randomized and non-randomized designs.[18] We have used this tool to assess the risk of bias among the included studies. Checklist item number 27 about sample size calculation was simplified to a score of 0 (no sample size calculation) or 1 (sample size calculation reported). Therefore, a maximum score of 28 could be achieved for randomized studies and 25 for non-randomized studies. The following cut-off points have been reported to categorize studies by quality: excellent (26–28), good (20–25), fair (15–19) and poor (≤ 14).[19,20] Two reviewers conducted the quality assessment independently. Disagreement between the reviewers was resolved through discussion. A third reviewer was involved in case of disagreement.

Implementation strategies

The different strategies that were used for implementation were categorised using the taxonomy developed by The Cochrane Effective Practice and Organisation of Care Group (EPOC) for dissemination and implementation strategies (Table 1).[21] Where more than one method was used within one of the categories this was measured as one strategy, i.e. if checklists and dashboards were used, this was categorised as a 'reminder' and was therefore measured as only one strategy.

Types of measurements for care bundle compliance

Four different types of measurements were described in the literature to calculate the levels of bundle compliance: 1) 'AON-measurement', which calculates the percentage of all indicated elements the patients actually have received, unless medically contraindicated[4,24,25]; 2) composite measurement, which can be calculated as a ratio between care that was actually given divided by the care that should have been given[24,25]; 3) item-by-item measurement, which presents the nominator and denominator of each bundle element separately[25]; 4) lowest level of compliance, which means that the lowest level of compliance to one of the elements is considered as the total bundle compliance.[5,7]

Data analysis/synthesis

We used the compliance levels, which were last recorded as the measure of effect of implementation. Compliance was summarised as a percentage and, if applicable, as a numerator and a denominator. When studies were described as quality improvement initiatives, we further classified the nature of the study design by two reviewers independently. In case of discrepancies, consensus was achieved through discussion. We determined if selective reporting of compliance levels occurred within the included studies. Data analysis was performed in two phases. Firstly, overviews were given of all included studies to give insight in the study characteristics, compliance levels, the implementation strategies used, the number and types of bundles and their elements and the methods used to calculate compliance. In this phase, studies were not excluded based on their methodological quality. Secondly, a subgroup analysis was performed. For the subgroup analysis, the methodological quality of studies was assessed. In case a study scored less than 14 points, i.e. poor quality, it was excluded. Furthermore, subgroup analysis was not performed if less than three data points were available per subgroup. Studies were stratified and analysed by study design, quality assessment outcome, type of compliance measurement and by type of bundle. Subsequently, data were grouped and analysed by factors that could influence compliance, i.e. number of implementation strategies, bundle elements, methods for calculating compliance. From this, we attempted to identify patterns in compliance levels. Pearson's product-moment correlation coefficient or Spearman's rank-order were used to assess the relationship of compliance to the number of implementation strategies and the relationship between compliance and the number of elements. Kendall's rank-correlation assessed the relationship of compliance to the time frame in which compliance was calculated. R (version: 3.1.3; R Foundation for Statistical Computing, Vienna, Austria) was used to perform subgroup analysis. Although a meta-analysis was planned, this could not be conducted due to the heterogeneity of the data in study designs, interventions and

outcomes. Therefore, a narrative synthesis of the data is presented. This systematic review follows the standards of the preferred reporting items for systematic reviews and meta-analysis (PRISMA).[26]

Table 1. Explanation of the implementation strategies using the EPOC taxonomy[21-23]

Implementation strategy	Examples within the implementation of care bundles
Professional interventions	
Distribution of educational materials	(Web based) toolbox with educational materials, written material for self-study
Educational meetings	Educational meetings, seminars, workshops, teaching sessions
Local consensus processes	Development care bundle or materials or discussing about patients who developed an infection.
Educational outreach visits	Use of a trained person who met professionals on the ICU to give information with the intent of changing practice.
Local opinion leaders	Nursing and/or medical leadership
Audit and feedback	Audits and feedback on infections rates or bundle compliance. Use of dash boards
Reminders	(Run) charts, checklists with bundle elements, daily goal sheets, insertion, HOB alarms
Tailored	Focus groups or (survey to) identify barriers
Mass media	Posters, fact sheets, newsletters, brochures to reach a great number of staff
Other; Time out procedure	Time out procedure, empower to stop procedure
Patient intervention	
Patient-family interventions	Family education of the bundle elements or family participation
Organizational interventions	
Revision of professional roles	Shifting of roles among staff
Clinical multidisciplinary teams	(Daily) multidisciplinary rounds, multidisciplinary teams
Skill mix changes	Changes in the number of staff
Continuity of care	Group of doctors to remove catheters daily
Satisfaction of providers	Nursing and medical champions, material rewards and staff engagement
Other; Implementation teams	Special team is actively involved to implement the care bundle, improvement teams
Structural interventions	
Changes in medical record system	Changes in a medical record system for electronic documentation

RESULTS

In total, 1533 records were identified for possible inclusion through the initial search, of which a final set of 47 studies met the inclusion criteria (Fig. 1).

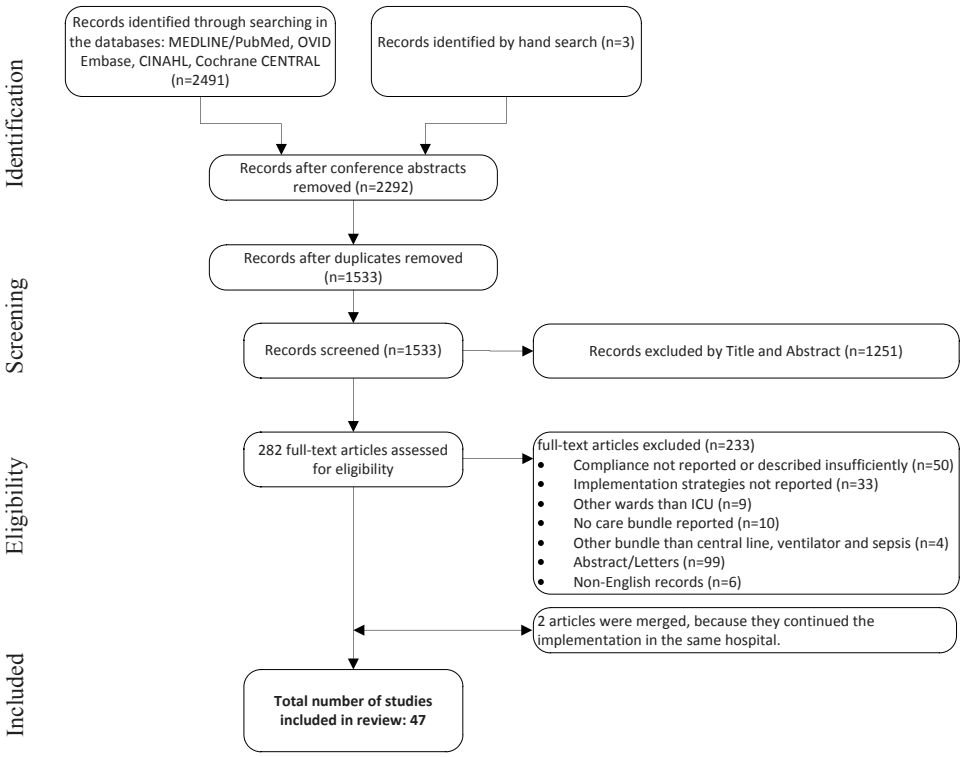

Figure 1. Flow chart of the study selection procedure

Quality assessment

Seventy-seven percent (36/47) of the studies scored between 15-19 points on the Downs and Black quality assessment scale and were classified as 'fair'. Thirteen % (6/47) of the studies scored 20 points or more and were classified as 'good'. Eleven percent of the studies were classified as 'poor' (5/47) (Supplementary File 2). We assessed reporting bias of the included studies, and no studies were found reporting negative results.

Study characteristics

Overall, 72% (34/47) of the studies were conducted in a single hospital and 28% (13/47) in two or more hospitals. The 47 studies that were included reported about the implementation of 49 care bundles. Thirteen studies described the implementation of the central line bundle, 27 studies described implementation of the ventilator bundle and nine studies described the sepsis bundle implementation (Supplementary File 3). Two studies reported the implementation of two bundles, i.e. both central line and ventilator bundle[35,39] and two studies were merged because they continued the implementation in the same hospital.[60,61] One study reported detailed information about the study participants, i.e. bundle users.[50] They described variables as age, gender and years of work experience. The remaining studies only mentioned the type of disciplines that used the bundle without reporting additional information about the users. Studies about central line implementation used pre/post designs in 46% (6/13), prospective cohort studies in 39% (5/13) and retrospective designs in 15% (2/13). Studies about the implementation of the ventilator bundle were conducted with pre/post designs in 48% (13/27), with prospective cohorts in 33% (9/27), as a longitudinal study in 4% (1/27) and as both interrupted time series and retrospective designs in 7% (2/27). For the studies about sepsis bundle implementation pre/post designs were used in 56% (5/9) and prospective cohort designs in 44% (4/9). A detailed description of relevant study characteristics is shown in Supplementary File 3, which is organized by type of bundle and study design.

Number of care bundle elements

Both the number of elements per bundle and the types of element varied (Supplementary File 4). Three types of central line bundles were described: 1) central line bundle in general (n=8), 2) insertion bundle (n=5) and 3) maintenance bundle (n=3). The range of elements within the central line bundle varied from three to seven elements (Supplementary File 4). In 8/16 central line bundles five elements were included and most of these elements were derived from the original IHI bundle.[5] The number of elements per ventilator bundle ranged from four to seven. In 12 studies (44%, 12/27) the bundle consisted of four elements and in three studies[50,58,62] (11%, 3/27) the bundle contained seven elements (Supplementary File 4). The most common element was 'elevation of the head-of-the-bed' in 96% (26/27), followed by deep venous thrombosis prophylaxis and peptic ulcer prophylaxis in 78% (21/27). The sepsis bundle was divided into the resuscitation bundle (n=5) and management bundle (n=6). In two studies[67,68] the general sepsis bundle contained six and 11 elements respectively. The resuscitation bundle has a range of five to seven elements while the management bundle contains two to seven elements (Supplementary File 4).

Implementation strategies

The three most frequently used strategies to implement care bundles were: educational activities in 88% (43/49) followed by reminders in 71% (35/49) and audit and feedback (A&F) in 63% (31/49). Family participation was only adopted as a strategy to implement the ventilator bundle (Table 2). Within each study about central line implementation a minimum of one strategy was described, ranging from one to a maximum of seven strategies. In all studies of central line bundle implementation, checklists were used. Education was used in 85% (11/13) and A&F in 77% (10/13). In 54% (7/13) the time-out procedure was reported (Supplementary File 3). In studies of the implementation of the ventilator bundle, there is a great variety in the number of strategies, ranging from one to nine strategies (Table 2). The three most frequently used strategies were education (85%, 23/27), reminders (78%, 21/27) and A&F (67%, 18/27). In studies of the implementation of the sepsis bundle, education was most frequently used (89%, 8/9) followed by mass media strategies, e.g. distribution of posters (44%, 4/9). In contrast with the strategies to implement the central line and ventilator bundles, the concept of a reminder was only used in one study of the implementation of the sepsis bundle (Table 2).[66]

Type of compliance measurements

In the majority of the studies the AON approach was used (n=36). The composite measurement was reported in four studies.[33,46,53,63] Three studies[38,39,52] reported the lowest level of compliance, two studies[45,72] used the item-by-item measurement (Supplementary File 3) and in two studies the type of measurement was not clearly reported. In nine studies on the central line bundle implementation, the AON approach was reported to calculate the compliance levels. In two studies the composite measurement was used and in one study the lowest level of compliance. In one study the type of measurement could not be identified. Exline *et al*. reported a high level of compliance of 100% with the insertion bundle, using the AON approach.[36] In the study of Render *et al*. the compliance with the central line bundle was 98% at the end of the study period using the composite measurement.[33] One study[27] reported a low compliance rate of 44%, which was measured over a period of 18 months (Supplementary File 3). In the calculation of the compliance of the ventilator bundle, four types of measurements were used. One study reported the compliance per single item[46], three studies used the composite measurement and two studies used the lowest level of compliance. In the remaining studies, the AON approach was used to measure the compliance of the ventilator bundle (Supplementary File 3).

Table 2. Implementation strategies

	Central line Bundle	Ventilator Bundle	Sepsis Bundle	Total number
Professional interventions				
Distribution of educational materials	27,32-34	10,40,41,46,52,56,	66-70,72	16
Educational meetings	28,30,35,36	35,41,42,53,59,	66,67,69,70,72	14
Local consensus processes		45,46,51,57		4
Educational outreach visits	27-29,31-34,36,37	10,40,42-60/61,63	64-66,68,	34
Local opinion leaders	34,36		65	3
Audit & Feedback	27,28,30-34,36-38	10,16,40,41,43,44,46, 49,52-54,56-62	65,66,70	30
Reminders	27-39	10,35,39-47, 49,51-54,56-59,63,	65,	35
Tailored		41,51,53,54,59		5
Mass media	27,28,30,32	10,40,44,45,47,52,53, 56,57,59-62	65-67,72	20
Other; Time-out procedure	28-30,34,36,38	49,54,60/61		9
Patient interventions				
Patient-family interventions		46,57,59		3
Organizational interventions				
Revision of professional roles		59		1
Clinical multidisciplinary teams	28,35	10,35,41,43,53,55,56, 57,59,63	68	13
Skill mix changes			68,69,71	3
Continuity of care	30			1
Satisfaction of providers	31,33,36	40,46,48,54,56		8
Other; Implementation teams	27,29,31,34-36	35,42,45,46,52,53,56	65,68,69	16
Structural interventions				
Changes in medical record system	38		64	2

The numbers in the table are reference numbers; except for those in the last column.
Central line bundle: 13 studies; Ventilator bundle: 27 studies; Sepsis bundle: 9 studies.

Time frame compliance calculation

Compliance was calculated over different time frames, i.e. some studies calculated compliance for each month, while others measured the overall compliance over a longer period, i.e. 1 or 2 years. In three studies about ventilator bundle implementation compliance rates of 100% were reached.[57,59-61] In these studies the compliance was calculated monthly by using the AON approach. Two studies reported low compliance levels of 30 and 34% respectively.[42,52] In these studies the compliance was measured using the AON approach over the whole study period (Supplementary File 3). In most studies about sepsis bundle implementation, the level of compliance was measured using the AON approach. Only one study used the item-by-item measurement to report compliance.[66] The compliance levels for sepsis bundles were exceptionally low compared to the central line and ventilator bundles (Supplementary File 3). Two studies reported compliance levels of 68% and 70% respectively.[64,68] However, these studies were performed in small patient numbers.

Effects on compliance

The first subset of studies that was analysed, included studies with pre/post designs, which were qualified as either 'good' or 'fair', and in which compliance was calculated by using the AON approach. Supplementary File 5, Figure S1 shows that, overall, there is no association between the number of strategies used and compliance levels (r = 0.118, 95% CI. -0.331 to 0.523, p = 0.612). The same applies when the bundles are analysed separately. As shown in Table 2, different strategies were used in combination for implementation of care bundles. For the implementation of the central line and ventilator bundle, the combination of education, reminders and A&F was used. For the implementation of the sepsis bundle, education is mainly used in combination with distribution of educational materials. Overall, there is neither an association between compliance and the number of elements ($\rho = 0.140$, $p = 0.545$) nor between compliance and the time frame used to calculate compliance ($\tau = -0.080$, $p = 0.639$). The second subset of studies that was analysed, included prospective cohort studies with quality assessments of either 'good' or 'fair' and in which compliance was calculated using the AON approach. Supplementary File 5, Figures S4 to S6 show that there is a variety in compliance levels. Moreover, no association can be found between the number of implementation strategies ($\rho = 0.539$, p =0.057), bundle elements ($\rho = -0.303$, $p = 0.314$) and time frame used for measuring compliance (τ =-0.189, p =0.417).

DISCUSSION

In this systematic review we identified the strategies that were reported to implement care bundles in ICU settings, and subsequently, we attempted to find the best strategies to achieve high levels of bundle compliance. Care bundles have already proven to be effective in reducing negative clinical outcomes.[7,9,10] This reduction is associated with the compliance rates to the care bundles.[12] It is important to mention that we, therefore, focused on finding the best implementation strategy to achieve high levels of bundle compliance and not on the outcome of care processes. Although care bundles are perceived as valuable, and are proven to have an effect on the quality of care, it is still a challenge to achieve high levels of bundle compliance.

Our results show that the three most frequently used implementation strategies were education followed by reminders and A&F. These findings are consistent with other reviews about implementation strategies in general[73,74], in which these three strategies were commonly used to implement best practices in hospitals[73] or critical care areas.[74] In 53% of the studies, a combined strategy consisting of education, reminders and A&F were used. This combination was mainly used to implement the ventilator bundle (57%), and only used in 11% for implementing the sepsis bundle. Overall, after implementation of the bundles, compliance levels varied, ranging from 33 to 100%. However, these findings should be interpreted with caution, because studies included in this systematic review showed a variety of designs. The majority of studies involved quality improvement initiatives with pre/post designs or prospective cohort studies without using controls. For these studies, secular trends that might have occurred at the same time were not taken into account. Furthermore, we assessed the quality of the individual studies by using the checklist of Downs and Black and the majority of the studies were classified as 'fair'.[18] Remarkably, none of the studies provided more detailed information about the participants, i.e. bundle users, except for one.[50] Information about the setting was reported in all studies. Such details about the context of an intervention should be reported to determine the generalizability, or external validity, of the study.[75,76] We furthermore determined great differences in the number and types of bundle elements between the studies, and in the measurements and calculations of bundle compliance rates. Due to this heterogeneity of data, even within the different subgroups (Supplementary File 5), we could not identify the most effective implementation strategy that resulted in the highest levels of compliance. In the next paragraphs we will discuss how these factors could have influenced the compliance levels.

Number of elements per bundle

The total number of elements per bundle varied, with a range of three elements in the central line bundle[36] to 11 in the sepsis bundle (Supplementary File 4).[68] The concept of a care bundle is to have a small number of elements to ensure that evidence based care will be delivered reliably.[4] Adding more elements is likely to affect the reliability of the bundle, i.e. if more elements are included, it is more difficult to perform all bundle elements at once. Consequently, this results in lower compliance levels.[4]

Differences in types of bundle elements

Our results show that even within one group of bundles, different types of elements were added. Hospitals design their own care bundle and when including elements, it is important that each element is generally accepted by hospital staff.[4,8] The reliability of these new elements, as well as the acceptance of an element (intervention), may affect the likelihood and motivation to use the bundle.[3,4] One study compared the compliance rates of three different sepsis bundles. In this comparative study several factors were observed which were affecting the compliance rates, such as the exclusion criteria for an intervention and the definition of an intervention.[77]

Time period compliance calculation

Our results show that four different types of measurements were used to calculate the compliance levels. In most studies detailed information about compliance rates was not reported at all. In most studies the AON approach was used[4-6] , and therefore, it is possible that lower compliance levels were reported. Compared to the AON approach, the composite measurement has greater sensitivity for giving insight in the changes in care processes.[24,25] Benneyan recommends both measurements because of their specific benefits.[24] In some studies the bundle compliance was measured monthly, while other studies measured compliance over a longer period of time, i.e. over a period of several months or years. In most studies detailed information about compliance, such as the monthly numerators and denominators, were not reported.

Among the included studies, the success of bundle implementation was highly variable, even when studies were stratified on design, methodological quality and type of measurement. This could be explained by either the number and types of bundle elements or by the ways compliance is measured and calculated as shown in this systematic review. Differences in measuring and reporting performance outcomes were observed by Dixon-Woods *et al.*.[78] In their analysis of a national program to reduce the rates of central-venous-catheter-related bloodstream infections, they found that the

standardised definitions and measurements of the study outcomes were interpreted differently between the participating ICUs. This resulted in differences in collecting data and therefore, data between ICUs were not fully comparable.[78]

The variety in compliance rates could be influenced by other factors. Bundle compliance is often monitored by using checklists (Supplementary File 3).[79] Besides auditing compliance, checklists are useful tools to standardise care processes, comparable to care bundles, and to improve the reliability of care to ensure patients receive all evidence-based interventions needed.[79] Although the use of checklists is promising, it is known that they are underused and barriers exist to use them which negatively influences the reliability of care.[79,80] Thus, there could be a discrepancy between actual delivered care and the use of checklists, resulting in lower compliance rates, while the care was actually performed. Another example is that, compliance of a new intervention could be negatively influenced when related to the habits and positive beliefs regarding the 'old' intervention even when the new intervention is based on robust science.[27] Furthermore, one study showed that lack of monitoring compliance was the reason for non-compliance.[50] Complementary, the frequency of monitoring compliance has resulted in positive effects on bundle compliance rates.[81] Monitoring data, e.g. on compliance and/or infection rates, results in increased awareness and encourage ICU staff to be compliant with the care bundle.

Although desirable, it can be challenging to achieve and maintain levels of bundle compliance of more than 95%.[4,9] In order to sustain the success of implementation, change of the organisational culture into a safety culture is required.[9,82] Creating a culture of safety includes the change of behaviour or attitudes of hospital staff to openly discuss about patient safety-related issues and to learn from mistakes without blaming.[13] Creating a culture of safety is necessary to enhance the adoption of care bundles, which subsequently contributes to redesign care processes and improve team work and communication between professionals.[4,9]

Implementation of quality improvement projects does not have to give the same positive findings when reproduced in other hospitals. One example is the Keystone project in Michigan which showed a sharp decline in the central line infection rates in ICUs.[9] Many of the components of this project were replicated in ICUs in the UK which also showed a reduction in infection rates. However, these positive findings were not only due to the multifaceted interventions of the programme used, but were part of a secular trend. Secular trends are not often measured in quality improvements[83,84], i.e. studies about implementing quality initiatives are often part of larger hospital or

nationwide improvement programs which positively influences patient outcomes as well. The context in which a program for quality improvement is launched contributes to different outcomes.[83,85]

Limitations

Our systematic review is hampered by several limitations. There is a chance that we missed some relevant studies, because different terms are given to care bundles. However, a broad search strategy was used and we have completed the search with a hand search. Two criteria for selecting studies, i.e. compliance rates and implementation strategies, were not (clearly) reported in abstracts, while these criteria were described in the full text. We included any article to the phase of full-text screening if there was any uncertainty about one of the inclusion criteria. Furthermore, our review was restricted to the inclusion of English language publications only and relevant studies published in other languages could have been missed. However, evidence for the effect of language restrictions on systematic bias remains inconclusive. Another important issue is that no studies with randomized designs were included. The majority of the studies included were quality improvements and before-and-after studies without controls. Thus, observed changes could be influenced by secular trends.[86] Furthermore, the overall methodology of the included studies was poor, involving an increased risk of bias.[86] Therefore, the results should be interpreted with caution. An important problem hampering a meta-analysis was due to the heterogeneity of the available data (Supplementary File 5). There was a high variability in study design, methodological quality, bundle characteristics, compliance measurements and the calculation of compliance within a specific time frame. Therefore, it was not possible to point out the superior implementation strategy. Moreover, complete data of compliance was lacking, e.g. most studies only reported compliance as a percentage, without explicitly reporting numerators and denominators. Although not all included studies show high compliance levels, publication bias could still have influenced our results since all included studies show positive results. Since compliance was reported as secondary outcome, the quality of reporting could have been influenced by this fact.

Future research

Further research is needed to identify the best strategy to implement care bundles to achieve high levels of compliance. To investigate the effects of implementation strategies on compliance levels, there is a need for robust study methods in implementation or quality improvement research. Studies using randomized designs should be considered to increase the internal and external validity, especially when the intervention is considered for widespread implementation.[87] However, randomization

is not always possible or suitable in quality improvement studies. Alternative designs could then be considered, such as controlled before and after trials or interrupted time series to control for confounding variables.[88] Otherwise, a combination of quantitative and qualitative designs could be conducted to assess if the intervention worked, how it worked and in what contexts.[83,88] Furthermore, it is imperative that studies are clearly and unambiguous reported. A clear description about the context in which the intervention was implemented should be stated, and a detailed description of the participants, i.e. the users of the intervention, should be provided.[75] These requirements are stipulated in the standards for quality improvement reporting excellence (SQUIRE) guidelines[75] which are strongly recommended when reporting quality improvement studies. To compare performance outcomes, there should be an unambiguous method for measuring compliance, i.e. the use of the AON and/or composite measurement.[24] Within current implementation research it is not only important to identify the most effective strategy, but also to better understand why, how and when the specific strategy works best.[89]

CONCLUSIONS

The three most frequently used implementation strategies were education, reminders and audit and feedback. We conclude that the heterogeneity among the included studies was high due to the variety in study design, difference in number and types of elements, types of compliance measurements calculation. Due to the heterogeneity of the data and the poor methodological quality of the studies, conclusions about which strategy results in the highest levels of care bundle compliance could not be determined and no recommendations can be made on which strategy should be selected to get the highest levels of compliance. We strongly recommend that studies in quality improvement should be reported in a formalised way in order to be able to compare research findings. It is imperative that authors follow the SQUIRE guidelines whenever they report quality improvement studies.

Acknowledgements

We thank Jet Zegers for her invaluable help editing the manuscript.

Competing interest

The authors declare that they have no competing interests.

Funding

This study was funded by ZonMw.

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Supplementary File 1

Search strategy MEDLINE/PubMed

((“Intensive Care Units”[Mesh] OR Intensive Care*[tiab] OR ICU*[tiab] OR critical care*[tiab] OR “Critical Care”[Mesh]) AND (bundle*[tiab] OR evidence based*[tiab] OR “evidence-based practice”[MeSH]) AND (ventilat*[tiab] OR pneumon*[tiab] OR sepsis[tiab] OR VAP[tiab] OR CRBI*[tiab] OR CLABSI*[tiab] OR CVL*[tiab] OR central line*[tiab] OR bloodstream*[tiab] OR “Pneumonia, Ventilator-Associated”[Mesh] OR “Catheter-Related Infections”[Mesh] OR sepsis[Mesh]) AND (“Guideline Adherence”[Mesh] OR compliance[tiab] OR adherence[tiab] OR guideline*[tiab] OR implement*[tiab] OR improve*[tiab] OR disseminat*[tiab] OR intervent*[tiab] OR mail*[tiab] OR educat*[tiab] OR leader*[tiab] OR remind*[tiab] OR didac*[tiab] OR multifaceted*[tiab] OR strateg*[tiab] OR tailored interv*[tiab] OR feedback*[tiab] OR audit*[tiab]))

Supplementary File 2

Quality assessments using the 27 criteria of the checklist of Downs and Black[18]

Central line bundle	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	Total score
Marra, 2010	1	1	1	1	0	1	1	0	1	1	1	1	1	0	0	1	1	1	1	1	1	1	0	0	0	1	0	19
Jeong, 2013	1	1	1	1	1	1	1	0	1	1	1	1	1	0	0	1	1	1	1	1	1	1	0	0	0	1	0	20
Richardson, 2012	1	1	0	1	0	0	0	0	1	0	1	1	1	0	0	0	1	0	1	0	1	1	0	0	0	0	0	11
Bonello, 2008	1	1	0	1	1	0	0	0	1	0	1	0	1	0	0	1	1	0	1	1	1	1	0	0	0	1	0	14
Exline, 2013	1	1	0	1	1	1	1	0	1	1	1	1	1	0	0	1	1	1	1	1	1	1	0	0	0	1	0	19
Longmate, 2011	1	1	1	1	0	1	1	0	1	1	1	1	1	0	0	1	1	1	1	1	1	1	0	0	0	1	0	19
McPeake, 2012	1	0	0	1	0	0	0	0	1	0	1	0	1	0	0	1	1	0	1	1	1	1	0	0	0	1	0	12
Hocking, 2013	1	1	1	1	0	1	1	0	1	1	1	0	1	0	0	1	1	1	1	1	1	1	0	0	0	1	0	18
Render, 2011	1	1	0	1	0	1	1	0	1	1	1	1	1	0	0	1	1	1	1	1	1	1	0	0	0	1	0	18
McNamara, 2011	1	1	0	1	0	1	0	0	1	0	1	1	1	0	0	1	1	0	1	1	1	1	0	0	0	1	0	15
Helmick, 2014	1	1	0	1	0	0	1	0	1	1	1	0	1	0	0	1	1	1	1	1	1	1	0	0	0	1	0	16
Khalid, 2013	1	1	0	1	0	0	1	0	1	1	1	0	1	0	0	1	1	1	1	1	1	1	0	0	0	1	0	16
Sacks, 2014	1	1	1	1	0	1	1	0	1	1	1	1	1	0	0	1	1	1	1	1	1	1	0	0	0	1	0	19
Ventilator bundle	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**Total score**
Hatler, 2006	1	0	1	1	0	0	0	0	1	0	1	1	1	0	0	1	1	0	1	1	1	1	0	0	0	1	0	14
Malouf T,2013	1	1	0	1	0	1	1	0	1	1	1	1	1	0	0	1	1	1	1	1	1	1	0	0	0	1	0	18
Lawrence, 2012	1	1	0	1	0	1	1	0	1	1	1	1	1	0	0	1	1	1	1	1	1	1	0	0	0	1	0	18
Morris, 2011	1	1	1	1	0	1	1	0	1	1	1	1	1	0	0	1	1	1	1	1	1	1	0	0	0	1	0	19
Hawe, 2009	1	1	1	1	1	1	1	0	1	1	1	1	1	0	0	1	1	1	1	1	1	1	0	0	0	1	0	20
Bloos, 2009	1	1	1	1	0	1	1	0	1	1	1	1	1	0	0	1	1	1	1	1	1	1	0	0	0	1	0	19
Rello, 2013	1	1	1	1	0	1	1	0	1	1	1	1	1	0	0	1	1	1	1	1	1	1	0	0	0	1	0	19
Bukhari, 2012	1	1	1	1	0	0	0	0	1	1	1	1	1	0	0	1	1	0	1	1	1	1	0	0	0	1	0	16
Marra, 2009	1	1	1	1	1	1	1	0	1	1	1	1	1	0	0	1	1	1	1	1	1	1	0	0	0	1	0	20
Caserta, 2012	1	1	1	1	1	1	1	0	1	1	1	1	1	0	0	1	1	1	1	1	1	1	0	0	0	1	0	20
Esmail, 2008	1	1	1	1	0	1	0	0	1	0	1	1	1	0	0	0	1	0	1	1	1	1	0	0	0	1	0	15

Youngquist, 2007	1	0	0	1	0	1	0	0	1	1	1	1	1	0	0	1	1	0	1	1	1	1	0	0	0	1	0	15
Zaydfudim, 2009	1	1	1	1	0	1	1	0	1	1	1	1	1	0	0	1	1	1	1	1	1	1	0	0	0	1	0	19
Al-Tawfiq, 2010	1	1	1	1	0	1	0	0	1	0	1	1	1	0	0	1	1	1	1	1	1	1	0	0	0	1	0	17
Bonello, 2008	1	1	0	1	1	0	0	0	1	0	1	0	1	0	0	1	1	0	1	1	1	1	0	0	0	1	0	14
Miller, 2010	1	1	1	1	0	1	1	0	1	1	1	1	1	0	0	1	1	1	1	1	1	1	0	0	0	1	0	19
DePalo, 2010	1	1	0	1	0	1	1	0	1	1	1	1	1	0	0	1	1	1	1	1	1	1	0	0	0	1	0	18
Jimenez, 2009	1	1	1	1	0	0	1	0	1	1	1	1	1	0	0	1	1	1	1	1	1	1	0	0	0	1	0	18
DuBose, 2008	1	1	0	1	0	0	1	0	1	0	1	1	1	0	0	0	1	0	1	1	0	0	0	0	0	1	0	12
Berenholtz, 2011	1	1	1	1	1	1	1	0	1	1	1	1	1	0	0	1	1	1	1	1	1	1	0	0	0	1	0	20
Crunden, 2005	1	1	1	1	0	1	1	0	1	0	1	1	1	0	0	1	1	1	1	1	1	1	0	0	0	1	0	18
Berenholtz, 2004	1	1	0	1	1	1	1	0	1	1	1	1	1	0	0	1	1	1	1	1	1	1	0	0	0	1	0	19
Eom, 2014	1	1	1	1	0	0	1	0	1	0	1	1	1	0	0	1	1	1	1	1	1	1	0	0	0	1	0	17
Hamishehkar, 2014	1	1	1	1	0	1	1	0	1	1	1	1	1	0	0	1	1	1	0	0	1	1	0	0	0	1	0	17
Helmick, 2014	1	1	0	1	0	0	1	0	1	1	1	0	1	0	0	1	1	1	1	1	1	1	0	0	0	1	0	16
Lim, 2013	1	1	1	1	0	1	1	0	1	1	1	1	1	0	0	1	1	1	1	1	1	1	0	0	0	1	0	19
Mukhtar, 2014	1	1	1	1	0	1	1	0	1	1	1	1	1	0	0	1	1	1	1	1	1	1	0	0	0	1	0	19
Al-Thaqafy, 2014	1	1	1	1	0	1	1	0	1	1	1	1	1	0	0	1	1	1	1	1	1	1	0	0	0	1	0	19
Sepsis bundle	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**Total score**
Memon, 2012	1	1	1	1	0	1	1	0	1	1	1	1	1	0	0	0	1	1	1	1	1	1	0	0	0	1	1	19
Schramm, 2011	1	1	1	1	0	1	1	0	1	1	1	1	1	0	0	1	1	1	1	1	1	1	0	0	0	1	0	19
Kim, 2012	1	1	1	1	0	1	1	0	1	1	1	1	1	0	0	1	1	1	1	1	1	1	0	0	0	1	0	19
Guilliano, 2011	1	1	1	1	0	1	1	0	1	1	1	1	1	0	0	1	1	1	1	1	1	1	0	0	0	1	0	19
Ferrer, 2008	1	1	1	1	0	1	1	0	1	1	1	1	1	0	0	1	1	1	1	1	1	1	0	0	0	1	1	20
Laguna Perez, 2012	1	1	1	1	0	1	1	0	1	1	1	1	1	0	0	1	1	1	1	1	1	1	0	0	0	1	0	19
Castellanos, 2010	1	1	1	1	0	1	1	0	1	1	1	1	1	0	0	1	1	1	1	1	1	1	0	0	0	1	0	19
Lefrant, 2010	1	1	1	1	0	1	1	0	1	1	1	1	1	0	0	1	1	1	1	1	1	1	0	0	0	1	1	20
Silverman, 2011	1	1	1	1	0	1	1	0	1	1	1	1	1	0	0	0	1	1	0	1	1	1	0	0	0	1	0	17

Supplementary File 3

Study characteristics in detail

First author, Publication year, country, care bundle	Design	Study Periods	ICU (number of beds)	Study outcomes	Participants (bundle users)	Model of theory/ program of patient safety	Type of compliance measurement/ Period in which compliance is calculated	Implementation details	Effects on compliance
Jeong[27] 2013, South Korea, Central line bundle	pre/post design	Baseline: Apr'09-mrt'10, Intervention phase: Apr'10-Dec'11 - Transition period: Apr-Sep'10 - Follow up: Oct '10-Dec'11	ICU (39 beds)	Bundle compliance. Incidence of CLABSI. Length of time between insertion and CLABSI occurrence	Health care professionals: nurses and physicians	NS	AON/ Overall: 18 months	1) Development Task Force team, 2) posters 3) distribution of educational programs and materials 4) feedback on unit level compliance with CL bundle and CLABSI incidence. 5) checklist. During follow up period (Oct '10-Dec '11): weekly feedback on compliance and monthly feedback on CLABSI rates. Task force team provided feedback on the overall follow up process. Educational programs and distributed materials to new professionals.	Phase 1: Baseline: 0% Phase 2: Intervention period: 44,3% ($p<0.001$)
Hocking[28] 2013, New Zealand, Central line bundle	pre/post design	Baseline: Oct '07-Dec '08 Post intervention: Jan '09 - Apr '11.	General ICU (7 beds. By July '08: 12 beds)	CLABSI rate. Bundle compliance.	Nurses and doctors. Nurse-pt ratio: 1:1 or 1:2	NS	AON/ Per month	1) education, 2) reminders during nurses shift handover and placed on computer screen, 3) checklist, 4) nurses observed insertion and they reminded doctors to comply with the bundle, 5) feedback on compliance, 6) posters, 7) teaching at the bedside in small groups. 8) face to face teaching sessions 9) Signs (updated each day) with run charts of CLAB rate and staff compliance, 10) daily rounds, 11) visual updates on staff compliance	Insertion bundle Dec'08: 36% to Apr '11: 81%. Maintenance bundle Jun '09: 76% to Apr '11: 80%. Compliance High risk bundle was not described
Sacks[29] 2014, USA, Central line bundle	Pre/post design	Baseline: Nov'04-Nov'05. Intervention: Dec'05-Mar'06. Post intervention	Tertiary care hospital, surgical ICU: 16 beds	CLABSI rates	Physicians and nurses	NS	AON/ Per month	1) multidisciplinary implementation team; 2) computerized training module and examination for all physicians and nurses involved; 3) nurses were instructed to stop the procedure if they noticed any violation; 4) checklist; 5) mobile central line insertion cart containing all equipment and supplies for insertion and management of CVCs	Overall compliance: March '06: 58% (19/33)
Marra[30] 2010, Brazil, Central line bundle	Quasi-experimental: pre/post design	Phase 1: Mrt'05- Mrt'07. Phase 2 (bundle implementation): Apr'07-Apr'09	Medical and surgical ICU (38 beds)	CLABSI rate	ICU-team: doctors and nurses	NS	AON/ Overall:2 years	1) Educational meetings, 2) monthly feedback on compliance via email. 3) Posters with bar charts displaying compliance + CLABSI rates. 4) Group of ICU doctors to remove catheters daily. 5) nurses intervened in the process at the same time if non-compliance with an element was detected, 6) insertion chart	Phase 2 on ICU: 1723/1833 (94%)

Longmate[31] 2011, UK, Central line bundle	Quality improvement: pre/post design	Baseline: 1 Sep'05- 31 Aug'06. Intervention: Mrt'08-Aug'09	Medical and surgical ICU, (9 beds)	CLABSI rates. Care processes: reliability.	Nurses and doctors	Scottish Patient Safety program.	AON/ Per month	1) Active engagement of staff, 2) educational programs, 3) measurement and feedback of outcomes, 4) insertion checklist, 5) organizational change, 6) introduction of the Scottish Patient Safety program, 7) measurement of insertion processes and feedback, 8) ownership of nurses of the two bundles	Insertion bundle compliance per month: Mar '08: 80% to Aug '09: 95%
Khalid[32] 2013, Saudi Arabia, Central line bundle	Quality improvement: pre/post design	Pre intervention: Febr '09-Jan '10 Postintervention yr1: Aug'10-Jul'11 Yr 2: Aug'11-Jul'12	Tertiary care hospital, medical/surgical ICU: 18 beds	CLABSI rates	Physicians and 101 nurses. Nurse-pt ratio: 1:1, 1:2	NS	Not clear/ Per month	1) education sessions; 2) audits, 3) checklists; 4) daily reminders; 5) flyers	Insertion bundle: Preint: 85% Postint yr 1: 96%, yr 2: 99%. Maintenance bundle: Pre intervention: 75%. Post int yr. 1: 91%, yr 2: 97%.
Render[33] 2011, USA, Central line bundle	Observational cohort study	Apr'06-Apr'09	Multicenter, General, medical, surgical and cardiac ICUs: 174 ICUs (1774 beds)	1. Adherence bundle elements 2. CLABSI rates	Nurses	PDSA cycles	Composite/ Per quarter	1) hospital leadership, 2) learning module, 3) physician champion, 4) use of central line cart, 5) checklist during line insertion as a forcing function, 6) addition of a daily goal sheet during physician rounds as a memory aid for CL removal. 7) feedback about CLABSI rate and bundle adherence 8) web based toolbox with education materials (for sharing in multicenter setting). 9) ICU dashboard progress in CLABSI rates in own ICU compared with national rates.	Apr to Dec '06: 85%, 2009: 98%
Richardson[34] 2012, USA, Central line bundle	Evidence Based Practice project/ quality improvement: Prosp cohort	May '06- May '10	Medical and surgical ICU (Number of beds NS)	Infection rates	Nurses and physicians	NS	AON/ Per quarter	1) Implementation team of clinical nurse specialists, 2) education every 6 months (didactic lectures simulation laboratory, emails, quiz format etc), 3) checklist en modified this when needed, 4) nurses empowered to stop the procedure if any of the required bundle item practices were not being followed, 5) nursing and medical leadership, 6) 'Hot team' facilitated the group in determining the logistics for the work that needed to be done, they met monthly, established a web page on intranet and posted literature, relevant policy, procedure statements, education files as pp presentations, auditing forms, 7) feedback on compliance and infection rates.	Compliance during the whole study period: >90%.
Bonello[35] 2008, USA, Central line bundle	Quality improvement: Prosp cohort	Jan'05 - Jun'06	Multicentre, 12 ICUs, (95 beds)	Process measures: adherence to CL insertion checklist. CRBSI rates.	ICU care providers	Quality Improvement Collaborative using the PDSA cycle	AON/ Per quarter	1) Educational symposia, 2) interdisciplinary team rounds, 3) checklist at bedside. 4) multidisciplinary implementation teams	CL bundle: First 3 months: 58%, Final 3 months: 74%

Exline[36] 2013, USA, Central line bundle	Observational cohort study with historical controls. Historic controls not used for compliance	Baseline: Jan'08-Dec'09. Intervention year 1: Jan-Dec'10, Intervention year 2: Jan-Dec'11	Medical ICU, (25 beds)	Quarterly CLABSI rates. Compliance with CVC insertion and dressing maintenance practices.	ICU nurses and physicians	NS	AON/ Audit per month	1) Insertion checklist, 2) Audit and feedback by infection preventionists: compliance per month and CLABSI per week, 3) Educational meetings, 4) Mandatory demonstration session for dressing change and proper line access on manikin, 5) Nurses were empowered to stop the procedure if sterile technique was not correctly employed. 6) Insertion trays were augmented with components to comply with central line bundle, 7) Coat pins 8) implementation teams, 9) unit physician and nursing leadership,10) case reviews	Compliance with insertion practices: 100%. Compliance with dressing maintenance: 80-100% during the intervention period.
McPeake[37] 2012, UK, Central line bundle	Quality improvement: Pros cohort	Jun '08-Dec '10	General ICU (Number of beds NS)	CLABSI rate Compliance	ICU nurses	PDSA cycles	AON/ Per month	1) checklist, 2) performance feedback, 3) education, 4) run charts on trolley, 5) Evaluation when compliance with an element was poor 6) checklists for insertion	Jun '08: 67% Dec '10: 100%
Mc Namara[38] 2011, USA, Central line bundle	Retrospective study	Oct'08- Apr'10	General ICU (89 beds)	Bundle documentation	Nurses	NS	Lowest level of compliance + item-by-item/ Per month	1) feedback to included units and nursing staff, 2) audit, 3) electronic insertion checklist, 4) time-out procedure	Compliance: Oct'08: 20% - Apr. '10: 80%.
Helmick[39] 2014, USA, Central line bundle	Retrospective review	2009-2011	Multicentre: 5 mixed, 4 medical, 4 surgical and 2 cardiac ICUs.	Mean rates of CRBI	NR	NS	Lowest level of compliance/ Per month	1) Checklists	2009: 95.86% 2010: 98.31% 2011: 97.51% P 0.38
Lawrence[16] 2012, Australia, Ventilator bundle	Pre/post design	Total period: Apr'09-Mar 10. Pre-intervention 6 months, Intervention: 6 months	2 General ICUs, 8 beds	Compliance	Nurses	NS	AON/ Overall: 6 months	1) feedback of compliance rates using a graphical presentation.	Pre intervention (n=164): 65.2% Intervention (n= 151): 67.5% (p-value Chi-square: 0.754)
Morris[40] 2011, UK, Ventilator bundle	Pre/post design	Baseline: Jan '05 - Feb '08. Run in period: Feb '08-Sept '08. Post VAP prevention period: Sept '08 - Aug '09.	Medical & surgical ICU, 18 beds	VAP incidence MRSA rates Duration of MV ICU LOS ICU mortality	Nurses and medical staff	PDSA-cycle	AON/ Overall: 1 year	1) distribution of teaching materials; 2) Education sessions; 3) Feedback on compliance at meetings, by email, with posters; 4) bedside cues; 5) changing the 24h observational chart (checklist); 6) nurse and medical champions.	Post implementation period: 70%

Hawe[41] 2009, UK, Ventilator bundle	Pre/post design	Passive implementation period: Sep '05-feb '07. Active period: 1 Mar '07-31 Dec '07	Medical & Surgical ICU	Compliance VAP incidence Unit mortality	Medical and nursing staff	NS	AON/ Per month	Passive period: 1) formally adopted as unit policy; 2) laminated copies of the bundle at pt bedside; 3) verbal and written encouragement for its use at ward rounds and other times. Active period: 1) educational intervention: multidisciplinary education meetings; 2) workshops for medical and nursing staff presenting the definition, pathogenesis, epidemiology and risk factors of VAP; 3) Written material for self-study was distributed; 4) assessment of bundle compliance during daily rounds; 5) Feedback of process measurement; 6) feedback of outcomes measurement and organizational change; 7) Barriers affecting delivery of care were identified and iteratively improved.	Passive period: Nov '06: 0% Active period: may '07 48%, Oct '07: 54% (chi square p value: <0.0001)
Bloos[42] 2009, Germany, Ventilator bundle	Pre/post design	Total period: Jun '05-Jun '06. Pre intervention: Jun-Sep '05, Post intervention Mar-Jun'06	General ICU, 50 beds.	Compliance ICU LOS Rates of pneumonia Days on MV ICU survival	ICU nurses and residents	NS	AON/ Overall: 4 months	1) educational meetings: scientific background and techniques of the bundle were taught to all nurses and residents in daily seminars for 2 months; 2) red marks on the wall to indicate a correct semi recumbent position; 3) individually training of nurses or residents if the bundle was not correctly applied (for 2 months); 4) change team (for training staff): consisting of ICU manager, ICU consultant, ICU residents and nurses.	Audit 1: 15%, Audit II: 33,8% (p<0,01)
Al-Tawfiq[43] 2010, Saudi Arabia, Ventilator bundle	Pre/post design	Pre intervention: Jan-Dec '06. Post implementation: Jan '07-Dec '08	Private general hospital, Medical, Surgical, Cardiac ICU 18 beds	Compliance Device utilization ratio VAP rate	Nurses, doctors and respiratory therapists	NS	AON/ Per quarter	1) education of staff; 2) feedback of compliance to team + quarterly feedback of compliance and VAP rates; 3) checklist; 4) audit tool; 5) daily multidisciplinary rounds; 6) team approach to drive and maintain the initiative (including infection control professional, nurse, respiratory therapist, intensivist and chairman of the infection control committee). 7) if non-compliance with an element was detected, the nurse intervened in this process at the time of monitoring process.	First 3 month of implementation period (first quarter 2006): 20%, Last 3 month (fourth quarter 2008) of implementation period 82%.
Jimenez[44] 2009, USA, Ventilator bundle	Pre/post design	Pre intervention 2 weeks. 4 months of non-measurements. Post intervention 2 weeks.	Neuro surgical ICU, 18 beds	Compliance	Nursing staff	NS	AON + Item-by-item/ Per 2 weeks	1) education sessions; 2) weekly feedback on compliance; 3) posters; 4) reminder cards;	Pre education: n= 102, compliance 6 %, Post education, n= 86, compliance 59%

DuBose[45] 2008, USA Ventilator bundle	Pre/post design	Baseline: 1 month. Intervention period 3 month	Single center, trauma ICU	Compliance	ICU staff	NS	Item-by-item measurement/ Per month	1) Quality Round Checklist (QRC) developed by multidisciplinary team; 2) education; 3) multidisciplinary team to enhance implementation; 4) laminated flyers,	Pre-intervention: HOB: 35,2%, PUD prophylaxis 76,2%, DVT prophylaxis (91,2%), Sedation holiday: 78%. Implementation month 3: HOB: 84,5%, PUD prophylaxis 92,3%, DVT prophylaxis 92,8, Sedation holiday: 86%
Berenholtz[46] 2011, USA, Ventilator bundle	Pre/post design	Baseline: 3 months. Post intervention: 0-30 months after implementation	Multi center, 112 mixed, medical, surgical/ trauma, cardiac ICUs	Quarterly VAP rates Compliance	ICU teams	Model for organizational change (i.e. engage, educate, execute, evaluate) Theory of planned behavior	Composite + Item-by-item/ Per quarter	1) local improvement team (ICU director and ICU nurse manager, ICU physician, nurse and senior hospital executive); 2) staff engagement by posting baseline compliance and VAP rates and discussing patients who developed VAP; 3) education (fact sheet, summary guidelines, a slide set en references); 4) daily goal checklist; 5) create protocols and order sets; 6) enlist support from clinicians and family members; 7) feedback: monthly number patients who developed VAP and bundle compliance and quarterly rates of VAP; 8) show reports of other ICUs to compare performance.	Baseline: 1881/5789 (32%) Intervention period: 48% Post intervention quarterly: 0-3 months: 50,%, 28-30 month: 84%
Lim[47] 2013, Taiwan, Ventilator Bundle	Pre/post design	Jan'06-Mar'13	Tertiary referral medical center. Surgical ICU 63 beds	ICU utilization, ventilator utilization, VAP incidence, compliance	Nurses, doctors, respiratory therapists	NS	AON/ Overall: 1 year	1) education; 2) posters; 3) checklists; 4) standardizing medical interventions and equipment.	Post intervention (after re-education): doctors: 99%, nurses: 89.3%, respiratory therapists: 84%.
Mukhtar[48] 2014, Egypt, Ventilator bundle	Pre/post design	Mar'11-Jun'12	University hospital. Surgical ICU: 8 beds	- VAP rates caused by MRSA - compliance	Nurses	NS	AON/ Overall: 1 year	1) education; 2) rewards to motivate nurses for perfect fulfilment of the VCB.	Compliance ranged from 60%-70%
Eom[49] 2014, South Korea Ventilator bundle	Quasi-exp: Pre/post design	Pre-intervention: Jul'11-Feb'11, Post intervention: Mar '11- Jun '11	Multicentre, 6 University hospitals. 196 ICU beds	VAP rates	23 doctors, 318 nurses	NS	AON + Item-by-item/ Overall: 4 months	1) Education on VAP and VAP bundle; 2) checklists; 3) regular feedback on compliance; 4) nurses intervened at the time of monitoring if non-compliance with a bundle element was detected.	Overall compliance (without CASS): Pre intervention: 41.1%, post intervention: 71.8%.
Hamishehkar[50] 2014, Iran, Ventilator bundle	Observational study Pre-post design	Pre-education phase: 45 days, education phase, post education phase: 1 month after the education phase ended.	Multicentre, 4 university affiliated hospitals. 3 surgical, 2 general, 2 pulmonary, 1 neurosurgical, 1 neuro ICU	Compliance	143 nurses: 127 (89%) females; age (mean±sd): 33±5; workexp: (mean±sd): 10±4yrs	NS	AON, Mean compliance/ Time period not clear	1) education, educational pamphlets containing results of VAP bundle compliance in each ICU and VAP bundle control guidelines and delivered them to every nurse whose practice was evaluated.	Pre-education (N=294): 36.5%, post education (N=258) 41.2%.P > 0.05

Malouf Todaro[51] 2013, USA, Ventilator bundle	Quality improvement: pre/post design	Pre intervention 2 months. Post intervention 6 months	Medical and surgical ICU, 24 beds.	Compliance	Nurses	NS	AON/ Overall: 6 months	1) education; 2) use of electronic checklists and developed in collaboration with focus groups of ICU nurses and physicians.	Pre intervention: 5/137 (3,7%) Post intervention: 464/504 (92.1%)
Rello[52] 2013, Spain, Ventilator bundle	Prospective cohort	Baseline: 3 months. Intervention period: 16 months	Multicenter, 5 general ICUs	Compliance VAP rates ICU length of stay Duration of MV	ICU teams	NS	Lowest level of compliance/ Overall: 6 months	1) feedback on VAP rates and compliance in the form of posters and feedback to improvement team; 2) local ICU improvement teams (incl medical leader and nurse manager); 3) posters; 4) cards and brochures to educate staff; 5) education; 6) checklist	Compliance rate complete bundle: 20%
Berenholtz[53] 2004, USA, Ventilator bundle	Prospective cohort	4 Mar '02-29 Apr '02 (8 weeks)	Tertiary hospital. Surgical ICU, 20 beds (14 in use).	Percentage of ventilator days per week Compliance	Nursing staff	NS	Composite / Per week	1) survey to identify barriers of compliance, 2) education to provide a summary of the evidence; 3) checklist to be completed daily during daily rounds; 4) billboard within ICU to highlights the project and post the performance; 5) interdisciplinary team to lead Quality Improvement effort; 6) discuss performance during daily rounds; 7) adding topics to the agenda at monthly performance improvement meetings	Before start intervention: 30%, after intervention: 96% (p<0.001)
DePalo[54] 2010, USA Ventilator bundle	Prospective cohort	Data reported from 1 Jan '06 - 30 Jun '08. Baseline period: 1 Jan '06- Mar '06.	Multi center, 11 hospitals, 23 ICUs, 263 beds	VAP rates	Not reported	Patient safety program	AON/ Per quarter	1) patient safety based program: educate staff on science of safety, learning from defects and implementing work tools and empowered to stop procedures. 2) Education, 3) feedback of infection rates 4) survey culture: culture assessment tool used to survey the culture of each ICU, administered at the start of the project and annually thereafter. 5) engagement, 6) empowering nurses to stop physicians who do not follow the checklist 7) implementation teams, 8) checklists	Quarter 1 '06: 60%, Quarter 2 '08: 78% (p<0.0001)
Al-Thaqafy[55] 2014, Saudi Arabia, Ventilator bundle	Prospective cohort	Jun'10-Dec'13	Tertiary hospital, medical, surgical and trauma ICU, 21 beds.	Compliance VAP rates Association between compliance and ventilator utilization	Nurses and physicians. Nurse to patient ratio is 1:1	NS	AON/ Per quarter	1) Periodic educational and training sessions; 2) daily multidisciplinary rounds; 3) no blame policy	Compliance Q2 2010: 86% to 99% in Q4 2013
Hatler[56], 2006, USA, Ventilator bundle	Quality improvement: prosp cohort	15 months	Medical ICU, 8 beds	Compliance VAP rates	Nursing staff	Theory of planned behaviour	AON/ Per month	1) education; 2) one-page document detailing new strategies to address prevention of VAP; 3) regular feedback infection rates and rates of adoption; 4) multidisciplinary project team to monitor progress and to make needed changes during implementation; 5) daily rounds; 6) daily goals were posted on white boards in patient rooms; 7) charts of expected activities were posted in each patient room; 8) reinforcement by giving movie tickets to nurses; 9) when sign. change was accomplished, staff members, managers and administrators celebrated with prizes; 10) newsletters	Begin: 73%, end of the intervention period: 98.6% (p<0.001)

Esmail[57] 2008, Canada, Ventilator bundle	Quality improvement: pros cohort	Start quality improvement project in 2002-jun'07	ICUs, 38 beds	Compliance VAP incidence	Critical care team	PDSA-cycle	AON/ Per month	1) educational sessions; 2) feedback of performance and VAP rates; 3) creation of a multidisciplinary team to work on VAP prevention; 4) family participation: checking bundle compliance; 5) checklists; 6) signs for HOB; 7) HOB alarm on all new beds; 8) newsletters; 9) review a VAP case at meetings;10) posters; 11) audits	Modified bundle: Sept '04: 45% Jun '07: 100%.
Young-quist[10] 2007, USA, Ventilator bundle	Quality improvement: prosp cohort	Jan '03-May '04	2 hospitals. Medical, surgical and cardiovascular surgery ICU, 40 beds	Compliance VAP rates	ICU staff	NS	AON/ Per month	1) fact sheets; 2) posters with VAP rates; 3) written communication to remind and motivate ICU staff; 4) education of nurses in July '03; 5) HOB added to preprint ventilator orders: Aug'03; 6) reminder signs for HOB signs at bedside: Sept '03; 7) daily multidisciplinary rounds with emphasis on bundle: Jun '04; 8) monthly feedback of compliance audits	Mercy hospital: May '03: 0%, Jun '04: 100%. Unity hospital: May '03: 0%, Jun '04: 89%. Mean compliance: 94.5%
Bonello[35] 2008, USA Ventilator bundle	Quality improvement: pros cohort	Jan '05-Jun '06	Multicenter, 8 hospitals, 12 ICUs, 95 beds	Compliance VAP rates	ICU care providers	PDSA-cycle	AON/ Per quarter	1) educational symposia; 2) interdisciplinary team rounds; 3) checklist at patient bedside; 4) multidisciplinary implementation teams	VAP bundle: First 3 months: 50%, final 3 months: 82%
Miller[58] 2010, USA, Ventilator bundle	Quality improvement: prosp cohort	1 Jan '06-30 Apr '08. VAP bundle implementation began in 2007	University hospital, Trauma ICU, 14 beds	Infections rates	Nursing staff	NS	AON/ Per month	1) feedback compliance and VAP rates; 2) online checklist for compliance; 3) real time dashboard view of compliance. For each element of the bundle an indicator is displayed showing status with regard to the desired intervention; 4) education; 5) auditors to monitor and ensure compliance; 6) modifications to clinical processes; 7) nursing leadership periodically audited compliance	Compliance with VAP bundle: Aug '07: 12%, Apr '08: 70%
Bukhari[59] 2012, Saudi Arabia, Ventilator bundle	Prospective longitudinal	Jan'10-Dec'10	Medical and surgical ICU, 18 beds	Compliance Rate of pneumonia Days on MV Lengths of ICU stay	Nurses and residents	NS	AON/ Per month	1) weekly seminars to staff; 2) checklists; 3) visitors and family education was given and if the bed is not in required position they should inform the treating nurse; 4) daily multi-disciplinary rounds to assess compliance and discuss bundle elements; 5) two surveys entitled: knowledge, attitude and practice of ICU staff on VAP bundles were conducted; 6) respiratory therapists worked collaboratively with nurses; compliance monitoring 8) auditing VAP and compliance; 9) VAP rates presented	Whole period: 78,9% Jan '10: 30%, Dec'10: 100%.

Marra[60] 2009 and Caserta[61] 2012, Brazil Ventilator bundle	ITS	Phase 1: Mar'01- Dec'02 (implementation HOB + vent circuits) Phase 2: Jan'03-Dec'06 (implementation HOB, vent circuits, heat and moisture exchange). Phase 3 implementation ventilator bundle: Jan'07-Sept '08 Oct '08-Dec '10	Medical and surgical ICU, 38 beds	Compliance In-hospital mortality VAP incidence	Nurses, doctors and respiratory therapists	NS	AON/ Per month	1) feedback on compliance; 2) posters on compliance rates and VAP rates; 3) performance monitoring each weekday and 4) intervene in this process at the same time that performance monitoring was occurring at the bedside if non-compliance was detected, 5) brief presentation of VAP to the staff, 6) encourage participation in the "ventilator bundle- getting to zero" program.	Phase 3: Apr '07: 57% - Sept 100% Oct '08: 95%, End: Dec '10: 99%.
Zaydfudim[62] 2009, USA, Ventilator bundle	ITS	Jan '05-Jul '08	Tertiary University hospital. Surgical ICU, 21 beds	VAP rates Compliance	ICU team	NS	AON/ Per month	1) electronic dashboard: displays compliance with the ventilator bundle parameters for each ventilated patient at timed intervals for each measure; 2) compliance with patient-level dashboard parameters were reviewed twice daily; 3) physician and nursing leadership received daily compliance reports.	Aug '07: 39% - Jul '08: 89% (p<0.001)
Crunden[63] 2005, UK, Ventilator bundle	Retrospective study	Group A: Jan '02 to14 Dec "02. Group B: 15 Dec'02 to 31 Dec '03	Single center, 6 ICU beds	Compliance Length of MV ICU LOS	ICU teams	NS	Composite/ Per month	1) checklists; 2) daily rounds: every day on the round the staff assess the appropriateness of implementing each element of the bundle per patient; 3) education	Audit 1 month. Baseline Oct '02: n=21 bundle compliance: 21%, July '03: n=24 bundle compliance 79,1%
Helmick[39] 2014, USA, Ventilator bundle	Retrospective review	2009-2011	Multicentre: 5 mixed, 4 medical, 4 surgical and 2 cardiac ICUs.	Mean rates of VAP	Not reported	NS	Lowest level of compliance/ Per month	1) Checklists	2009: 86.2% 2010: 81.1% 2011: 89.8% P 0.76
Guiliano[64] 2011, USA Sepsis resuscitation/ management bundle	Pre/post design, pilot	Mar 1, '06 – Aug 5, '08. The 2 phases of the study were completed between this time periods. Phase 1= before intervention, phase 2 after intervention	2 hospitals	-compliance -time to completion -time to administration	ICU nurses	NS	Mean percentage of the completion of the bundle/ Time period not clear.	1) education; 2) protocol watch: this is a proprietary CDSS application for bedside monitoring of patients that was designed by Philips Healthcare to assist clinicians in implementing the SSC guidelines.	Resuscitation bundle (%, mean (SD)): Phase 1: 57.6 (19.8), phase 2: 68.2 (20), p0.003 Management bundle: (%, mean (SD)): Phase 1: 84.5 (19) Phase 2: 86.8 (17), p 0.48

Ferrer[65] 2008, Spain, Sepsis resuscitation/ management bundle	Pre/post design	Pre intervention: 2 months: Nov-Dec'05 Post intervention: 4 month: March-Jun'06 Long term follow up 1yr later on a subset of 23 ICUs: Nov-Dec'06	Multicenter, Medical and surgical ICUs, 59	-hospital mortality -adherence -ICU mortality -28-day mortality -HLOS -ICU LOS	Physicians and nurses	NS	AON + Item-by-item/ Overall: 4 months	1) educational program: training physicians and nursing staff in definitions of severe sepsis and septic shock, their early recognition and the treatment included in the guidelines; 2) posters; 3) pocket cards; 4) audit and feedback 5) the principal investigator acted as local champion; 7) creation of local multidisciplinary teams: they reviewed the pre-intervention performance data and shared ideas about the process improvement goals and strategies.	Resuscitation bundle: Pre intervention: n=854: n, (%) [CI 95%]: 45 (5.3%), [BI 4-7] p<0.01, Post intervention: 147 (10), [BI 8-12]. Management bundle: pre intervention: n=1465: 93 (10.9), [9-13] Post intervention: 230 (15.7), [14-18]. P <0,001.
Castellanos-Ortega[66] 2010, Spain, Sepsis management bundle	Quasi exp: pre/post design	Pre intervention baseline: 12 months: Jan '04- May '05. Implementation period: 3 months: June - Aug '05. Post intervention: 3 yrs: Sept '05-Aug '08.	Single center, Medical and surgical ICU, 30 beds	-in-hospital mortality -LOHS -ICU mortality -compliance	Physicians and nurses	NS	AON + Item-by-item/ Overall: 3 years	A hospital wide implementation program. 1) educate staff in recognizing severe sepsis and septic shock + intervention included in guidelines; 2) audit; 3) feedback; 4) posters; 5) pocket cards; 6) lectures; 7) sepsis profile: optional tool to facilitate an early diagnosis of sepsis and severe sepsis.	The management bundle in only implemented within the ICU. 24h-management bundle: Historical group (baseline): n=96: 0 (0), Intervention group: n=384: 5 (1.3%).
Lefrant[67] 2010, France Sepsis bundle	Quality improvement: pre/post design	1 Jan - 30 jun'06 (observational period), 1 Jul-31 dec'06	Multicenter, 15 ICUs	-28-day mortality -compliance	Nurses, physicians and residents	NS	AON + Item-by-item/ Overall: 6 months	1) educational meetings; 2) distribution of educational materials; 3) posters and pocket cards with bundle; 4) video transmission meeting	Baseline (observational period): 1/230 (0.5%), Interventional period: 9/215 (4%).
Silverman[68] 2011, USA, Sepsis bundle	NS Pre/post design	Phase 1: historic cohort Phase 2: 2006: bundle implementation Phase 3: from Sept'08 bundle plus implementation	Single center, Surgical ICU	-mortality rate -costs	NR	NS	AON/ Overall: 2 years	Phase 2: 1) education of staff; 2) multidisciplinary sepsis team created: one member rounded 2-4 times per week to ensure all appropriate patients were on the bundle. Team developed tools and order sets to facilitate the use of the bundle. Phase 3: addition of an intensivist in 2008: Surgical ICU care team created	Phase 2: Bundle group: 19/186 (10%), Phase 3: Bundle plus group: 47.6/68 (70%)
Memon[69] 2012, Saudi Arabia, Sepsis resuscitation bundle	Quasi experimental prospective study	Pre intervention: 15 **months**: Jan '08-March 09. Intervention period: 3 month:Apr-Jun'09 Post intervention: 24 month: Jul '09- Jun '11	Medical and surgical ICU, 10 beds	-overall compliance -30-day mortality -ICU mortality -ICU LOS -LOHS	Physicians, nurses and respiratory therapists.	NS	AON/ Overall: 2 years	1) educational lectures; 2) special Task Force Teams; 3) they developed a written protocol to prepare the sepsis bundle for the management of patients with severe sepsis or septic shock	Pre intervention (historic group): 5/99 (5.1%) Post intervention: 47/199 (23.6%)

Schramm[70] 2011, USA, Sepsis resuscitation bundle	Prospective interventional cohort study	Overall: jan'07-sept'09. Baseline: jan'07-28dec'07 Weekly feedback: 29dec'08-26sept'08 Inzet SRT: 27sept'08-30sept'09	Single center, Medical ICU, 24 beds	-compliance -mortality	ICU healthcare providers	NS	AON + Item-by-item/ Overall: 1 year	1) educational meetings/teaching session; 2) distribution of educational materials; 3) daily auditing and weekly feedback; 4) multidisciplinary bedside response teams (SRT)	Baseline: 34/268 (12.7%), Period of weekly feedback: 107/284 (37.7%), Sepsis Response Team period: 232/432 (53.7%). P<0.001
Kim[71] 2012, South Korea, Sepsis resuscitation/ management bundle	Prospective observational study.	July '09	Multicenter, Medical and surgical ICU, 28 ICUs	-overall hospital mortality -28-day mortality -ICU mortality -ICU LOS -duration of MV	Critical care personnel	NS	AON/ Per month	1) full time intensivists available by turns of duty for 24h and nurse to patient ratio of 1:2	n=251. Complete Resuscitation bundle: 31/251 (12.35%), Management bundle: 39/251 (15.54%)
Laguna Perez[72] 2012, Spain, Sepsis resuscitation/ management bundle	Quasi experimental prospective study	Control group: Jun'08-Jul'09 Intervention group: Oct'09-March'10	Single center	-compliance -survival rates -LOHS	NR	NS	Item-by-item/ Overall: 6 months	1) education and training programs; 2) posters with protocol algorithms and diagrams were made; 3) developing reference guides and made available at nursing controls and on intranet	6- hour bundle: control group: element 1. 55/84 (64,7%), 2. 44/84 (52.4), 3. 33/84 (40.7%), 4, 35/84 (41.7%) 16/84 (19%), 11/84 (13.1%), 60/84 (71.4%) Intervention group: 1, 30/41 (60%), 2, 29/41 (70.7%), 3, 17/41 (41.5%), 4, 32/41 (78%), 5, 22/41 (53.6%), 6, 18/41 (43.9%), 7, 32/41 (78%). 24-hour bundle: Control group: 1. 26/85 (30.5%). 2, 39/76 (51.3%), 3, 16/84 (19%), 4, 6/58 (10.3%) Intervention group: 1. 40 (40), 2. 22/36 (61.1%), 3, 32/40 (80%), 19/23 (82.6%).

CL: Central Line, CLABSI: Central Line Associated Blood Stream Infection, CRBSI: Catheter Related Bloodstream Infections, PDSA-cycle: Plan Do Study Act-cycle, NS: Not Stated, MV: Mechanical ventilation, LOS: Length of Stay, ICU: Intensive Care Unit, SSC: Surviving Sepsis Campaign, MRSA: Methicillin Resistant *Staphylococcus Aureus*.

Supplementary File 4

Bundle elements

Central line bundle	Exline et al. Insertion bundle	Longmate et al, Insertion bundle	McPeake et al. insertion bundle	Hocking et al, Insertion bundle	Khalid et al., insertion bundle	Khalid et al., maintenance bundle	Hocking et al. Maintainance	Exline et al. Maintainance	Marra et al, Central line bundle	Bonello et al, Central line bundle	Jeong et al, Central line bundle	Richardson et al, Central line bundle	Helmick et al. Central line bundle	Sacks et al. Central line bundle	Render et al, Central line bundle	McNamara et al. Central line bundle
Hand hygiene			x	x	x				x	x	x	x	x	x	x	x
Maximal barrier precaution	x	x	x	x	x				x	x	x	x	x	x	x	x
Full body drape				x												x
Chlorhexidine skin antisepsis	x	x	x	x		x			x	x	x	x	x	x	x	x
Optimal catheter site selection, with avoidance of femoral vein	x	x	x	x	x				x	x	x	x	x		x	
Daily review of line necessity with prompt removal of unnecessary lines						x	x	x	x	x		x	x	x	x	
PIC placement with ultrasound guidance to avoid CVC placement and to facilitate removal.	x															
Removal within 24h of all CVC's placed emergently								x								
Use of a checklist for insertion		x	x						x							
Time out note	x															x
Daily checking of central line site for inflammation							x									
Cleaning of all ports with 2% chlorhexidine and 70% alcohol prior to assessing CL							x									
Chlorhexidine impregnated dressings and/or AB impregnated CLs for high risk pt.							x									
Intervene at the same time when non-compliance was detected (=time out procedure?)									x							
Sterile techniques while inserting the CL and applying the dressing				x												
Dressing with Chlorhexidine gluconate material								x								
Preferential use of the subclavian vein														x		
Patient hygiene					x											
Catheters coated internally with silver sulfadiazine and chlorhexidine acetate					x											
Chlorhexidine mouthwash for oral care						x										

Ventilator bundle	Hatler et al., 2006	Malouf Todaro et al, 2013	Lawrence et al, 2012	Morris et al, 2011	Hawe et al, 2009	Bloos et al, 2009	Rello et al, 2013	Bukhari et al, 2012	Marra, 2009/Caserta, 2012	Esmail et al, 2008	Youngquist et al, 2007	Zaydfudim et al, 2009	Al-Tawfiq et al, 2010	Bonello et al, 2008	Miller et al, 2010	DePalo et al, 2010	Jimenez et al, 2009	Dubose et al, 2008	Berenholtz et al, 2011	Crunden et al, 2005	Berenholtz et al, 2004	Helmick et al., 2014	Eom et al., 2014	Hamishehkar et al. 2014	Lim et al., 2013	Mukhtar et al. 2014	Al-Thaqafy et al., 2014
Elevation of the head of the bed (HOB)	x	x	x	x	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Daily sedation vacation		x	x	x	x		x					x	x	x	x			x	x		x	x				x	
Assessment of readiness to extubate				x	x								x	x								x					
Peptic ulcer disease prophylaxis	x	x	x			x		x	x		x		x	x	x	x	x	x	x	x	x	x	x		x	x	x
Deep Venous Thrombosis prophylaxis	x	x	x			x		x	x		x		x	x	x	x	x	x	x	x	x	x	x		x	x	x
Daily oral care		x		x	x		x					x			x							x	x	x	x	x	x
Hand hygiene		x					x																	x			
Intra cuff pressure							x																				
Tubing management					x		x																				
Subglottic suctioning					x					x		x			x									x			
Preferential use of oral vs nasal tubes for access to the trachea or stomach										x																	
Spontaneous breathing trials												x															
Lung protective ventilation in patients with ALI						x																					
Daily sedation vacation and assessment of readiness to extubate	x							x	x	x	x				x	x	x		x	x					x		x
Dental care												x															
Continuous aspiration of subglottic secretions (CASS)												x											x				
Maintain endotracheal cuff pressure (ETCP)																								x			
Use of a closed suction system																								x			
Use of a endotracheal tube with a separate dorsal lumen																								x			
Spontaneous breathing trial																										x	

Sepsis bundle	Memon et al, 2012	Laguna Perez et al, 2012	Kim et al, 2012	Guiliano et al, 2011	Schramm et al, 2011	Ferrer et al. 2008	Castellanos-Ortega et al, 2010	Silverman et al, 2011, Sepsis bundle	Lefrant et al, 2010, Sepsis bundle
Sepsis management bundle									
Appropriate use / no use steroids		x		x		x	x	x	
Appropriate use / no use Xigris		x		x		x	x	x	x
Maintain adequate glycemic control		x	x	x		x	x	x	x
Appropriate management of inspiratory plateau pressures (IPP)		x	x	x		x	x	x	
Low tidal volume									x
Sepsis resuscitation bundle									
Serum lactate measured	x	x	x	x	x	x		x	
Blood cultures obtained prior to antibiotic administration	x	x	x	x	x	x		x	x
Improve time to broad spectrum antibiotics	x	x	x	x	x	x		x	x
Apply vasopressors for ongoing hypotension			x		x				
Maintain adequate central venous pressure	x	x	x	x		x		x	
Intravenous fluids delivered	x	x	x		x			x	
Maintain adequate central venous oxygen saturation	x	x	x	x		x		x	
Achieve and maintain mean arterial pressure ≥65 mmHg	x								x
Fluids resuscitation / vasopressors (if appropriate)				x		x		x	
Blood pressure ≥90 mmHg in case of hypotension		x							

Supplementary File 5

Effects on compliance

Subset 1

In the first subset, studies are included when pre/post designs were used, methodological quality scored 'fair' or 'good', and when compliance was calculated by using the all-or-none approach. The blue bar within the figures represents the 95% compliance level, thus the level of compliance which should have been achieved.

Figures S1 to S3:

- Overall, 19 studies were included in this first subset, describing the compliance of 21 care bundles.
- Central line bundle: 5 studies included, describing 6 care bundles
- Ventilator bundle: 10 studies included, describing 10 care bundles
- Sepsis bundle: 4 studies included, describing 5 care bundles.

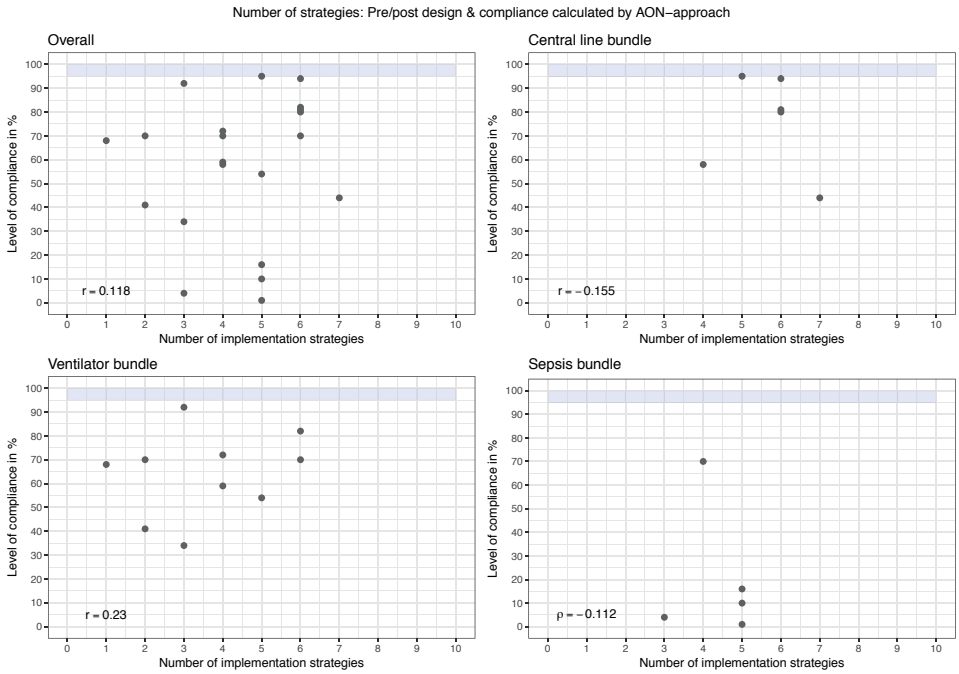


Figure S1. Number of implementation strategies and compliance levels

Figure S1 shows that overall, there is no relation between the compliance level and the number of implementation strategies used (r = 0.118, 95% CI. -0.331 to 0.523, p = 0.612), neither for each bundle separately: central line bundle: r = -0.155, 95% CI. -0.859 to 0.751, p = 0.769; ventilator bundle: r = 0.230, 95% CI.-0.467 to 0.751, p = 0.522; sepsis bundle: ρ = -0.112, p = 0.858.

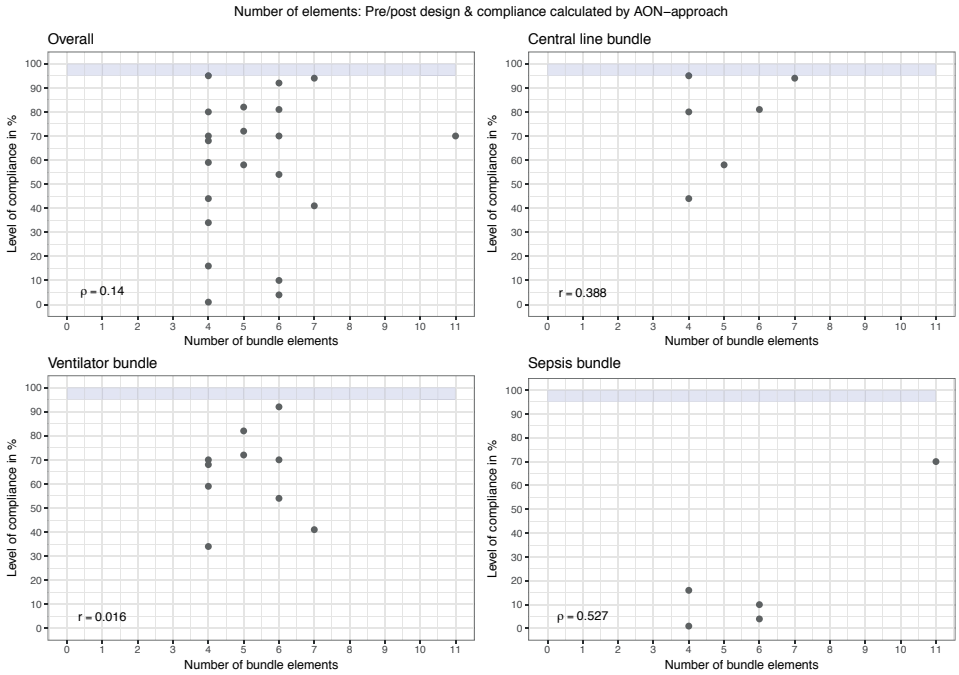


Figure S2. Number of bundle elements and compliance levels

Overall, there is no relation between the number of bundle elements and the level of compliance (ρ = 0.140, p = 0.545), neither for each bundle separately: central line bundle: r = 0.388, 95% CI. -0.618 to 0.912, p = 0.447; ventilator bundle: r = 0.016, 95% CI.-0.620 to 0.639, p = 0.965; sepsis bundle: ρ = 0.527, p = 0.362.

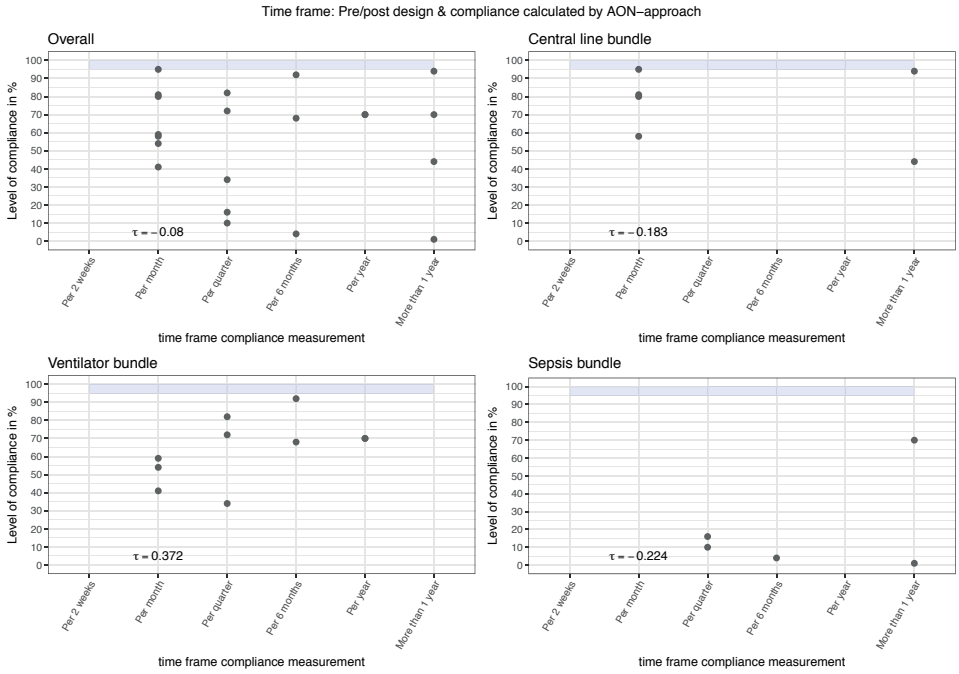


Figure S3. Relation between compliance and time frame in which compliance is measured

Overall, there is no relation between the time frame and compliance (τ = -0.080, p = 0.639), neither for each bundle separately: central line bundle: τ = -0.183, p = 0.643; ventilator bundle: τ = 0.372, p = 0.162; sepsis bundle: τ = -0.224, p = 0.602).

Subset 2:

In the second subset, studies are included when prospective cohort designs were used, methodological quality scored 'fair' or 'good', and when compliance was calculated by using the all-or-none approach. The blue bar within the figures represents the 95% compliance level, thus the level of compliance which should have been achieved.

Figures S4 to S6:

- Overall, 10 studies are included in this subset, describing the compliance of 12 care bundles.
- Central line bundle: 1 study included, describing the compliance of 2 care bundles
- Ventilator bundle: 5 studies included, describing 5 care bundles
- Sepsis bundle: 4 studies included, describing 6 care bundles.

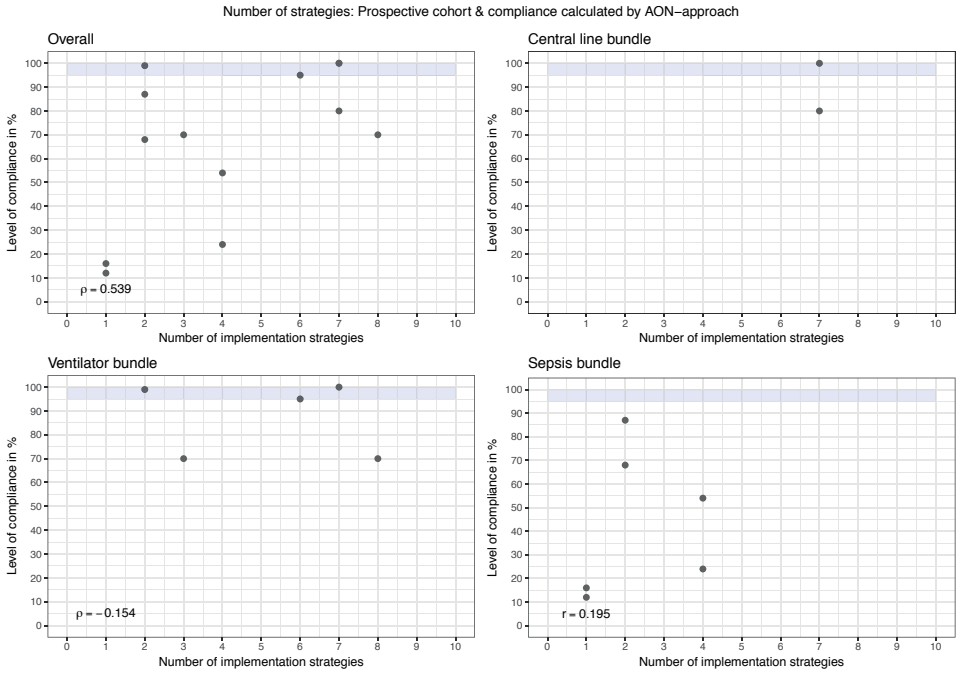


Figure S4. Number of implementation strategies and compliance levels

Figure S4 shows that there is no relationship between the number of implementation strategies and the level of compliance (ρ = 0.539, p = 0.057). Correlation coefficients could not be determined for the central line bundle, due to the small number of observations. Ventilator bundle: ρ = -0.154, p = 0.805; Sepsis bundle: r = 0.195, 95% CI. -0.732 to 0.870, p = 0.711.

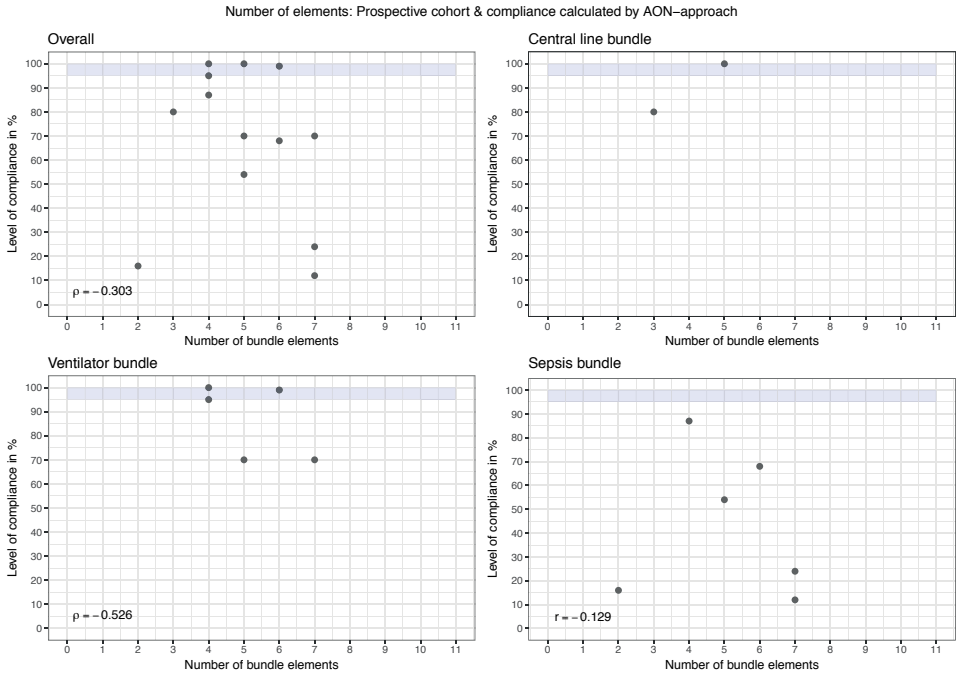


Figure S5. Number of bundle elements and compliance levels

There is no relationship between the number of bundle elements and the level of compliance (ρ = -0.303, p = 0.314). Correlation coefficients could not be determined for the central line bundle due to the small number of observations. Ventilator bundle: ρ = -0.526, p = 0.362; Sepsis bundle: r = -0.129, 95% CI. -0.851 to 0.762, p = 0.808.

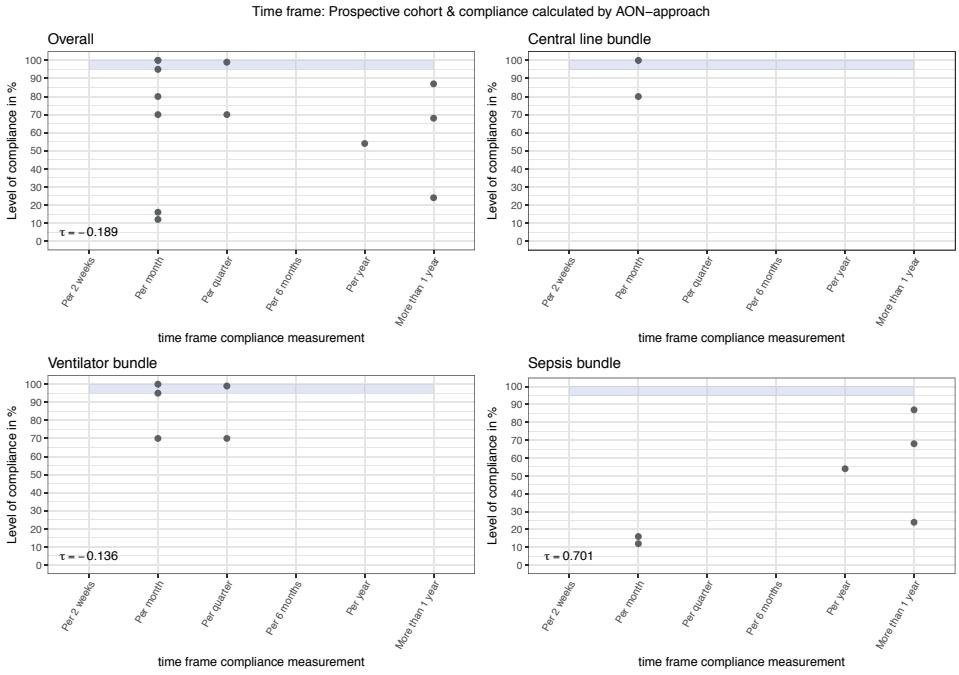
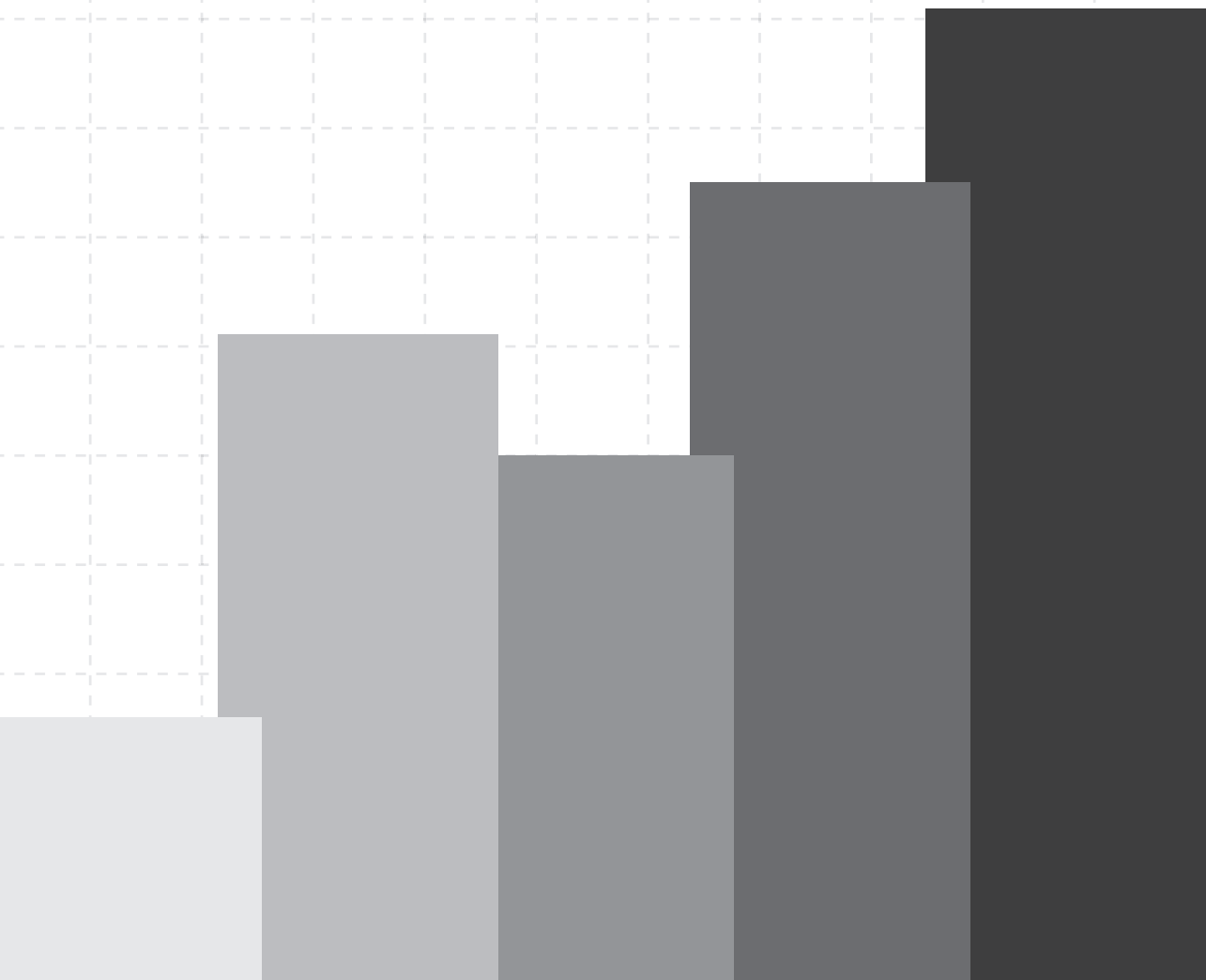


Figure S6. Relation between compliance and time frame in which compliance is measured.

For the ventilator bundle as well as the central line bundle, compliance is mostly calculated per months and in some studies quarterly. For these studies relatively high compliance levels were measured. Only for the sepsis bundle long time frames were used in which compliance is calculated. However, overall, there is no relation between the time frame and compliance (τ = -189, p = 0.417), neither for each bundle separately: ventilator bundle: τ = -0.136, p = 0.767; sepsis bundle: τ = 0.701, p = 0.064). Correlation coefficients could not be determined for the central line bundle due to the small number of observations.



07

TIMELY INDIVIDUAL AUDIT AND FEEDBACK SIGNIFICANTLY IMPROVES TRANSFUSION BUNDLE COMPLIANCE - A COMPARATIVE STUDY

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Int J Qual Health Care 2016;28:601-607.

ABSTRACT

Objective. To investigate the difference in effect on transfusion bundle compliance between two Audit and Feedback (A&F) strategies to implement the transfusion bundle.

Design and setting. This implementation study was conducted in an ICU of a university hospital from May to December 2014. The ICU consists of two nursing teams containing 63 and 62 nurses.

Participants. All ICU nurses participated in this study.

Intervention. Monthly A&F on team level versus a combination of monthly A&F on team level plus timely individual feedback.

Measurements. The primary outcome was bundle compliance. Compliance was measured after every single transfusion.

Results. Monthly A&F on team level with timely individual A&F significantly improves bundle compliance during implementation compared to monthly A&F on team level alone. The overall effect of compliance during the study period was significantly higher with an OR of 4.05 (95% confidence interval, CI: 1.62 to 10.08), $P < 0.001$. This indicates that when using the combined A&F strategy nurses are more likely to be compliant to the bundle than when monthly A&F was used alone.

Conclusions. Compared to monthly team A&F alone, providing timely individual A&F plus monthly A&F on team level significantly improves the success of implementing a transfusion bundle on the ICU during the implementation period. Providing timely individual A&F plus monthly A&F on team level might also be effective for the implementation of other bundles in healthcare. Future research could elaborate on longer duration of the intervention, the use of information and computer technology to lower costs of the intervention, and to enhance sustainability.

INTRODUCTION

Transfusion of blood products is a frequently used life-saving therapy in critically ill patients. Besides the positive treatment effects, it can cause serious complications such as pulmonary oedema, infections and transfusion-related acute lung injury (TRALI).[1,2] Although reported incidences of these complications are low, they are an important cause of transfusion-related morbidity and mortality.[3,4] Results from the UK have shown that risks of morbidity from transfusion is 1 in 322 580 components transfused.[3] In the last decade, changes have been made in transfusion practice to further reduce these complications. For instance, screening of donors to reduce infections[5] or excluding female donors to reduce the incidence of TRALI.[6]

However, it is known that most transfusion-related incidents are caused by human errors.[3] The blood transfusion process is complex and involves multiple disciplines.[7] This results in multiple moments in which errors could occur.[7] Estimates of the risks of transfusions were calculated in the UK.[7] The risk of an error during blood transfusion is estimated at 1:16 500 units transfused, transfusion a wrong blood product at 1:100 000 and the risks of death in case a wrong blood product was transfused at 1:1 500 000.[7,8] However, the true incidence may be higher since not every error is reported. Most errors are made during the collection and labelling of blood samples or at the final bedside checks.[3,4] For instance, identifying the wrong blood product patient combination could lead to transfusion of incompatible blood.[7]

To improve transfusion practice and to reduce errors, guidelines should be used.[9] However, despite intensive implementation programs, it is known that guidelines are not followed consistently.[10,11] In order to improve guidelines adherence, the Institute for Healthcare Improvement (IHI) has developed the concept of care bundles.[12] They consist of three to five evidence-based interventions for a predefined patient population or clinical process.[12] The strength of bundling interventions in care bundles is to ensure that evidence-based care will be uniformly applied and improve clinical outcomes.[12] Care bundles have already proven to be effective in improving clinical outcomes.[13,14]

In order to improve transfusion practice, we have developed a care bundle for the transfusion of red blood cells (RBCs). We used the IHI process steps to design the transfusion bundle and included five evidence-based interventions (Supplementary File 1).[12,15,16] All interventions are aimed to reduce unnecessary, incorrect or unsafe transfusions.

The implementation of care bundles is challenging. Different implementation strategies are described with varying success rates.[17] A frequently used strategy is Audit and Feedback (A&F). Although A&F tends to be effective, there is a great variability in the effectiveness on implementation.[18]

Several frameworks and theories have been designed in order to understand how A&F could change professionals' behaviour. Zajonc showed that the combination of A&F strategies on group and individual level has positive effects on performance.[19] Hysong *et al.* developed a model in which it is postulated that feedback should be given timely, individualized and non-punitive in order to be effective.[20] An important difference between our study and the study of Hysong *et al.* is that they have chosen a month as a threshold for timely feedback. We considered timely feedback as given within a maximum time span of 72 hours. The reason behind this shorter time span is that it would ensure nurses to clearly remember their actions and gave them the possibility to change their behaviour before the next transfusion occurred. This is in line with Sinuff *et al.* who also found that the timeliness of feedback is an important factor in changing behaviour.[21] Ivers *et al.* suggested that implementation studies should focus on comparing different A&F strategies and on how to optimize their effectiveness.[22] In this present study, we aim to investigate the difference in effect on transfusion bundle compliance between monthly team level A&F versus monthly team level A&F with the addition of timely individual A&F.

METHODS

This implementation study with a quasi-experimental comparative study design was conducted from May to December 2014. We implemented the transfusion bundle from May to August. This implementation period denotes the transition period and post-implementation refers to the period in which the intervention is considered fully implemented as intended.

Context

The study was conducted in a 28-bed mixed medical-surgical ICU of a university hospital. The ICU is a 'closed format' department with four units in which patients are under the direct care of the ICU team. The ICU team consists of 10 full-time intensivists, 8 subspecialty fellows, 12 residents and 125 ICU nurses. The ICU has a stable nursing staff and all nurses were qualified as critical care nurses. Fellows rotate on a yearly basis and

residents half-yearly. Depending on the estimated workload and the severity of illness, the nurses are assigned to one or two patients. The ICU is divided into two nursing teams, working on two units each. Nurses are working in either one of the two teams.

Study subjects

The study included ICU nurses of two nursing teams who transfused at least one unit of RBCs from May to December 2014. Per nursing team a different A&F strategy was used to introduce the transfusion bundle. One team was randomly assigned to the intervention group and the other to the control group. Nurses' individual performances, i.e. transfusion bundle compliance, was measured. Nurses' compliance to the bundle was measured by the researcher after every transfusion. In both teams, nurses were excluded from the analysis with long-term illness, pregnancy leaves, and newly employed during the study period. Transfusion in patients for whom hemapheresis was indicated or for whom the massive blood transfusion protocol was activated were excluded due the urgency of the situation. The massive blood transfusion protocol was activated in case of the presentation of the following signs or symptoms: (i) decrease in blood pressure; (ii) not responding to fluid therapy; and (iii) existence of a high suspicion for bleeding. Furthermore, blood products other than RBCs were excluded.

Introduction of the transfusion bundle

The ICU consists of two nursing teams containing 63 and 62 nurses. Both teams work separately of each other and have their own nursing management. In both teams, we first provided education about the transfusion bundle in order to explain the rationale behind each element. During the implementation period, A&F was provided. Both teams received monthly A&F. On top of this, timely individual A&F was provided in only one of the two teams.

Education

Since we introduced a new transfusion bundle in our ICU, we provided education to both teams in order to explain the concept of care bundles in general, the risks of transfusion and the reasons for using the transfusion bundle. Education was provided in April and May 2014. The way the information was provided and the content of the information was equally in both teams. Nurses first received information by email containing the following items: (i) explanation of the concept of care bundles; (ii) aim of the transfusion bundle; (iii) explanation of the background/evidence per element. By explaining the risks of transfusion in combination with the aims of the transfusion bundle and the importance of the bundle interventions, we expected this would help to stimulate bundle compliance. Subsequently, nurses were asked to fill out a web based

questionnaire containing information and questions about the transfusion procedure including the transfusion bundle. Online participation was registered to ensure nurses had read the information and answered the questions. Two senior ICU researchers, an intensivist and one junior researcher, the head nurse and five ICU nurses were involved in the development process of this educational program. The content was pilot tested by two physicians and two ICU nurses. Furthermore, two information sessions were held for ICU nurses. A presentation about the transfusion bundle was given during hand over meetings to inform residents and physicians.

Audit and feedback intervention

In this study, we used A&F as the intervention to implement the transfusion bundle. In both teams monthly A&F was provided. On top of this, individual A&F within 72 hours after transfusion was provided in only one of the two teams. The definition of A&F was in accordance with the Effective Practice and Organisation of Care (EPOC) taxonomy: 'A summary of health workers' performance over a specified period of time, given to them in a written, electronic or verbal format. The summary may include recommendations for clinical action'.[23]

Team A: monthly provided A&F on team level

In team A, monthly A&F was provided. At the end of each month, the team received a standardized feedback report by email. This report contained the compliance levels per team for that given month. Feedback was provided by the researcher from the ICU together with the intensivist. Simultaneously, posters were used to show compliance levels. Posters were updated each month. Posters were used as a method to visualize the feedback on compliance levels and to further stimulate compliance.

Team B: monthly provided A&F on team level plus timely individual A&F

In Team B, the same A&F strategy was used as in Team A. Additionally, individual A&F was provided to the nurse within 72 hours after each RBC transfusion, i.e. further referred as timely individual feedback. Feedback was provided by the researcher and was given either by face-to-face contact or by email in case personal contact was not possible within 72 hours. A standardized report was used. This contained compliance levels of the complete bundle and compliance per element. The time span of 72 hours was chosen so that nurses would still remember the actions they had performed.

Study of the intervention

Data was collected prospectively from the electronic registration system (Patients Data Management System, PDMS). The occurrence of a RBC transfusion was audited by the researcher three times daily in the PDMS during week days. Transfusions that occurred during the weekends were audited on Mondays. Bundle checklists were used to track compliance (see Supplementary File).

Measures

Compliance with the completion of each element of the bundle was assessed during the eight study months. Each administered unit of RBC was counted as one inclusion. Compliance was calculated by using the all-or-none (AON)-approach.[24] If one of the interventions was not performed, the nurse was considered as non-compliant. Moreover, if checklists were not found, nurses were considered as non-compliant. The denominator is the total number of RBC units administered per month. The numerator is the total number of applied transfusion bundles per month. Bundle checklists were available in prominent places in the ICU. These places were equal in both teams. Bundle checklists were collected daily by the researcher during weekdays or on Mondays after weekends. Compliance data was entered in a database by the researcher. Compliance levels were calculated at the end of each month per nursing team.

Analysis

Continuous normally distributed variables will be expressed by their means and standard deviations or when not normally distributed as medians and their interquartile ranges. Categorical variables will be expressed as n/N (%). To test groups Student's t-test will be used, if continuous data is not normally distributed the Mann-Whitney U-test will be used. Categorical variables will be compared with the Chi-square test or Fisher's exact test. The goal of the primary analysis was to quantify the net effect of the A&F intervention on transfusion bundle compliance, controlling for other variables. Exploration of interaction (effect modification) and confounding was considered methodologically relevant. We first focussed on the crude (uncorrected) effect of A&F (independent variable) on transfusion bundle compliance (dependent variable). Then statistical and clinically relevant covariates were added as an interaction term (implementation and post-implementation period, nurses' characteristics: age, gender and work experience, and patient characteristics: Apache IV, ICU mortality). If the interaction term appeared to be significant ($P < 0.05$), this would indicate that the relation between A&F and transfusion bundle compliance could be different for various levels of the covariate. This indicates the need for separate models for the levels of the covariate. As a significant

interaction was not found, the model was examined for confounding. Confounding was defined as ≥ 10% change in the coefficient of the central determinant (transfusion bundle compliance) as a consequence of adding a covariate.

Because each nurse can be responsible for the performance of one or more transfusions for the same or different patients we accounted for dependence of transfusion bundle compliance data within nurses by including the nurses as a random effect in the model. Statistical significance is considered to be at $P < 0.05$. When appropriate statistical uncertainty will be expressed by the 95% confidence levels. All data were entered into a Microsoft Access database. Analyses were performed using R (version: 3.1.3; R Foundation for Statistical Computing, Vienna, Austria). We used Stata software (version 14) for the multilevel logistic regression analysis.

Ethical considerations

The study was approved by the Medical Ethics Committee of the Academic Medical Center of Amsterdam, the Netherlands and the need for informed consent was waived.

RESULTS

Nurses demographics

In total, 120 of the 125 nurses participated in this study, 59 in Team A and 61 in Team B. Five nurses were excluded. There were no significant differences in age between the nursing teams, neither in gender or years of work experience (Table 1). In team A, 61% (36/59) of the nurses followed the web-based educational program, compared to 100% (61/61) in Team B (difference 39% (95% CI: -51 to -27, $P < 0.001$).

Individual A&F

In Team B, feedback was given in 32% (40/124) via face-to-face contact. In 68% (84/124), a personal feedback report was sent by email. Emails were sent when face-to-face contact was not possible due to the following reasons: change of shifts in 35% (29/84), too busy in 2% (2/84), days off/holiday in 63% (53/84).

Patient demographics

During the implementation period 101 patients received at least one unit of RBCs and 116 post-implementation. Table 2 shows that the cohorts were similar in both groups with respect to age, gender, severity of illness (Apache IV), ICU LOS and ICU mortality.

Table 1. Nurses demographics

	Team A	Team B	95% CI of difference, *P*-value
Number of nurses, n/N (%)	59	61	-
Gender (female), n/N (%)	44/59 (75)	46/61 (75)	-0.008 (-16.33 to 14.67), 0.92[a]
Age, median (IQR)	41 (32-50)	44 (32-49)	0.99 [b]
Work experience (yrs), median (IQR)	10 (4.5-18.5)	14 (6-20)	0.44 [b]

[a] Chi-square test; [b] Mann-Whitey U-test

Transfusion bundle compliance

Implementation period

The overall compliance rate during the four months of implementation was 67% (83/124) in Team B versus 36% (58/160) in Team A (difference -31%, 95% CI: 20 to 42, P < 0.001). Figure 1 shows the compliance over time. In Table 3 the compliance levels per month are shown, including the differences per Team. Compliance significantly differed between the Teams, except for May and August 2014.

Post-implementation period

The overall compliance rate during the post-implementation period was 58% (94/162) in Team B versus 22% (47/216) in Team A (difference -36%, 95% CI: 22 to 58, P < 0.001). Although compliance gradually decreased in both teams, there is still a significant difference in compliance between both teams at the end of the post-implementation period, difference -36% (95% CI: -52% to -18.5%, P < 0.001).

Difference of compliance within the teams

The difference in compliance within Team B between the implementation period and post-implementation period was 9% (95 CI: -2.33 to 20.15, $P = 0.124$). In team A, a difference of 14.5% was observed (95% CI: 5.25 to 23.75, $P = 0.002$).

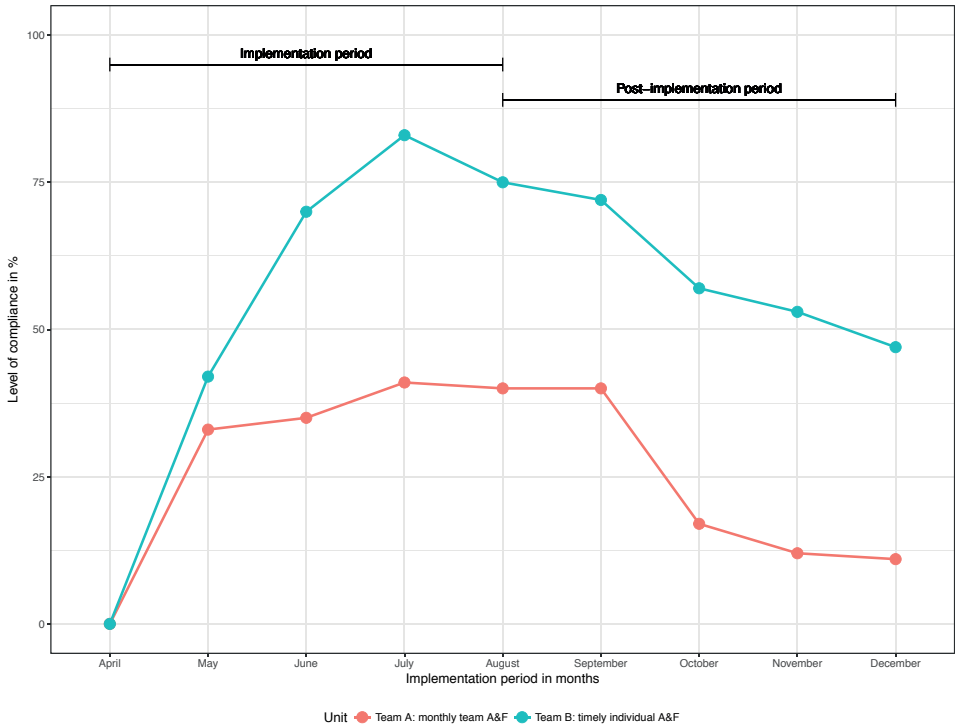

Figure 1. Compliance levels per team during the implementation and post-implementation period.

Multilevel logistic regression analysis

In Table 4, the results from the univariate model are shown. We found a significant interaction between the 'type of A&F' and 'time of intervention'. Therefore, we analysed two models. One for the implementation period and one for the post-implementation period. Both models show a large difference in compliance effect between the implementation period with an OR 4.05 (95% CI: 1.62 to 10.08), $P < 0.001$)) and the post-implementation period, OR 12.51 (95% CI: 4.1 to 38.13), $P < 0.001$. Both models were corrected for confounding for the nurses response to the educational questionnaire.

Table 2. Patient demographics

	Implementation period				Post-implementation period			
	Team A	**Team B**	**95% CI of difference**	***P*-value**	**Team A**	**Team B**	**95% CI of difference**	***P*-value**
Number of unique patients (N)	57	55	-	-	67	61	-	-
Number of transfused RBCs [a]	160/284	124/284	12.7 (4.5 to 20.7) [a]	0.0025	216/378	162/378	14.3% (7.2% to 21.2%) [a]	< 0.001
Age in years, mean (SD)	62.5 (12.2)	58.8 (16.7)	3.70 (-1.8 to 9.2) [b]	0.19	59.4 (17.1)	63.3 (14.44)	-3.90 (-9.5 to 1.6) [b]	0.16
Gender (male), n/N (%) [a]	33/57 (58)	31/55 (56)	1.5% (-16.3 to 19.2) [a]	0.87	35/67 (52)	36/61 (59)	-6.8% (52.2 to 59.0) [a]	0.44
Apache IV, median (IQR)	57 (51-81)	62 (48-83)	-	0.66 [c]	66.5 (47-75)	76.5 (63-97.5)	-	0.17 [c]
ICU LOS in days, median (IQR)	6 (3-12)	6 (3-12)	-	0.63 [c]	4 (2-14)	7 (3-13)	-	0.57 [c]
ICU mortality, n/N (%) [a]	13/57 (23)	13/55 (24)	-0.8 (-16.4 to 14.7) [a]	0.92	16/67 (24)	12/61 (20)	4.2% (-10.3 to 18.2) [a]	0.57

[a] Chi-square test; [b] Unpaired t-test; [c] Mann-Whitey U-test; LOS: Length of stay; Apache: Acute physiology and chronic health evaluation

Table 3. Transfusion bundle compliance

Time of intervention	**Month**	**Team A** n/N (%)	**Team B** n/N (%)	**95% CI of difference**	***P*-value [a]**
Implementation period	May	16/49 (33)	15/36 (42)	-9% (-28.8 to 11.1)	0.40
	June	20/57 (35)	14/20 (70)	-35% (-53.9 to -9.5)	0.007 [b]
	July	12/29 (41)	33/40 (83)	-41% (-59.2 to -18.1)	0.000 [b]
	August	10/25 (40)	21/28 (75)	-35% (-55.7 to -8.4)	0.01
Post-implementation period	September	28/70 (40)	33/46 (72)	-32% (-47.0 to -13.0)	0.001 [b]
	October	7/41 (17)	25/44 (57)	-40% (-56.0 to -19.0)	0.000 [b]
	November	5/41 (12)	18/34 (53)	-41% (-57.8 to -19.8)	<0.001 [b]
	December	7/64 (11)	18/38 (47)	-36% (-52.8 to -18.5)	0.000 [b]

[a] Chi-square test; [b] significant; no missing values

Table 4. Univariate logistic regression covariates for transfusion bundle compliance

	Compliance	
Covariates	**OR (95% CI)**	***P*-value[a]**
Type of A&F (Team A and Team B)	4.19 (3.01 to 5.82)	< 0.001
Time of intervention (impl. and post-impl.)	0.60 (0.44 to .82)	0.002
Nurses' age	0.99 (0.98 to 1.01)	0.59
Nurses' gender	1.38 (0.98 to 1.96)	0.07
Nurses' years of work experience	0.99 (0.98 to 1.01)	0.54
Response to educational questionnaire	2.17 (1.48 to 3.22)	< 0.001
Patient: Apache IV score	0.99 (0.99 to 0.99)	0.03
Patient: died in ICU	1.21 (0.87 to 1.69)	0.26

[a] significant when *P*-value is ≤ 0.20.

DISCUSSION

Our implementation study has shown that during the active period of implementation the combination of monthly A&F on team level with timely individual A&F, significantly improves short-term bundle implementation, compared to monthly A&F on team level alone. This resulted in significantly higher compliance levels in Team B. Even though significantly more transfusions were given in the team that received monthly A&F, our results also indicates that when using the combined A&F strategy nurses are four times more likely to be compliant to the bundle than when monthly team A&F was used alone.

When we stopped the A&F intervention during the post-implementation period, compliance dropped in both teams. However, even though in both teams compliance reduced in the four months after implementation, compliance levels were still significantly better in in the team that was exposed to the combined A&F strategy. These findings are consistent with Zajonc.[19] He showed that individual knowledge about team performance combined with knowledge on performance on an individual level enhances team performance.[19]

We have shown low compliance levels in the team where monthly A&F was given. This is in contrast to Lawrence and Fulbrook[25] who implemented the ventilator bundle.[25] They reported compliance levels of 68% by using monthly A&F. However, they provided A&F over a longer period of time, i.e. six months. The difference in our compliance data between the nursing teams could be explained by the time span in which feedback was delivered as well as the level on which the data was aggregated, i.e. team or individual

level. This is consistent with the model of actionable feedback.[20] This model posits that A&F is the most effective when it is timely given, individualized and in a non-punitive way. An important difference is that we have used a shorter time span in which feedback was provided compared to Hysong *et al.*.[19] The reason was that nurses would still clearly remember their actions and it gives nurses the opportunity to change their behaviour before the next transfusion occurred. Furthermore, we provided individual feedback in a non-punitive way. Feedback was also given when the performance of an individual was optimal i.e. compliance was 100%. This respectful and non-punitive way may have improved bundle compliance.[20]

Although this study has shown a significant effect on compliance during implementation when using the combination of monthly A&F plus timely individual A&F, there are reasons for not reaching the optimal effect. One of the reasons could have been that it was not always possible to meet the nurse within 72 hours. As per protocol, we then sent personal feedback by email. Even though the report was personalized and written in a non-putative manner, this might have had less impact than actual face-to-face feedback. As there is evidence that providing feedback face-to-face improves implementation.[18] Furthermore, there is evidence that when team members know each other's individual performance levels, this will lead to an improved level of overall compliance.[19] This means that when we showed the compliance level of each individual nurse to the whole nursing team, higher bundle compliance levels would have been achieved for that nursing team. Moreover, by expending the implementation period higher compliance levels could have been achieved. In studies that achieved high levels of bundle compliance periods were used of at least one year.[26] Providing timely individual feedback is labour intensive especially when the teams are large and the implementation period is long. A cost-effectiveness analysis would be recommended for future research.

Cost-effectiveness of A&F could be enhanced using information and computer technology. Zaydfudim *et al.* used an electronic monitoring and compliance system to sustain the implementation effect of the ventilator bundle.[27]

Achieving sustainability is a major challenge in implementation.[28] In our study, compliance gradually decreased in both teams during the post-implementation period. This so-called 'washout phenomenon' is a well-known factor in implementation.[28] Although compliance levels did not significantly decreased between the implementation and post-implementation period. Continuing the combined A&F strategy might have had a sustained effect on bundle implementation.[29]

Limitations

Our study was conducted in a single hospital in a 'closed-format' ICU. This limits the external validity of our results. Although the compliance outcomes of one team were not shown to the other team, the Hawthorne effect could have had influenced our results. This would result in less differences between groups and thus to an underestimation of the effect of our intervention. In this study, we did not measured the quality of the transfusion bundle itself. However, even though evidence-based interventions are added to a care bundle, in theory, this could lead to unforeseen consequences. We used bundle checklists to track compliance as recommended by the IHI.[12] There could be a discrepancy between actual delivered care and the reported care. This may have given an underestimation of compliance levels. Bundle compliance was self-reported by nurses. We did not perform a double check of how well it was done. It might be possible that self-reporting leads to an overestimation of the results. This could especially be the case in the team that received individual A&F, since these nurses knew they would receive comments on their individual performances. Our results show a difference in bundle compliance. Reasons for the differences in compliance might be that barriers exist when changing professional behaviour, affecting knowledge, attitude and behaviour.[10] We attempted to overcome the barrier of knowledge deficit by educating nurses. To create support, nurses were involved in the bundle design and in developing the educational questionnaire. Nonetheless, we did not attempt to determine nurses' knowledge or their willingness to change behaviour. Other barriers could exist which we may not have taken into account, such as leadership.[30] However, nursing management were requested not to stimulate implementation to minimize bias. Moreover, there were differences in the number of nurses who responded to the educational questionnaire. Before nurses answered the questions, they received educational materials by email. Thus, nurses might be educated in the transfusion bundle without filling out the questionnaire.

CONCLUSIONS

Compared to monthly team A&F alone, providing timely individual A&F plus monthly A&F on team level significantly improves the success of implementing a transfusion bundle on the ICU during the active period of implementation, which is expressed in significantly better short-term compliance rates. Providing timely individual A&F plus monthly A&F on team level might also be effective for the implementation of other evidence-based care bundles in healthcare. Future research could elaborate on longer duration of the intervention, the use of information and computer technology to lower costs of the intervention, and to enhance sustainability.

Competing interest

The authors declare that they have no competing interests.

Funding

This study was funded by ZonMw.

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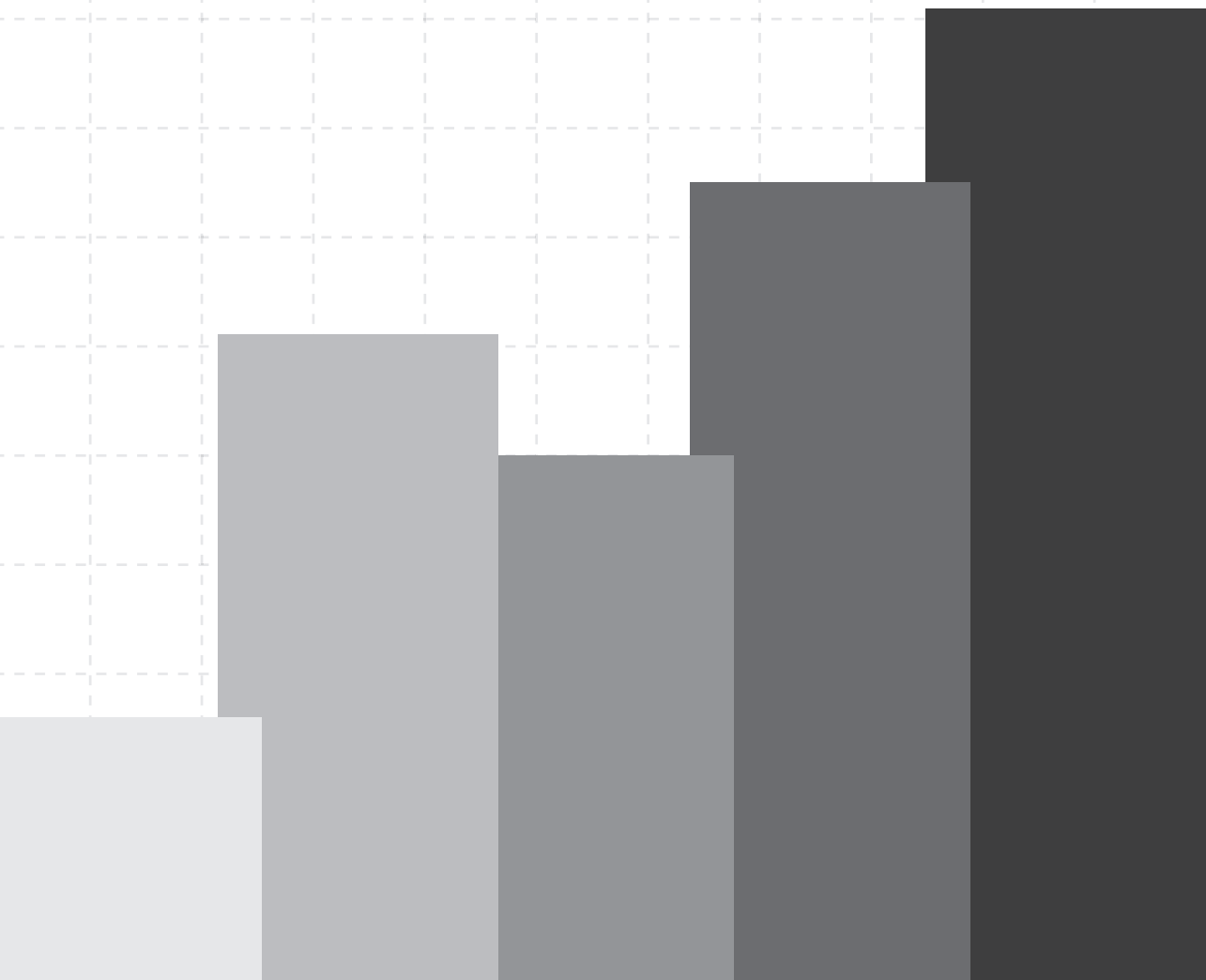
Supplementary File

Transfusion bundle

Transfusion bundle

Patient data	**Transfusion of Red Blood Cells**
Patient Identification Number:	Date of transfusion: ___-___- 20___
Name:	Time of transfusion: ___:___ hours
Date of birth:	Name of the nurse:

Transfusion bundle	**Yes**	**No**	**If no, give reason**
1. Is the haemoglobin (Hb) result considered reliable?	□	□	
2. Have you verified if the Hb transfusion threshold was reached?	□	□	
3. Have you verified if informed consent was obtained?	□	□	
4. Is the identity of the patient checked by two persons independently before transfusion?	□	□	
5. Is the blood product checked by two persons independently before transfusion?	□	□	



08

IMPLEMENTATION OF A TRANSFUSION BUNDLE REDUCES INAPPROPRIATE RED BLOOD CELL TRANSFUSIONS IN INTENSIVE CARE - A BEFORE AND AFTER STUDY

Marjon Borgert, Jan Binnekade, Frederique Paulus, Margreeth Vroom, Alexander Vlaar, Astrid Goossens, and Dave Dongelmans

Transfus Med. 2016;26:432-439.

ABSTRACT

Background. Restrictive red blood cell (RBC) transfusion has been widely described in transfusion guidelines. However, compliance with these guidelines is often poor. Therefore, we developed a care bundle for the transfusion of RBCs in intensive care. We investigated the effect of the application of the transfusion bundle on transfusion practice, hypothesizing that the implementation of the transfusion bundle would lead to a reduction of inappropriate RBC transfusions.

Study design and methods. We conducted a before and after study between January to December 2014 in a medical-surgical intensive care unit (ICU) of a university hospital in Amsterdam, the Netherlands. The primary outcome was the percentage of appropriate transfusions, referring to those transfusions that were in accordance to the patients' individual preset haemoglobin threshold.

Results. The mean pre-transfusion haemoglobin level was 7.3 g/dL^{-1} (SD=1.15) during baseline and significantly decreased to 7.1 g/dL^{-1} (SD=1.04) after transfusion bundle implementation, 95% confidence interval (CI): 0.009 to 0.308, *P*-value = 0.04. The number of inappropriate transfusions significantly decreased from 25% (111/439) during baseline to 15% (42/280) during implementation, difference 10%, 95% CI: -0.164 to -0.042, *P*-value 0.001.This further decreased to 12% (45/370) in the post-implementation phase. A logistic regression analysis showed that the chance to find an appropriate transfusion is approximately twice as high after transfusion bundle implementation.

Conclusions. Introduction of a transfusion bundle results in a significant reduction of the number of inappropriate RBC transfusions in the medical-surgical ICU. Our results show that the introduction of a transfusion care bundle helps to improve compliance with transfusion guidelines in daily practice.

INTRODUCTION

In the past decades randomized trials have shown that a restrictive red blood cell (RBC) transfusion policy is safe for most critically ill patients and even results in improved survival in specific critically ill patients.[1,2] A restrictive (7g/dL^{-1}) RBC transfusion policy has now been widely implemented in transfusion guidelines for critically ill patients. Unfortunately, compliance with these guidelines is poor.[3,4] It is important to improve compliance as this reduces mortality in critically ill patients and reduces waste of scarce as well as expensive RBC products.

To improve adherence to guidelines, the Institute for Healthcare Improvement (IHI) developed the concept of care bundles.[5,6] Care bundles consist of a small set of evidence-based key interventions.[6-8] These interventions should be performed together for every patient.[7,8] The idea behind bundling evidence-based interventions is that bundles improve the reliability of care so that all patients receive the care they need.[6-8] The first designed care bundles were the ventilator bundle and central line bundle. They aimed to reduce the incidence of ventilator-associated pneumonia (VAP) and catheter-related bloodstream infections respectively.[6-8] Both bundles are nowadays widely used in intensive care units (ICUs), showing significant improvements in clinical outcomes and in reducing costs.[5,9-11] Care bundles might also be effective in transfusion medicine. Therefore, we have developed a care bundle for the transfusion of RBCs in the ICU. We have selected those interventions that have proven to have a great impact on RBC transfusion safety or on decision making regarding RBC transfusion[1,2,12-15], which will subsequently lead to a reduction in costs and in improved clinical outcomes. For instance, adequate pre-transfusion 'bedside' checks should be carried out and decisions for transfusion should be made on reliable haemoglobin (Hb) results.[12,13,16] Moreover RBCs should only be transfused when the preset Hb threshold is reached.[1,2]

Nurses play a significant role in transfusion decision making.[4] Vlaar *et al.* showed that the need for transfusion is often pointed out by nurses.[4] Greater involvement of nurses in reviewing the appropriateness of a transfusion order before blood is given might be effective in reducing inappropriate transfusions. In this study, we quantified the true effect of the transfusion bundle by assessing, per transfusion, whether the decision to transfuse was based on a lower pre-transfusion Hb-level than the patients' individual preset Hb threshold. The objective of this study was to investigate whether application of the transfusion bundle would reduce the number of inappropriate red blood cell transfusions in an ICU setting.

METHODS

Design

A before and after study was conducted from January to December 2014. We primarily assessed the effect of the transfusion bundle on the percentage of appropriate transfusions. To objectively assess this effect, we focused on the number of appropriate transfusions. Appropriate transfusions were defined as transfusions for which the last recorded pre-transfusion Hb level was lower than the patients' individual preset Hb threshold as registered in the electronic patient file by the ICU physicians. A secondary outcome was the likelihood of appropriate transfusions, controlling for other variables. We implemented the transfusion bundle from May to August 2014. This implementation period denotes the transition period. The post-implementation, from September to December 2014, refers to the period in which the intervention is considered fully implemented as intended.

Setting

The study was conducted in a 28-bed mixed medical-surgical ICU of a university hospital in Amsterdam, the Netherlands. The ICU is a 'closed format' department for adult patients (≥ 18 years) with four units in which patients are under the direct care of the ICU team. The patient-nurse ratio is 1:1 or 1:2, depending on the patients' severity of illness.

Study population

The transfusion bundle was applied by nurses to every eligible ICU patient who received at least one unit of RBCs. Transfusion in patients for whom therapeutic haemapheresis was indicated or patients who were massively bleeding were excluded due the urgency of the situation. The massive blood transfusion protocol was activated in case of the presentation of the following signs or symptoms: (i) rapid decrease in blood pressure (systolic < 90mmHg; and (ii) not responding to fluid therapy; and (iii) existence of a high suspicion for bleeding. Furthermore, blood products other than RBCs were excluded.

Transfusion bundle

We have developed the transfusion bundle by using a prospective risk analysis, i.e. the Bow-Tie analysis model.[17] A multidisciplinary expert team of two ICU nurses, three intensivists, one haemovigilance officer and one laboratory analyst from the blood bank joined the Bow-Tie analysis session. The results of the Bow-Tie analysis were used to identify the potential interventions to include in the transfusion care bundle. The expert team selected the final set of five key interventions through discussion until consensus was achieved. In Table 1, the interventions are shown. The interventions were

underpinned with evidence and/or were reported in the (inter)national transfusion guidelines. All interventions aimed to reduce unnecessary, inappropriate or unsafe transfusions.[1,2,12-14,16] The transfusion bundle was actively implemented from May to August 2014 by using educational activities and audit & feedback (A&F). A&F was given monthly to the nursing teams. Half of the nurses received additionally individual A&F after every transfusion. However, the implementation of the bundle itself was not the subject of this study. In this study, we focused on the effect of the bundle on inappropriate transfusions.

Table 1. Transfusion bundle interventions

Transfusion bundle interventions
1. Verification of the Hb measurement reliability
2. Transfusions given according to patients' individual Hb-threshold, i.e. transfusion trigger
3. Verification of obtained Informed Consent
4. Verification of the right patient by two persons independently
5. Verification of the right blood product by two persons independently

Data collection

Data about transfusions were collected at baseline (4 months), during the implementation period (4 months) and during the post-implementation period (4 months). Transfusions during the baseline period were collected retrospectively from the electronic Patients Data Management System (PDMS) (Metavision, Ite medical Tiel). All patient and transfusion data during the baseline period were reviewed one by one and entered into the study database. Data during the implementation and post-implementation periods were prospectively collected from the PDMS. During week days the occurrence of a RBC transfusion was audited in the PDMS three times per day by the researcher. Transfusions that had occurred during the weekends were audited on Mondays. Bundle checklists were used to track the levels of bundle compliance. Compliance with the completion of each element of the bundle was assessed by reviewing the bundle checklist. Compliance levels were calculated using the all-or-none approach.[18] This means that all five bundle-interventions had to be completed in order to be labelled as compliant to the transfusion bundle.

Analysis

Continuous variables that were normally distributed were expressed as means with standard deviations (SD) and not normally distributed variables as medians and inter-quartile ranges (IQR). To test independent groups of not normally distributed continuous variables, the Kruskal Wallis test was used or Mann-Whitney U test when appropriate. Categorical variables were expressed as percentages, numerators and denominators and were compared with the Chi-square test or Fisher's exact test. Analysis of variance (ANOVA or unpaired t-test) was used to test for differences in means across the study periods. In some cases the denominator does not correspond fully with the overall number of patients. This difference is due to missing values on some variables.

The goal of the logistic regression analysis was to quantify the net effect of the implementation of the transfusion bundle on the likelihood of appropriate transfusions, controlling for other variables. Exploration of interaction (effect modification) and confounding was considered methodologically relevant. We first focused on the crude (uncorrected) effect of the implementation of the bundle (independent variable) on appropriate transfusions (dependent variable). Then, statistical and clinically relevant covariates were added as an interaction term. If the interaction term appeared to be significant ($P < 0.05$), this would indicate that the relation between the implementation and appropriate transfusions could be different for various levels of the covariate. This indicates the need for separate models for the levels of the covariate. As a significant interaction was not found, the model was examined for confounding. Confounding was defined as ≥ 10% change in the coefficient of the central determinant implementation as a consequence of adding a covariate. Statistical significance was considered to be at $P < 0.05$. When appropriate statistical uncertainty was expressed by the 95% confidence levels. Analyses were performed using R (version: 3.1.3; R Foundation for Statistical Computing, Vienna, Austria).

Ethics

The study was approved by the Medical Ethics Committee of the Academic Medical Center of Amsterdam, the Netherlands and the need for informed consent was waived.

RESULTS

Patient demographics

A total of 386 patients were included in this study, 146 patients during baseline, 112 during implementation and 128 during the post-implementation period. Each patient received a median of 2 units of RBCs during their ICU admission (IQR=1-4). In total, 1128 units of RBCs were transfused. Table 2 shows that the cohorts were similar during the baseline, implementation and post-implementation period with respect to age, gender, type of admission and ICU mortality. Most admissions were medical admissions, followed by cardio-surgical admissions. During the phase of active implementation, less units of RBCs were administered compared to the baseline and to the post-implementation period (difference baseline 16%, 95% CI: 0.122 to 0.200, *P*-value < 0.001; difference post-implementation: -9%, 95% CI: -0.122 to -0.045, *P*-value < 0.001).

Table 2. Patients demographics

	Baseline period	**Implementation period**	**Post-implementation**	***P*-value**
Number of patients receiving ≥1 RBC transfusions during ICU admission*	146	112	128	0.03
Total number of transfused RBCs	466/1128 (41)	284/1128 (25)	378/1128 (34)	<0.001
RBCs per patient, median IQR	2 (1-4)	2 (1-4)	2 (1-3)	0.49
Age in years, median (IQR	67 (54-75)	62 (52.8-72.0)	62 (52.5-74.0)	0.54
Gender (male), n/N (%)*	78/135 (58)	64/112 (57)	71/128 (56)	0.93
Type of admission* Medical case	88/135 (65)	63/102 (62)	76/106 (72)	0.30
Surgical case	9/135 (7)	11/102 (11)	9/106 (5)	0.53
Cardio-surgical case	38/135 (28)	28/102 (28)	21/106 (20)	0.29
APACHE IV, median (IQR)*	69 (52.5- 96.0)	61 (48.3-82.8)	74.5 (54.5-99.8)	0.005
ICU LOS (days), median (IQR)*	5.02 (2.6-10.1)	6 (3.0-12.0)	5.5 (2.0-14.0)	0.26
ICU mortality, n/N (%)*	36/135 (27)	26/112 (23)	28/128 (22)	0.64
Hospital mortality	40/130 (31)	28/101 (28)	33/116 (29)	0.86

RBC= Red Blood Cells, ICU= Intensive Care Unit, APACHE= Acute Physiology and Chronic Health Evaluation; LOS=Length Of Stay; *including ICU readmissions; In some cases the denominator does not correspond fully with the overall number of patients receiving ≥ 1 RBC transfusions during ICU admission. This difference is due to missing values on some variables.

Transfusion bundle

During the baseline period 466 units of RBCs were transfused, 284 during the implementation period and 378 units post-implementation. After introducing the transfusion bundle, compliance was 50% (141/284) during implementation, and 37% (141/378) during the post-implementation period (difference -13%, 95% CI: 0.045 to 0.202, *P*-value = 0.002).

Red Blood Cell transfusions

In Figure 1, the preset Hb thresholds and the last recorded pre-transfusion Hb levels are shown. The mean pre-transfusion Hb level was 7.3 g/dL^{-1} (SD=1.15) during the baseline period. After introducing the bundle the mean pre-transfusion Hb level decreased to 7.1 g/dL^{-1} (SD=1.04), difference 0.2 g/dL^{-1}, 95% CI: 0.009 to 0.308, *P*-value = 0.037.

In Figure 2, the percentage deviation between the preset Hb thresholds and the last recorded pre-transfusion Hb levels is shown. In the vast majority of transfusions the pre-transfusion Hb was below the Hb thresholds, i.e. appropriately transfused. Compared to the baseline period, the number of inappropriate transfusions significantly decreased during implementation from 25% (111/439) to 15% (42/280) during implementation, difference 10%, 95% CI: -0.164 to -0.042, *P*-value 0.001. During the post-implementation period, the number of inappropriate transfusion further decreased to 12% (45/370). Table 3 shows the results from the univariate analysis. The covariates 'intervention', i.e. transfusion bundle, and 'pre-transfusion Hb' showed a statistical significant effect on the appropriateness of transfusions. The logistic regression analysis shows that the chance (Odds) to find an appropriate transfusion is approximately twice as high after the implementation of the transfusion bundle (Table 4). The pre-transfusion Hb level influences this effect. The direction of this odds ratio shows that a lower pre-transfusion Hb level is associated with better protocol compliance, resulting in more appropriate transfusions when lower pre-transfusion Hb levels were measured.

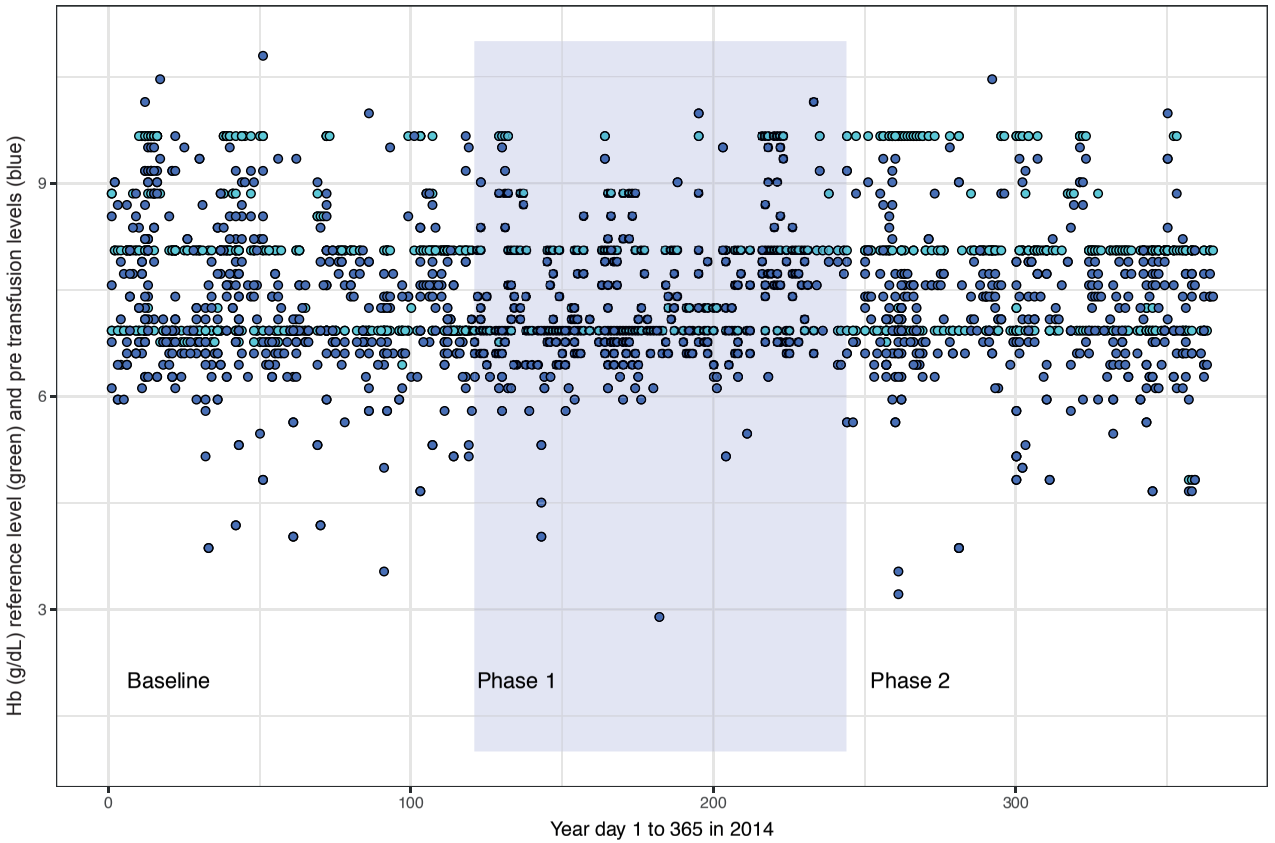


Figure 1. Patients' individual pre-set Hb threshold as green dots and pre-transfusion Hb level as blue dots

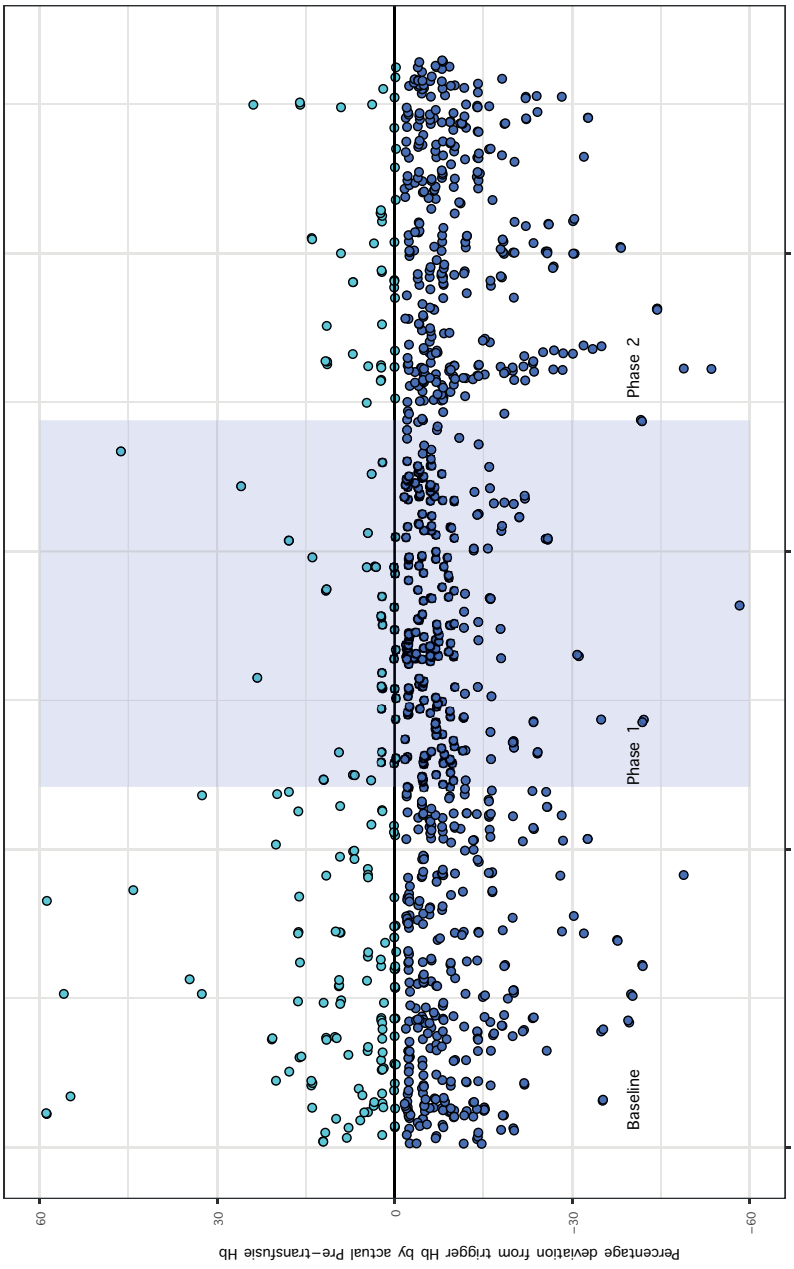


Figure 2. Percentage deviation from patients' individual pre-set Hb threshold by pre-transfusion Hb level. Light blue dots reflect the transfusions associated with a higher pre-transfusion Hb level than the patients' individual pre-set Hb threshold

Table 3. Logic regression model for appropriate transfusions

Univariate analysis	OR (95% CI)	*P*-value
Baseline (reference)	1	
Baseline – intervention[a]	2.26 (1.65 to 3.10)	< 0.001
Age	1 (0.99 to 1.02)	0.26
Gender	1.35 (0.85 to 2.13)	0.20
Apache IV score	0.99 (0.99 to 1)	0.11
Pre transfusion Hb	0.25 (0.19 to 0.32)	< 0.001
Transfusion delay (hours)	0.99 (0.91 to 1.07)	0.79
Medical/surgical admission	0.82 (0.59 to 1.15)	0.26

Dependent variable: transfusion according to protocol = 1 (Hb reference value), protocol deviation = 0;
[a]Intervention: use of the transfusion bundle during (post) implementation periods

Table 4. Multivariable analysis

	OR (95% CI)	p-value
Baseline – interventions*	2.05 (1.47 to 2.86)	<0.001
Pre transfusion Hb	0.26 (0.20 to 0.34)	<0.001
*Intervention: use of the transfusion bundle during (post) implementation periods		

DISCUSSION

The main finding of the current study is that the introduction of a transfusion bundle has resulted in a significant reduction of the percentage of inappropriate transfusions. Effectively, using the transfusion bundle helps to improve compliance to transfusion guidelines in daily practice. Since the landmark of Hébert *et al.* attempts have been made to reduce the number of transfusions given the concerns about the safety of transfusion as well as the rising costs and shortage of blood products.[1,19,20] Reducing the number of inappropriate transfusions is expected to result in improved clinical outcomes and reduced health care costs.[21] The transfusion care bundle may therefore diminish costs by reducing waste of scarce and expensive RBC products.

We implemented the transfusion bundle in the ICU nursing teams. Vlaar *et al.* showed that most often, it is the nurse who points out the need for transfusion.[4] Therefore, the use of the transfusion bundle by nurses might have had an important effect on reducing inappropriate transfusions.

In the literature, care bundles are often evaluated by measuring the effect of the bundle by using compliance levels. These compliance levels are often calculated by using bundle checklists.[6] In this study, we were primarily interested in the reduction of the number of inappropriate RBC transfusions. For this we assessed per transfusion if this was based on lower pre-transfusion Hb levels than the patients individual preset Hb thresholds.

Our results showed a significant reduction in the number of inappropriate transfusions. Remarkably, compliance-levels of the whole bundle remained low during the study period. It is known that the reported levels of bundle compliance are widely variable between studies.[22] This might, for example, be due to the way compliance was calculated or the number of bundle interventions included. In our study, we have calculated bundle compliance by using the all-or-none approach. This means that if one of the bundle interventions was not performed, the whole bundle was considered as non-compliant. It may also be possible that the bundle interventions were actually performed without using the bundle checklist. The use of paper-based bundle checklists could have influenced this effect and may have led to a documentation burden.[23,24] However, the intention of care bundles is not to use them as checklists but to improve habits and processes and to internalize the bundle interventions.[25] The latter might be true in our study. This might be due to an increased awareness of the risks of RBC transfusion due to the implementation of the transfusion bundle.

In our study, we have examined whether transfusions were based on lower pre-transfusion Hb levels than the preset Hb threshold per individual patient. We have not assessed whether the pre-set threshold was considered adequate for each individual patient according to the transfusion guideline. Interestingly, our results show that in most cases, restrictive Hb thresholds were used as stated in the transfusion guideline.[16] Hébert *et al.* showed that in most critically ill patients the Hb threshold can be safely lowered without influencing clinical outcomes negatively.[1] To further improve the effect of the transfusion bundle, the preset thresholds could be reviewed and discussed by peers. This might have an effect in lowering the preset Hb thresholds for more patients. Using the transfusion bundle on these preset Hb levels may lead to a larger reduction of inappropriate transfusions. However, to sustain the implementation effect for appropriate transfusions, real-time clinical decision support systems for ordering blood

products appear to be effective.[26,27] Such systems are integrated in a blood ordering system in electronic patient files. Several studies showed significant reductions in blood products when a clinical decision support system was implemented.[26,28] Decision support systems complements might be used in conjunction with the transfusion bundle.

According to (local) transfusion guidelines and the Joint Commission International (JCI) standards, informed consent should be obtained before transfusion.[16,29] Obtaining informed consent is one of the five bundle interventions. Not obtaining informed consent was considered as one of the problems that can occur according to the Bow-Tie analysis. Additionally, obtaining informed consent is one of the JCI standards. Because of these reasons, the expert team have chosen to include this element in the transfusion bundle. Moreover, informed consent could have an indirect impact on reducing transfusions since patients are making well-informed decisions whether or not to receive blood products. Obtaining informed consent does not fully comply with the bundle requirements as set by the IHI, i.e. level one evidence.[6] However, according to the IHI, bundle interventions that are already recommended in (inter)national guidelines and by consensus of clinicians as being applicable to most patients might be considered for inclusion.[6]

The strength of a care bundle is that a maximum of five interventions can be included.[6] Not all recommendations can be put into care bundles. Other important problems or risk factors in the blood transfusion procedure could have been selected by the expert team as well, for instance, the mislabelling of blood samples, transfusion of two units of RBCs per transfusion without a re-check of the Hb after each transfused unit or wrong storage of RBCs.[15,16,20] We have chosen to include those intervention in the transfusion bundle that were marked as serious problems or risks in the Bow-Tie analysis and were based on evidence or international guidelines.

The transfusion care bundle could result in diminishing costs by reducing the waste of scarce and expensive RBC products. These savings are apart from the indirect savings of transfusion-related adverse events when the restrictive policy is applied to the majority of the patients.[21]

Limitations

Our study has some limitations. The study was a single-center study, which limits the external validity of our results. Furthermore, a before and after design was used. Therefore secular trends may have influenced our results. Baseline transfusions were retrospectively collected; however, each transfusion was thoroughly reviewed in the

PDMS. We quantified the net effect of the bundle by using one of the bundle interventions, i.e. transfusions given according to the patients' individual Hb-threshold, as we could objectively measure this intervention. We have not actively observed the effect of the other bundle interventions. However, during the study period no transfusion-related incidents were reported in our ICU incident-reporting system. A mixed method study design, using both qualitative and quantitative research methods, would have given insight in the effect of the bundle on all interventions, e.g. on the performance of the final bedside checks. Furthermore, we have not assessed whether the preset threshold was considered adequate for each individual patient as we have chosen to follow clinical practice. Implementation of the transfusion bundle showed moderate levels of bundle compliance. However, high levels of bundle compliance of more than 95% are associated with improved clinical outcomes. In this study, we focused on the number of inappropriate transfusions without taking the cost effectiveness into account.

Future research

Future research should focus on implementing a transfusion bundle for other type of blood products, such as fresh frozen plasma or platelets. The transfusion bundle might be an effective tool to reduce the overall number of inappropriate transfusions. Furthermore, future research should focus on the cost effectiveness of implementing the transfusion bundle.

CONCLUSIONS

Introduction of a transfusion bundle results in a significant reduction of the number of inappropriate RBCs transfusions in the medical-surgical ICU. Our results show that introduction of transfusion care bundles helps to improve compliance with transfusion guidelines in daily practice.

Competing interest

The authors declare that they have no competing interests.

Funding

This study was funded by ZonMw.

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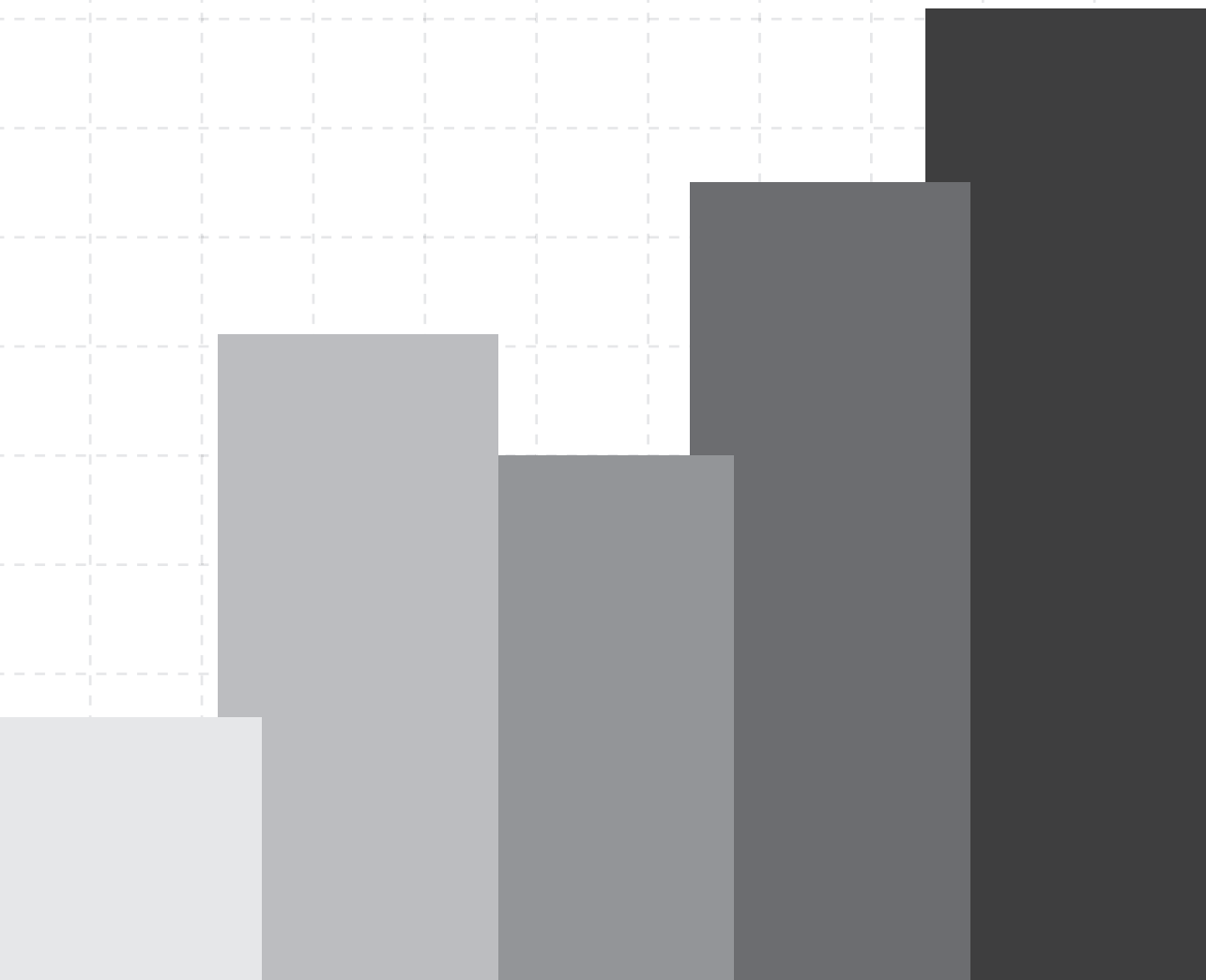
Supplementary File

Transfusion bundle

Transfusion bundle

Patient data	**Transfusion of Red Blood Cells**
Patient Identification Number:	Date of transfusion: ___-___- 20___
Name:	Time of transfusion: ___:___ hours
Date of birth:	Name of the nurse:

Transfusion bundle	**Yes**	**No**	**If no, give reason**
1. Is the haemoglobin (Hb) result considered reliable?	□	□	
2. Have you verified if the Hb transfusion threshold was reached?	□	□	
3. Have you verified if informed consent was obtained?	□	□	
4. Is the identity of the patient checked by two persons independently before transfusion?	□	□	
5. Is the blood product checked by two persons independently before transfusion?	□	□	



09

SUMMARY AND FUTURE PERSPECTIVES

SUMMARY

Actually integrating new research findings into daily practice is challenging, especially if they require changes to behaviour, clinical practices, the organization, or the way professionals collaborate. In many cases patients come to harm because evidence-based recommendations or guidelines are not followed consistently. Multiple studies have shown that patients receive only half of the recommended care.[1,2] In health care, there is a slow uptake of new research findings in guidelines and daily care.[3] This thesis focuses on the implementation of strategies for improving patient safety and quality of care of critically ill patients. **Part I** focuses on improving patient safety for critically ill patients on nursing wards by implementing a rapid response system (RRS). **Part II** focuses on improving patient safety for critically ill patients in the intensive care unit (ICU) by implementing evidence-based care bundles.

Part I. Improving patient safety of critically ill patients on nursing wards.

In part I, we focusses on the implementation of the RRS on nursing wards. RRSs are developed to improve the care for deteriorating patients in hospitals.[4,5] Previous studies have shown that most patients who suffer from serious adverse events, such as an unplanned ICU admission, cardiac arrest and unexpected death, have vital sign abnormalities prior to these adverse events.[6,7] However, these signs are not always recognized in time by nurses or are not adequately and timely acted upon.[8] RRS involves the recognition of patients' conditions prior to deterioration by using a 'track-and-trigger system', such as the modified early warning score (MEWS).[9] The rapid response team (RRT) should be called in case the patient's condition deteriorates beyond a certain MEWS threshold. **Chapter 2** describes the implementation of the MEWS on nursing wards of the Academic Medical Center in Amsterdam. In this quasi-experiment, we studied the effects of protocolized measurement (i.e. three times daily) of the MEWS versus measurement when clinically indicated. The study was conducted between September and November 2011. All patients admitted to the hospital for at least one overnight stay were included. Nursing wards were randomized to measure the MEWS three times daily or on indication. In total, 902 patients were included in this study, and a set of 6598 vital sign measurements were registered in the patient files during the three study weeks. The results showed that in the protocolized randomization arm, the MEWS was calculated in 70%. On wards were the MEWS was measured on indication the MEWS was measured in only 2%, difference 67.9%, 95% confidence interval 66.3 to 77.0, *P*-value < 0.001. Furthermore, there were 90 calls to the primary physician on the ward in the protocolized arm versus nine calls on the wards randomized on indication. The results indicate that measuring the MEWS three times daily results in improved compliance to

the protocol and better detection of physiological abnormalities, compared to leaving the frequency of measurement up to nurses themselves. In **Chapter 3** we analysed the so called 'false arrests' in order to determine the 'level of urgency'. False arrests were defined as activations of the cardiac arrest team while patients do not actually suffer from it.[10-13] This study was conducted in order to find a scope for improvement in efficiency within the emergency care, thereby saving time and money. Cardiac arrest team activations for false arrests from September 2009 to 2012 were retrospectively analysed. These calls were classified as urgent or less-urgent. The results showed that a large part of the activations of cardiac arrest teams for false arrests were classified as less urgent. In these cases activation of a RRT might be more appropriate and efficient. It may be suggested that to minimize the activations of cardiac arrest teams for false arrests, nurses need to early recognize patients who clinically deteriorate. In order to do so, the MEWS screening tool should be used correctly.

Part II. Improving patient safety of critically ill patients in the ICU.

In part II, we describe the development and implementation of evidence-based care bundles. The concept of care bundles was developed by the Institute for Healthcare Improvement (IHI).[14-16] Care bundles were developed in order to enhance the reliability of care and to improve the quality of care.[14-17] They consist of a small set of three to a maximum of five evidence-based interventions for clinical processes or patient populations. The strength of bundling a small set of interventions together is that evidence-based care will be uniformly applied to every eligible patient, which may result in better patient outcomes than when the interventions were implemented individually.[15,16]

In **Chapter 4** we conducted a systematic review to identify what methods were available that could support the development of new care bundles for the ICU besides the approach of the IHI. The IHI described the methods used on how to develop care bundles.[15,16] However, these methods may not always be applicable to all ICUs and in every situation. In the literature, other useful methods to design care bundles were published as well. Electronic databases were searched for eligible studies from January 2001 to August 2014. We identified useful methods for designing evidence-based care bundles. The results were used to build a comprehensive flowchart to provide an overview of the methods used to design care bundles so that others could choose their own applicable method. It guides through all necessary steps in the process of designing care bundles.

The delivery of care, such as the delivery of enteral nutrition (EN), consist of a complex series of interactions between physicians, nurses, patients and medical interventions.[18] Monitoring and systematically analysing these interactions can be helpful in identifying those areas where optimal care is potentially at risk. The identification of those risks is important in finding opportunities in improving the quality of care.[18] And thus, an area were care bundles could be effective. Malnutrition is a serious problem in critically ill patients.[19,20] We do, however, not exactly know to what extent patients are at risk in receiving adequate EN therapy. In **Chapter 5** we conducted a retrospective cohort study, in which we identified patients who were at risk for malnutrition in order to find ways of improving the quality of care. Patients admitted to the ICU from January 2012 to December 2014 were included. Ideal calorie intake was calculated as 25 Kcal/kg/day. Ideal protein intake as 1.2 to 1.5 g/kg/day. Multilinear regression was used to describe the factors of success of EN intake. The results showed that, the delivery of EN in critically ill patients was moderate to high in the majority of the patients. However, a substantial part of the EN delivery was still suboptimal during admission and need to be improved. This implies a strong argument to support ICU staff in the adequate delivery of EN. This could be facilitated by a nutritional care bundle to support guideline uptake and thereby improve the delivery of EN. In **Chapter 6** a systematic review was performed to determine the strategies used to implement care bundles in adult ICUs. Furthermore, we assessed the effect of these strategies when implementing bundles. The electronic databases, PubMed, Ovid Embase, CINAHL and CENTRAL, were searched for eligible studies. The most frequently used strategies were education (86%), reminders (71%) and audit and feedback (A&F) (63%). Our results showed that compliance was influenced by multiple factors, i.e. types and numbers of elements varied and different compliance measurements were reported. Furthermore, compliance was calculated within different time frames. Also detailed information about compliance, such as numerators and denominators, was not reported. Therefore, recalculation of consistent monthly compliance levels was not possible. We concluded that the heterogeneity among the included studies was high, caused by the variety in study designs, number and types of elements and types of compliance measurements. Due to the heterogeneity of the data and the poor quality of the studies, conclusions could not be determined about which strategy results in the highest levels of bundle compliance. Therefore, it is recommended that studies in quality improvement should be reported in a formalised way in order to be able to compare research findings.

In **Chapter 7** we developed and implemented a transfusion care bundle for the delivery of red blood cells (RBCs). In this implementation study, with a quasi-experimental study design, we investigated the difference in effect on transfusion bundle compliance between monthly team level A&F versus monthly team level A&F with the addition of

timely individual A&F. The results showed that monthly A&F on team level with timely individual A&F significantly improved bundle compliance during implementation compared to monthly A&F on team level alone. The overall effect of compliance during the study period was significantly higher with an OR of 4.05 (95% confidence interval: 1.62 to 10.08), $P < 0.001$. This indicates that when using the combined A&F strategy nurses are more likely to be compliant to the bundle than when monthly A&F was used alone. Providing timely individual A&F plus monthly A&F on team level might also be effective for the implementation of other bundles in healthcare. Future research could elaborate on longer duration of the intervention, the use of information and computer technology to lower costs of the intervention and to enhance sustainability.

In **Chapter 8** we investigated whether the application of the transfusion bundle would reduce the number of inappropriate RBC transfusions in an ICU setting. Restrictive RBC transfusion has been widely described in transfusion guidelines.[21] However, compliance to these guidelines is often poor.[22,23] In this before and after study, we quantified the true effect of the transfusion bundle by assessing, per transfusion, whether the decision to transfuse was based on a lower pre-transfusion haemoglobin (Hb) level than the patients' individual preset Hb threshold. The primary outcome was the percentage of appropriate transfusions, referring to those transfusions that were in accordance to the patients' individual preset Hb threshold. The results showed that the introduction of the transfusion bundle has resulted in a significant reduction of the percentage of inappropriate transfusions. The number of inappropriate transfusions decreased from 25% (111/439) during baseline to 15% (42/280) during implementation, a difference of 10%; 95% CI: -0.164 to -0.042, $P < 0.001$. This further decreased to 12% (45/370) in the post-implementation phase. Effectively, using the transfusion bundle helps to improve compliance with transfusion guidelines in daily practice. We have not assessed whether the preset Hb threshold was considered adequate for each individual patient according to the transfusion guideline. Interestingly, our results show that in most cases, restrictive Hb thresholds were used as stated in the transfusion guideline.[21]

FUTURE PERSPECTIVE

A hospital is a highly complex system. This complexity is due to the many interactions between humans (patients, family, health care professionals), the organization (teams, wards, hospital) and the financial and political environment.[24] Dynamic systems such as ICUs are particularly complex, given the multitude of technologies, treatments, medications, severity of the illnesses of patients, and the fact that professionals work in multidisciplinary teams. Errors are very likely to occur in dynamic and complex systems.[18,25,26] In hospitals patient safety is an important issue that is also complex. Patient safety is broad-based, and operates at various levels of the system. It applies to various patient categories that employ multiple techniques and interventions, and can be influenced by cultural, technical, clinical, psychological, and financial aspects.[27] We conducted the studies included in this thesis within these complex contexts.

One of the most challenging aspects of increasing patient safety in a hospital setting is the successful implementation of new evidence-based practices (Chapters 2 and 7). For each new implementation activity, there are a large number of factors that hamper implementation. Cabana *et al.* conducted a systematic review in which they identified barriers to physicians' compliance with clinical guidelines.[28] These were barriers related to professionals' knowledge and attitudes as well as to external barriers such as patient-, guideline-, or environment-related factors. Successful implementation depends on considering these various barriers and searching for adequate implementation strategies to overcome them.[2,29,30] To achieve effective implementation, a systematic approach and a well-designed implementation plan are imperative. The plan should include an analysis of the target group, the setting, and the existing barriers.[29] This information is necessary to tailor the implementation strategy to a specific situation. Although audit and feedback (A&F) is a widely used implementation strategy for improving patient safety and quality of care, it appears to be only moderately effective.[31] A&F is more likely to be successful when the source is a senior colleague or supervisor, when it is provided in both written and verbal formats, when the goals are measurable, or when it is provided in a timely fashion (i.e. at least once a month).[31] However, given the heterogeneity in outcome measures and methodology in the available studies, no strong conclusions can be drawn about A&F.[31]

A wide variety of implementation strategies can be used, including reminders, A&F, and educational activities. These implementation strategies show varying effects (Chapter 6),[32] and the most effective strategy or combination of strategies for successful implementation remains elusive.[31] According to current thinking on this subject, to increase the chances of success, a tailored and often multifaceted approach is required

to overcome existing barriers. The implementation strategies should be evidence-based and have a theoretical foundation.[33,34] However, given the uncertainty of the outcome of each implementation activity, cost and time investment should be taken into account. The additional costs of multifaceted implementation strategies should be weighed against the realistic chance of (regularly) achieving only small improvements.[31]

As described in the Introduction section, we should realize that errors inevitably occur in hospitals.[35,36] Human errors are hardly ever caused in isolation by one person, but can occur due to underlying flaws within the organizational system.[37] To protect patients against these human errors, the working environment, or so called 'system', needs to be redesigned. This can, for instance, be achieved by the simplification and standardization of processes, automation, standardization of equipment and functions, or by decreasing simple reliance on memory (Chapters 2 and 7).[27,38,39] With these methods, care processes can be optimized to improve the reliability of care. Improving reliability means that clinical procedures need to be applied reliably, such as compliance with hand hygiene or timely administration of antibiotics for septic patients.[40] The use of care bundles or early warning score systems to detect clinical deterioration, are also useful strategies to improve the reliability of care processes (Chapters 2 and 7). Such quality improvement strategies are necessary and widely applied on hospital wards. However, they are never the complete solution for achieving improvements. These interventions could for instance be complemented by strategies to enhance the safety culture itself.

The concept of a 'safety culture' has become an important one for hospitals striving to improve patient safety.[41] Safety culture reflects the attitude, values, perceptions and beliefs of leaders and health care providers towards taking risks, following rules, speaking up about safety and the values of risk management and safety.[42,43] Safety culture can vary significantly between different wards and different groups, and each group or discipline has its own culture and habits.[27] What are known as 'high safety cultures' are more willing to change behaviour and are associated with improved reliability of care.[44] Pronovost *et al.* showed that promoting the safety culture, in combination with the implementation of a central line bundle, resulted in large improvements in infection reductions.[44] But, improving the safety culture is a real challenge at every organizational level. This can only be achieved when leaders are visibly willing to change and when they encourage health care providers to openly talk about and share safety issues. If such a safety culture is not achieved, it can lead to an unwillingness to report adverse or other unsafe events. Professionals may fear disciplinary measures, or believe that reporting will not result in change.[41-43] A safety culture needs to be present at all levels of the organization in order to improve quality of care.

Risk management in hospitals is crucial to improving quality and increasing patient safety.[35] Care processes should be systematically monitored and analysed to identify potential risks. This provides valuable information about the variability that occurs within care processes, and the results can then be used to find opportunities for managing and reducing risks.[18] Care bundles are frequently used as tools to continuously monitor care processes.[14,17] They monitor the performance of professionals over time for a single process, which can be helpful in tracking progress towards outcomes and in making adjustments to performance if necessary (Chapter 7). They can be used to monitor predefined outcome measures (i.e. quality indicators).[14,46] The quality indicator reflects a change that result from the implementation of the intervention. Thus, continuously monitoring the effect the care bundle has on the predefined quality indicator detects changes in a professional's performance (Chapter 8). The use of quality indicators together with quality improvement interventions has proven to be effective in improving quality of care.[47] However, general safety in hospitals cannot be improved by just one indicator for a single process. Multiple indicators should be used in combination with other approaches for monitoring safety on both hospital wards and across the organization, such as safety walks, monitoring safety at handovers, incident reporting, complaints procedure, complication registries and clinical audits.[40] Because health care practice and scientific evidence changes over time, it is important to periodically evaluate and revise the set of quality indicators used.[47,48] One realistic aspect of monitoring indicators that needs to be addressed is that it implies an administrative burden for health care providers. Even though automated electronic data extraction can help to reduce the registration workload,[47] the decision to monitor indicators should be worth the effort.

Improving patient safety also involves being fully committed to the quality and safety of the entire organization. The concept of high reliability is often mentioned as facilitating risk management in hospitals and changing hospital systems and processes to achieve high quality of care. It is designed for those organizations that deal with dynamic, variable and unexpected circumstances, and has been adapted from industries outside of health care such as commercial aviation and nuclear power.[49] In organizations in these industries, humans work under hazardous and complex conditions, and safety has an extremely high priority, which results in exceptionally high levels of reliability. These high reliability organizations (HROs) are constantly searching for methods to reduce errors and harm, and are urged to cope with errors and quickly recover when things do go wrong.[49,50] Even though hospitals differ from the aviation and nuclear power industries, they can learn from how they think.[49,51] High reliability is a way of thinking about quality and safety, and a concept that helps hospitals achieve their quality and safety goals. Striving to become an HRO can be achieved by creating a safety culture and by optimizing processes that are effective at reducing system errors, and can effectively

anticipate when errors will occur.[49] Transforming hospitals into HROs is impossible unless leaders at all organizational levels are fully committed to achieving safe and high-quality patient care. There are five principles that guide HRO thinking, and help to focus on emergent risks and select the right set of interventions for addressing them: 1) preoccupation with failure; 2) reluctance to simplify interpretations; 3) sensitivity to operations; 4) deference to expertise; and 5) commitment to resilience.[52] Embracing the HRO approach might be challenging in hospitals, where there are cost restraints and a high turnover of team members. It will be interesting to see whether hospitals can achieve this state of high reliability, how they achieved this, and, most importantly, how they sustain this state.

Healthcare is rapidly changing in many different ways. More people live with one or more chronic disease such as kidney disease, diabetes, cardiovascular disease or cancer. Diseases that were once fatal have become more and more chronic conditions.[35] In the near future, hospitals will be focussing more on treatments and procedures requiring high levels of expertise using innovative techniques. More innovative medications, procedures, techniques, therapies have been developed and introduced leading to much shorter hospital stays. Patients will be discharged from the hospital sooner and care will be delivered in the patients homes or in centres outside the hospital. The changes in healthcare has implications for professionals as well. One interesting change is the role and tasks of physicians and nurses. This is rapidly changing since more care can be provided by specialized nurses instead of by physicians. Physicians will have a greater role in supervising and in making complex decisions.[35] These are only a few examples that indicates that healthcare is rapidly changing. Due to these changes new risks will be created. Like Vincent argues, we must expand our view on patient safety.[35] An interesting development is the approach of resilient healthcare.[53] This approach is often called the 'Safety II' approach. Safety II is not meant as a replacement of the current approach on safety rather to use complimentary.[53] From this point of view healthcare is resilient and the daily care is more often successful than that it fails. Thus, instead of focussing on the errors and the things that go wrong, the focus should be the other way around, i.e. focussing on the positive things and learn from it. This forms the basis of understanding why errors sometimes do occur in healthcare. Errors do not occur because healthcare providers react as they are told to, but they adjust to the varying circumstances to do the right thing for the patient. In the future, methods for such analyses should be more explored and investigated in different contexts.[35]

Conclusion

Over the past decades, improving patient safety in hospitals has become an extremely important issue worldwide. However, there are still significant challenges to the uptake and implementation of quality improvement interventions. To encourage this and to increase the chances of successful interventions, a tailored and often multifaceted implementation strategy is required to overcome existing barriers. Throughout the implementation process it is essential to continuously monitor and analyse data to track progress towards outcomes, and adjust the chosen strategy if necessary. As patient safety evolves over time within the context of the ongoing development of innovative techniques and increasingly complex hospital care, it will continue to receive considerable attention in the decades to come.

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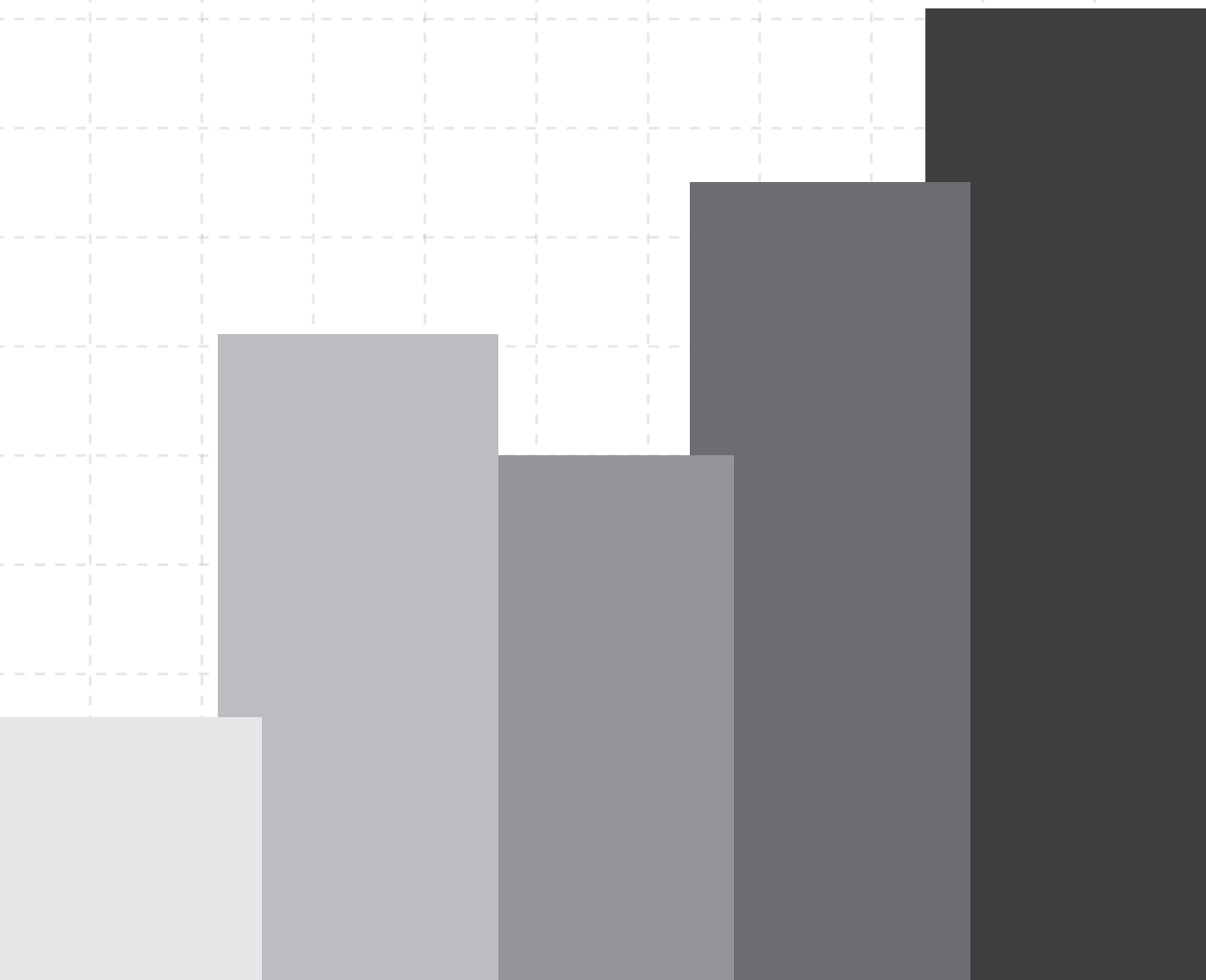

10

NEDERLANDSE SAMENVATTING EN UITDAGINGEN VOOR DE TOEKOMST

NEDERLANDSE SAMENVATTING

Het is een uitdaging om nieuwe bevindingen verkregen uit wetenschappelijk onderzoek te implementeren in de dagelijkse praktijk. Met name als het gaat om veranderingen in het menselijk gedrag, de klinische praktijk, de organisatie of in de samenwerking tussen professionals. Uit onderzoek is gebleken dat veel patiënten schade oplopen in ziekenhuizen doordat evidence-based richtlijnen niet consistent worden opgevolgd.[1,2] Meerdere studies tonen aan dat patiënten slechts de helft van de aanbevolen zorg ontvangen.[1,2] Het duurt relatief lang voordat nieuwe wetenschappelijke bevindingen worden opgenomen in klinische richtlijnen en dat deze interventies vervolgens worden uitgevoerd in de dagelijkse praktijk.[3] Dit proefschrift richt zich op de implementatie van evidence-based interventies om de patiëntveiligheid te verbeteren alsmede de kwaliteit van zorg van ernstig zieke patiënten. **Deel I** van dit proefschrift gaat in op het verbeteren van de patiëntveiligheid voor de vitaal bedreigde patiënt door de implementatie van het Spoed Interventie Systeem (SIS) op verpleegafdelingen. **Deel II** richt zich op het verbeteren van de patiëntveiligheid op de intensive care (IC) door de implementatie van evidence-based zorgbundels.

Deel I. Verbeteren van de veiligheid van de vitaal bedreigde patiënt op de verpleegafdelingen.

In **deel I** hebben wij ons gericht op de implementatie van het SIS op de verpleegafdelingen van een ziekenhuis. Een SIS is ontwikkeld om de kwaliteit van zorg te verbeteren voor vitaal bedreigde patiënten in een ziekenhuis.[4,5] Voorgaande studies laten zien dat patiënten die een ernstige gebeurtenis doormaakten, zoals een ongeplande IC opname, reanimatie of onverwacht overlijden, reeds enkele uren voorafgaand aan deze ernstige gebeurtenissen afwijkingen vertoonden in de vitale functies.[6,7] Echter, deze afwijkingen werden niet tijdig opgemerkt door verpleegkundigen of er werd niet adequaat op gehandeld.[8] Een SIS draagt zorg voor het tijdig signaleren van vitaal bedreigde patiënten door allereerst het toepassen van de Modified Early Warning Score (MEWS). De MEWS is een screeningsinstrument om vitale dreiging in een vroeg stadium te ontdekken. Wanneer een verhoogde MEWS wordt gemeten bij de patiënt en een initiële behandeling niet tijdig tot een klinische verbetering leidt, moet het Spoed Interventie Team (SIT) worden ingeschakeld.

Hoofdstuk 2 beschrijft de implementatie van de MEWS op de verpleegafdelingen van het Academisch Medisch Centrum in Amsterdam. In deze quasi-experimentele studie is het effect onderzocht van het geprotocolleerd (d.w.z. drie maal daags) meten van de MEWS versus het meten van de MEWS wanneer klinisch geïndiceerd. De studie vond plaats in de periode van september tot en met november 2011. Alle patiënten

die tenminste voor één nacht werden opgenomen op een verpleegafdeling werden geïncludeerd in deze studie. De verpleegafdelingen werden gerandomiseerd om de MEWS drie maal daags te meten of op indicatie. In totaal werden 902 patiënten geïncludeerd in deze studie. Bij deze patiënten werden 6598 sets van vitale functies geregistreerd in de patiënten dossiers. De resultaten laten zien dat de MEWS in 70% werd gemeten in de 'geprotocolleerde groep', terwijl de MEWS in 2% was gemeten in de 'indicatie-groep' (verschil: 67,9%, 95% betrouwbaarheidsinterval (BI): 66,3 tot 77,0, *P*-waarde < 0.001. Daarnaast werd in de 'geprotocolleerde-groep' de behandelend arts 90 maal opgeroepen om de patiënt te beoordelen bij een verhoogde MEWS versus negen maal in de 'indicatie-groep'. De resultaten indiceren dat het opleggen van het drie maal daags meten van de MEWS resulteert in een hogere mate van adherentie aan het SIS-protocol en in een betere detectie van afwijkingen in vitale functies, dan dat de inschatting voor het meten van de MEWS wordt overgelaten aan de verpleegkundige zelf.

In **hoofdstuk 3** zijn de zogenaamde 'false arrests' geanalyseerd om hiervan de mate van urgentie te bepalen. False arrests zijn oproepen waarvoor het reanimatieteam wordt ingeschakeld, terwijl patiënten niet daadwerkelijk een hartstilstand doormaken.[10-13] Deze verkennende studie werd uitgevoerd om een mogelijkheden te vinden voor het efficiënter inrichten van de spoedzorg om daarmee uiteindelijk kosten te kunnen besparen. In deze studie werden alle reanimatieteamoproepen voor false arrests geanalyseerd die hebben plaatsgevonden in de periode van september 2009 tot 2012. De oproepen werden geclassificeerd als 'urgent' of 'minder urgent'. De resultaten laten zien dat een aanzienlijk deel van de false arrest oproepen zijn geclassificeerd als 'minder urgent'. In deze gevallen zou een activatie van een SIT mogelijk beter geschikt en efficiënter zijn, dan de inzet van een reanimatieteam. Daarnaast zou het gebruik van de MEWS mogelijk kunnen leiden tot minder oproepen van het reanimatieteam voor false arrests, mits de MEWS op correcte wijze wordt gebruikt.

Deel II. Verbeteren van de veiligheid van patiënten op de intensive care.

In deel II wordt de ontwikkeling en implementatie beschreven van evidence-based zorgbundels. Het zorgbundel concept is ontwikkeld door het Amerikaanse 'Institute for Healthcare Improvement' (IHI).[14-16] Zorgbundels zijn ontwikkeld om de betrouwbaarheid en kwaliteit van zorg te verhogen. Een bundel bestaat uit drie tot maximaal vijf evidence-based interventies van een klinisch proces of voor een bepaalde patiëntenpopulatie. De kracht van een zorgbundel is dat de set aan evidence-based interventies in gezamenlijkheid en op uniforme wijze moeten worden uitgevoerd. Dit resulteert in betere patiënt uitkomsten dan wanneer de interventies afzonderlijk van

elkaar worden geïmplementeerd.[14-17] **Hoofdstuk 4** beschrijft een systematisch literatuur onderzoek waarin werd gezocht naar de verschillende methoden die zijn gehanteerd om zorgbundels te ontwikkelen voor het gebruik op de IC voor volwassenen. De IHI heeft het zorgbundelconcept ontwikkeld en heeft hiervoor bepaalde methoden gebruikt, zoals een systematisch literatuuronderzoek.[15,16] Echter, de methoden die de IHI heeft toegepast zijn niet altijd even geschikt voor andere ICs om een zorgbundel te ontwikkelen. Andere methoden zijn wellicht ook gepubliceerd en zouden ook nuttig en bruikbaar kunnen zijn voor het ontwikkelen van nieuwe zorgbundels. Voor deze studie werden elektronische databases doorzocht op relevante studies die zijn gepubliceerd in de periode van januari 2001 tot en met augustus 2014. Uit deze literatuurstudie zijn relevante en bruikbare methoden gevonden die toegepast kunnen worden om evidence-based zorgbundels te ontwikkelen. Deze resultaten zijn vervolgens gebruikt om een uitgebreid stroomschema op te stellen om nieuwe evidence-based zorgbundels te kunnen ontwikkelen. Dit stroomschema geeft een overzicht van alle processtappen die moeten worden doorlopen om een zorgbundel te ontwikkelen en toont per processtap de methoden die gebruikt kunnen worden.

Een zorgproces, zoals de toediening van enterale voeding, bestaat uit een serie van complexe interacties tussen artsen, verpleegkundigen, patiënten en medische interventies.[18] Het monitoren en systematisch analyseren van deze interacties kunnen de hiaten in de zorgverlening blootleggen en inzicht geven in de potentiele risico's. Inzicht verkrijgen in deze risico's is belangrijk om de juiste interventies in te zetten om daarmee de zorg te verbeteren.[18] Zorgbundels kunnen hier dus ook een belangrijke rol in spelen. Ondervoeding is een belangrijk probleem bij patiënten op een IC.[19,20] Echter, onduidelijk is in hoeverre patiënten optimaal enteraal gevoed worden op de IC van het AMC of hoe groot het probleem van ondervoeding bij het gebruik van enterale voeding daadwerkelijk is. **Hoofdstuk 5** geeft een beschrijving van de patiënten die enterale voeding kregen toegediend op de IC. Deze retrospectieve cohort studie is uitgevoerd om te onderzoeken welke patiënten een verhoogd risico hebben op een inadequate enterale voedingsinname, zodat daar gerichte interventies op ingezet kunnen worden om de zorg voor enteraal gevoede IC patiënten te verbeteren. Patiënten die zijn opgenomen op de IC in de periode van januari 2012 tot en met december 2014 werden geïncludeerd in deze studie. De ideale calorie inname was 25 Kcal per kilogram lichaamsgewicht per dag. De ideale proteïne inname werd berekend als 1,2 tot 1,5 gram per kilogram lichaamsgewicht per dag. Een multiple lineaire regressie analyse werd uitgevoerd om de factoren voor succesvolle enterale voeding te beschrijven. De resultaten laten zien dat het merendeel van de patiënten dagelijks een acceptabele hoeveelheid enterale voeding toegediend kregen. Echter, een aanzienlijk deel van de IC patiënten blijkt niet de dagelijkse aanbevolen hoeveelheid calorieën of proteïnen

via enterale toediening te ontvangen. Bij deze patiënten kan de voedingsinname geoptimaliseerd worden. Dit pleit voor de inzet van een zorgbundel voor het toedienen van enterale voeding. De zorgbundel kan worden gebruikt om de adherentie aan de voedingsrichtlijn te verhogen en daarmee de enterale voedingsinname te verbeteren. **Hoofdstuk 6** toont de resultaten van een systematische literatuur review. Deze studie is uitgevoerd om vast te stellen welke strategieën zijn beschreven in de literatuur om zorgbundels te implementeren en daarnaast om te bepalen welke van deze strategieën effectief blijken te zijn. De elektronische databases PubMed, Ovid Embase, CINAHL en CENTRAL, zijn doorgenomen om relevante studies te selecteren voor deze literatuur studie. De resultaten laten zien dat educatie (86%), herinneringen (71%) en audit & feedback (A&F) (63%) de meest gebruikte strategieën zijn voor de implementatie van zorgbundels op een IC. Echter, de waarde van de gerapporteerde compliance aan een zorgbundel lijkt te worden beïnvloed door meerdere factoren. Dit komt bijvoorbeeld doordat compliance werd berekend over verschillende tijdsperioden of dat aanvullende informatie over de berekende compliance ontbrak, zoals de tellers en de noemers. Om deze redenen was het niet mogelijk om een herberekening op de compliance waarden te maken. Deze herberekening was zinvol geweest om de gerapporteerde compliance waarden te standaardiseren, zodat de verschillende studies met elkaar vergeleken konden worden. De heterogeniteit tussen de geïncludeerde studies was groot vanwege de verscheidenheid aan studie designs, het aantal elementen per zorgbundel, de soorten elementen en de wijze waarop compliance was berekend. Wegens de heterogeniteit alsmede de lage kwaliteit van de geïncludeerde studies was het niet mogelijk om conclusies te trekken over welke combinatie van strategieën het meest effectief zijn om zorgbundels te implementeren. Het is aan te bevelen dat studies over kwaliteitsverbeteringen op gestandaardiseerde wijze gerapporteerd worden om onderzoeksresultaten beter met elkaar te kunnen vergelijken.

In **hoofdstuk 7** is een zorgbundel ontwikkeld voor de toediening van rode bloedcellen bij IC patiënten. Vervolgens is in deze implementatiestudie, met een quasi-experimenteel studie design, onderzocht welke van de twee volgende A&F implementatiestrategieën het meest effectief is: 1) maandelijks leveren van A&F op teamniveau, versus 2) maandelijkse leveren van A&F op teamniveau aangevuld met tijdige A&F op individueel niveau. Tijdige A&F betekende dat A&F werd gegeven aan de verpleegkundige binnen 72 uur na iedere transfusie. Deze persoonlijke feedback werd bij voorkeur mondeling overgedragen. Indien dit niet mogelijk was werd de betreffende verpleegkundige per email geïnformeerd. De resultaten laten zien dat het geven van tijdige individuele A&F plus maandelijkse A&F op teamniveau tot aanzienlijk betere adherentie aan de transfusiebundel heeft geleid, dan wanneer enkel maandelijkse A&F op teamniveau werd gegeven. Het algemene effect op adherentie aan de transfusiebundel was

significant hoger met een OR van 4,05 (95% BI: 1,62 tot 10,08, $P < 0.001$). Dit impliceert dat wanneer de gecombineerde A&F strategie werd gehanteerd het aannemelijker was dat verpleegkundigen een hogere adherentie hadden aan de transfusiebundel dan wanneer alleen A&F op teamniveau werd gebruikt. Het verstrekken van tijdige A&F op individueel niveau is mogelijk ook effectief bij de implementatie van andere zorgbundels. Vervolgonderzoek zou zich moeten focussen op het verder verhogen van de adherentie aan de transfusiebundel en aan het behouden van het implementatie effect. Hiervoor zou een langere implementatieperiode gebruikt kunnen worden. Daarnaast zou het onderzoek zich moeten richten op het gebruik van informatie- en computertechnologie om de kosten in het toepassen van de implementatiestrategie te verminderen. **Hoofdstuk 8** beschrijft de toepassing van de transfusiebundel op het transfunderen van rode bloedcellen volgens de individueel gestelde hemoglobine (Hb) transfusietrigger. In deze studie hebben we onderzocht in hoeverre de transfusiebundel heeft geleid tot het transfunderen conform de gestelde transfusietrigger. Over het algemeen wordt een restrictief transfusiebeleid nagestreefd bij IC patiënten. Deze aanbeveling is opgenomen in de nationale en internationale transfusierichtlijnen.[21] Echter, de adherentie aan deze richtlijnen is vaak laag.[22,23] In dit onderzoek, waarbij een voor- en nameting is uitgevoerd, hebben we beoogd het werkelijke effect van de transfusiebundel te meten door per transfusie aan te geven of de beslissing tot transfusie gebaseerd was op een lagere pre-transfusie Hb waarde dan de vooraf gestelde individuele Hb drempelwaarde. De primaire uitkomstmaat was het percentage correct toegepaste transfusies. Correct toegepaste transfusies werd gedefinieerd als een transfusie conform de individueel gestelde transfusietrigger. De resultaten laten zien dat de introductie van de transfusiebundel heeft geleid tot een significante daling van het aantal onterechte transfusies. Het aantal onterechte transfusies daalde van 25% (111/439) gedurende de baseline periode tot 15% (42/280) tijdens de implementatieperiode (verschil 10%, 95% BI: -0,164 tot -0,042; $P < 0.001$). Deze daling is doorgezet tot 12% (45/370) tijdens de post-implementatieperiode. De resultaten indiceren dat het gebruik van de transfusiebundel de adherentie aan de transfusierichtlijn ondersteunt in de dagelijkse praktijk. Interessant is dat de resultaten laten zien dat de meeste transfusies restrictieve transfusietriggers hanteren zoals aanbevolen in de transfusierichtlijn.

UITDAGINGEN VOOR DE TOEKOMST

Een ziekenhuis kan worden beschouwd als een zeer complexe organisatie vanwege de diverse interacties tussen mensen (patiënten, familie, ziekenhuispersoneel), de organisatie (teams, afdelingen, ziekenhuis) en de financiële en politieke omgeving.[24] Complexiteit bestaat voornamelijk in dynamische systemen. Een IC is een voorbeeld van een dynamisch systeem vanwege de verscheidenheid in technologieën, behandelingen, medicatie, ernst van ziekte van de patiënt en de omstandigheden waarin gewerkt wordt.[18,25,26] De kans op het ontstaan van fouten is hoog in dynamische systemen. Vandaar dat patiëntveiligheid in een IC-omgeving een uitermate belangrijk onderwerp is, doch zeer complex. Patiëntveiligheid is een breed onderwerp dat zich afspeelt op verschillende organisatieniveaus. Het wordt toegepast op verschillende patiëntencategorieën en waarvoor veel verschillende technieken en interventies bestaan. Tevens wordt patiëntveiligheid beïnvloed door culturele, technische, klinische, psychologische en financiële aspecten.[27] In deze context, gekarakteriseerd door complexiteit, zijn de onderzoeken in dit proefschrift uitgevoerd.

Het is een enorme uitdaging om nieuwe evidence-based interventies succesvol te implementeren in de dagelijkse praktijk (Hoofdstuk 2 en 7). Bij iedere verandering in een organisatie zijn er verschillende factoren die de implementatie daarvan belemmeren. Cabana *et al.* heeft een systematisch literatuur onderzoek uitgevoerd waarin belemmerende factoren werden geïdentificeerd bij het naleven van klinische richtlijnen door artsen.[28] De factoren kunnen grofweg worden geclassificeerd als weerstanden met betrekking tot kennis, attitude en externe factoren, zoals patiënt-, richtlijn- of omgevingsfactoren.[28] Een succesvolle implementatie hangt samen met de bewustwording dat er voor vrijwel iedere zorgverandering belemmerende factoren aanwezig zijn en dat er zorgvuldig gezocht wordt naar gepaste interventies om deze factoren aan te pakken.[2,29,30] Voor een effectieve aanpak van een implementatietraject is het aan te bevelen om een gedegen en goed onderbouwd implementatieplan op te stellen. Dit plan moet minimaal een analyse bevatten van de doelgroep, de omgeving en van de aanwezige belemmerende factoren.[29] Deze informatie is nodig om een gepaste implementatiestrategie in te zetten voor die specifieke situatie. Een vaak toegepaste strategie om kwaliteitsverbeteringsinterventies te implementeren is audit en feedback (A&F).[31] Uit de literatuur blijkt dat A&F matig effectief is.[31] A&F lijkt het meest effectief wanneer dit wordt toegepast door een senior collega of supervisor, wanneer dit zowel schriftelijk als mondeling wordt overgedragen, wanneer de doelen meetbaar zijn of wanneer het tijdig wordt verstrekt, d.w.z. minstens een maal per maand.[31] Gegeven de heterogeniteit van de studies in uitkomst of methodologie waarin dit is afgeleid, kunnen hier echter geen harde conclusies aan worden verbonden.[31]

Er zijn diverse implementatiestrategieën die zouden kunnen worden toegepast. Reminders, A&F of educatie zijn enkele voorbeelden van strategieën die zeer frequent worden ingezet. De verschillende strategieën variëren in effectiviteit (Hoofdstuk 6).[32] Tot dusver is in de literatuur niet aangetoond welke implementatiestrategie of combinatie van strategieën het meest effectief is. De actuele status is dat iedere zorgverandering of vernieuwing maatwerk vereist, waarbij vaak meervoudige strategieën ingezet dienen te worden om alle weerstanden te overwinnen, dus om de implementatie te laten slagen. De implementatiestrategieën moeten bij voorkeur met evidence worden onderbouwd en gebaseerd zijn op een wetenschappelijke theorie.[33,34] Echter, vanwege de onzekerheid in uitkomst van iedere implementatieactiviteit, zullen de kosten en tijdsinvesteringen van de implementatie telkens opnieuw goed in ogenschouw moeten worden genomen. De additionele kosten van een meervoudige implementatiestrategie moeten worden afgewogen tegen de reële kans dat de implementatie enkel zal leiden tot een geringe verandering van het professionele gedrag.[31]

Zoals beschreven in de introductie sectie, moeten wij ons realiseren dat fouten in de zorg zullen blijven bestaan.[35,36] Echter, menselijke fouten worden niet veroorzaakt door een individu, maar ontstaan doordat er tekortkomingen zijn in het systeem of in de organisatie.[37] Om patiënten beter te beschermen tegen het ontstaan van menselijke fouten in de zorg, zullen klinische processen of werkomgevingen opnieuw ingericht moeten worden. Dit kan bijvoorbeeld worden gerealiseerd door het simplificeren of standaardiseren van zorgprocessen, het automatiseren of standaardiseren van technische (hulp)middelen of door het verminderen van het simpelweg vertrouwen op het geheugen van mensen (Hoofdstuk 2 en 7).[27,38,39] Door het gebruik van dergelijke methoden kunnen zorgprocessen worden geoptimaliseerd om betrouwbare zorg te leveren. Dit laatste houdt in dat zorgverleners klinische procedures uitvoeren volgens de richtlijnen, zoals het toepassen van handhygiëne of het tijdig starten van antibiotica bij septische patienten.[40] De toepassing van zorgbundels of instrumenten om vitale dreiging eerder te herkennen zijn voorbeelden van interventies om de adherentie aan richtlijnen te bevorderen (Hoofdstuk 2 en 7). Dergelijke kwaliteitsverbeterings-interventies zijn noodzakelijk en worden wereldwijd toegepast in ziekenhuizen. Echter, om grote verbeteringen in de kwaliteit van zorg door te voeren is meer nodig. Deze kwaliteitsverbeterings-interventies kunnen bijvoorbeeld worden toegepast in combinatie met strategieën om de veiligheidscultuur binnen de organisatie te verbeteren.

Een veiligheidscultuur wordt steeds belangrijker voor ziekenhuizen die streven naar een hoge mate van patiëntveiligheid.[41] Een veiligheidscultuur weerspiegelt de houding, waarden en normen, beleving en levensovertuiging van leidinggevenden

en medewerkers in relatie tot het nemen van risico's, naleven van regelgeving, zich uitspreken over veiligheid en waarde hechten aan risicomanagement.[42,43] De veiligheidscultuur kent sterke verschillen tussen afdelingen of groepen mensen. Iedere groep of discipline heeft zijn eigen cultuur en gebruiken.[27] Organisaties met zogenoemde 'hoog veiligheidsculturen' zijn meer bereid om gedrag te veranderen en zijn daarnaast geassocieerd met betere en meer betrouwbare zorgprocessen.[44] Pronovost *et al.* laat in zijn studie naar de implementatie van de centrale lijn bundel zien, dat het promoten van een veilige cultuur resulteert in een sterke reductie van het aantal centrale lijn infecties.[44] Echter, het verbeteren van een veiligheidscultuur op een afdeling of binnen een organisatie is niet eenvoudig. Dit kan alleen worden bewerkstelligd wanneer leiders zichtbaar bereid zijn om te veranderen en wanneer ziekenhuismedewerkers door leidinggevenden worden aangemoedigd om openlijk te spreken over veiligheidsproblemen. Het niet bereiken van een dergelijke veiligheidscultuur kan bijvoorbeeld leiden tot het niet melden van (ernstige) incidenten. Ziekenhuismedewerkers kunnen angst hebben om afgerekend te worden op de fouten die zijn gemaakt of denken dat het melden van incidenten niet leidt tot verbetering van zorg.[41-443] Een veiligheidscultuur dient op alle lagen van een organisatie aanwezig te zijn om de kwaliteit van zorg te kunnen verbeteren.

In ziekenhuizen is risicomanagement cruciaal om de kwaliteit van zorg te verbeteren en de patiëntveiligheid te verhogen.[35] Zorgprocessen dienen systematisch gemonitord en geanalyseerd te worden om potentiële risico's te signaleren. Dit geeft belangrijke informatie over de mate van variabiliteit binnen zorgprocessen. De resultaten zijn bruikbaar om vervolgens risico reducerende maatregelen in te zetten.[18] Zorgbundels worden vaak gebruikt als instrumenten om zorgprocessen continu te monitoren.[14,17] Met behulp van zorgbundels kan worden gemeten in hoeverre interventies binnen een bepaald proces al dan niet worden uitgevoerd. Met deze bevindingen kunnen de nodige aanpassingen worden gedaan om de adherentie aan de zorgbundel te verhogen (Hoofdstuk 7). Tevens kan een zorgbundel worden gebruikt om vooraf gedefinieerde kwaliteitsindicatoren te meten.[14,46] Een kwaliteitsindicator geeft een verandering weer als gevolg van de invoering van een bepaalde interventie. Door het continu monitoren van het effect van een zorgbundel op de kwaliteitsindicator, kunnen veranderingen in de uitvoering van het zorgproces worden ontdekt (Hoofdstuk 8). De inzet van kwaliteitsindicatoren in combinatie met kwaliteitsverbeteringsinterventies zijn reeds effectief gebleken om de kwaliteit van zorg te verbeteren.[47] De veiligheid in ziekenhuizen kan echter niet worden verbeterd met een kwaliteitsindicator gericht op één zorgproces. Meer indicatoren zijn nodig in combinatie met andere methoden om veiligheidsgerelateerde onderwerpen te monitoren op afdelingen of binnen de gehele organisatie. Voorbeelden van de andere methoden zijn veiligheidsvisiterondes,

overdrachten, incidentmeldingen, klachten procedures, complicatieregistraties of klinische audits. Het is belangrijk om de set van indicatoren periodiek te evalueren en zo nodig aan te passen, omdat wetenschappelijke bewijsvoering verandert over de tijd.[47,48] Een belangrijk aspect dat meegenomen dient te worden in de overweging om de kwaliteit van zorg te monitoren is de administratieve last die het met zich mee kan brengen voor zorgverleners. Ondanks dat een elektronisch patiëntendossier de registratielast kan doen verminderen, moet de keuze om indicatoren op te stellen een absolute meerwaarde hebben.[47]

Om de patiëntveiligheid te verbeteren is een volledige inzet vereist van de gehele organisatie. Om dit te bewerkstelligen wordt het concept van een 'Hoog Betrouwbare Organisatie' vaak genoemd.[49] In Engelse termen wordt dit een High Reliability Organization (HRO) genoemd. Een HRO wordt toegepast in organisaties waar fouten maken desastreuze gevolgen kunnen hebben, zoals luchtvaartorganisaties, vliegdekschepen of kerncentrales.[49] Dit zijn voorbeelden van dynamische organisaties waarin onvoorspelbare situaties voorkomen. In dergelijke organisaties werken medewerkers onder gevaarlijke of complexe omstandigheden, terwijl aan veiligheid zeer hoge prioriteit wordt gegeven. Medewerkers leren om gericht te kijken naar fouten en bijna-fouten en weten daarop te handelen. Zij zijn veerkrachtig en vasthoudend in het continu focussen op veiligheid. Hierdoor zijn medewerkers van een HRO beter in staat om te anticiperen op ongewenste en onverwachte gebeurtenissen. Daarnaast zijn zij in staat om zich sneller te herstellen wanneer fouten toch ontstaan.[49,50] Ziekenhuizen hebben overigens weinig overeenkomsten met luchtvaartorganisaties, vliegdekschepen of kerncentrales. Desalniettemin kunnen ziekenhuisorganisaties veel leren van de wijze waarop deze organisaties handelen.[49,51] HRO is een bepaalde manier van denken over kwaliteit en veiligheid en dit kan ziekenhuizen helpen om de kwaliteitsdoelen te behalen en om daarmee de patiëntveiligheid te verhogen. Een HRO kan worden nagestreefd door een veiligheidscultuur te creëren, door het aanpassen en optimaliseren van processen om systeemfouten te reduceren en door effectief te handelen wanneer fouten wel ontstaan.[49] Het transformeren van ziekenhuizen naar een HRO is niet mogelijk zonder de inzet van leidinggevenden op ieder niveau van de organisatie.[49] Een HRO kenmerkt zich door de volgende vijf principes: 1) de focus is gericht op fouten en bijna-fouten; 2) er wordt niet vereenvoudigd; 3) er wordt gecommitteerd aan het operationele proces; 4) expertise van medewerkers wordt optimaal benut; 5) medewerkers tonen veerkracht en zijn vasthoudend.[51]

Voor ziekenhuisorganisaties zal het een uitdaging zijn om de HRO principes toe te passen, vanwege bezuinigingen in kosten en de hoge personeelswisselingen. Het zou zeer interessant zijn dat wanneer ziekenhuizen HRO waardig zijn, de kennis wordt gedeeld op welke wijze zij hiertoe zijn gekomen en hoe dit resultaat kan worden behouden.

De gezondheidszorg is aan sterke verandering onderhevig en de gevolgen daarvan zullen in de nabije toekomst dan ook meer zichtbaar worden. Steeds meer mensen leven met één of meerdere chronische aandoeningen, zoals nierziekten, diabetes mellitus, cardiovasculaire aandoeningen of kanker. Aandoeningen of ziekten die voorheen dodelijk waren, worden nu meer van chronische aard.[35] In de nabije toekomst zullen ziekenhuizen zich steeds meer focussen op behandelingen en procedures die een hoge mate van expertise vereisen waarbij innovatieve technieken worden gebruikt. Daarnaast zal er een toename zijn in innovatieve ontwikkelingen op het gebied van medicatie, technieken en therapieën, met als gevolg dat de opnameduur van patiënten in ziekenhuizen drastisch afneemt. Patiënten worden sneller ontslagen, zodat de zorg wordt overgenomen door extramurale zorgcentra.[35]Deze veranderingen zullen grote implicaties hebben voor ziekenhuismedewerkers. Een interessante ontwikkeling is de veranderende rol en taak van artsen en verpleegkundigen. Er is een taakverschuiving gaande van arts naar verpleegkundige. Voornamelijk gespecialiseerd verpleegkundigen nemen daarbij steeds meer taken over van de arts. Artsen vervullen steeds meer de rol van supervisor. Daarbij gaan zij zich steeds meer richten op complexe zorg en besluitvormingen.[35] Dit zijn maar enkele voorbeelden om aan te geven dat de gezondheidszorg aan het veranderen is. Het geeft echter wel weer dat door deze veranderingen nieuwe risico's gecreëerd worden. Zoals Vincent aangeeft: 'wij moeten onze kijk op patiëntveiligheid verbreden'.[35] Een interessante ontwikkeling daarbij is de benadering van 'resilient gezondheidszorg'.[53] De Nederlandse vertaling van resilient is veerkracht. Deze benadering wordt ook vaak 'Safety II' genoemd. Safety II is bedoeld als aanvulling op de huidige benadering van patiëntveiligheid. De huidige focus ligt op het leren van fouten. Daarentegen gaat Safety II in op dat er in de gezondheidszorg juist heel veel goed gaat in plaats van fout.[53] Dus in plaats van de nadruk te leggen op de fouten die worden gemaakt, richt Safety II zich juist op het positieve en de dingen die wel goed gaan om daar vervolgens van te leren. Dit vormt de basis van het begrijpen waarom fouten soms ontstaan in de zorg. Fouten in de zorg ontstaan niet omdat zorgmedewerkers handelen zoals dat aan hen is opgelegd, maar zij bezitten het vermogen om zich aan te passen aan de steeds wisselende omstandigheden in de zorg, om daarmee de juiste zorg te leveren aan de patiënt. In de nabije toekomst zal deze benadering meer moeten worden geëxploreerd en worden onderzocht in verschillende settingen.[35]

Conclusie

De afgelopen decennia is het verbeteren van de patiëntveiligheid wereldwijd een zeer belangrijk thema geworden in ziekenhuizen. Desalniettemin is de uitdaging groot om interventies te implementeren die in de dagelijkse praktijk leiden tot kwaliteitsverbetering. Vaak zijn er factoren aanwezig die de beoogde verandering belemmeren en die zijn zelden identiek. Om die reden vereist implementatie van kwaliteitsverbeteringsinterventies vrijwel altijd maatwerk, waarbij steeds opnieuw gezocht moet worden naar een passende implementatiestrategie of combinatie van strategieën om de implementatie te laten slagen. Het is belangrijk om gedurende de implementatieperiode data continu te monitoren en te analyseren om de voortgang te volgen en zo nodig de ingezette implementatiestrategieën tijdig aan te passen. Patiëntveiligheid groeit mee met de sterke ontwikkelingen in innovatieve technieken en de toenemende complexiteit in de ziekenhuiszorg. Voor de komende decennia dient het verbeteren van de patiëntveiligheid daarom continue aandacht te blijven krijgen.

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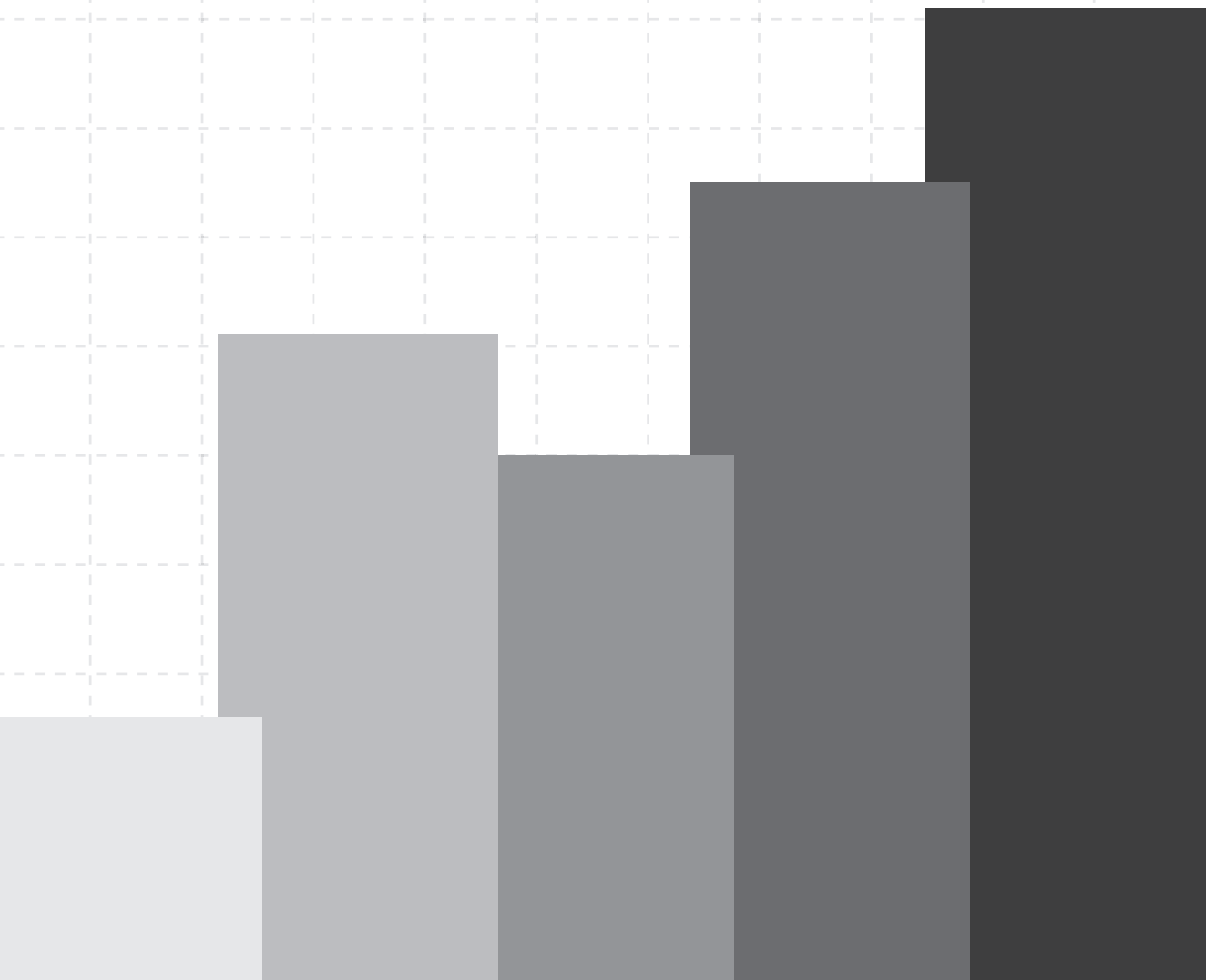

APPENDICES

CURRICULUM VITAE

Maria Johanna (roepnaam: Marjon) Borgert is geboren op 12 februari 1981 te Gramsbergen. In 1999 behaalde zij haar HAVO diploma aan het Vechtdal College te Hardenberg. Daarna startte zij met de opleiding HBO-Verpleegkunde aan de Hanzehogeschool te Groningen. Na afronding van deze studie in 2003 is zij gestart met de opleiding Gezondheidswetenschappen aan de universiteit van Maastricht met als afstudeerrichting Zorgwetenschappen. Naast deze studie heeft zij gewerkt bij de medische dienst van diverse penitentiaire inrichtingen in Groningen, Friesland en Drenthe. Na afronding van de studie Gezondheidswetenschappen in 2007 is zij haar carrière begonnen bij GGD Hollands Midden te Gouda in de functie van infectieziekteverpleegkundige. In 2011 werd zij aangenomen in het Academisch Medisch Centrum (AMC) te Amsterdam op de afdeling Kwaliteit en Procesinnovatie als junior onderzoeker voor de implementatie van het Spoed Interventie Systeem. In 2013 werd haar de mogelijkheid geboden om het onderzoek voort te zetten in een promotietraject op de intensive care van het AMC. Dit heeft geleid tot dit proefschrift. Momenteel is zij werkzaam als stafadviseur Kwaliteit voor de divisie in- en uitwendige specialismen in het AMC.

PHD PORTFOLIO

Name:	M.J. Borgert
PhD period:	2013-2017
PhD supervisor:	Prof. dr. M.B. Vroom
PhD co-supervisors:	dr. D.A. Dongelmans dr. A. Goossens

PHD TRAINING	**Year**	**Workload (ECTS)**
AMC World of Science	2013	0.7
Practical Biostatistics	2013	1.1
Clinical Data Management	2013	0.8
Scientific Writing in English for publication	2013	1.5
Computing in R	2013	0.4
Systematic Reviews	2014	0.3
Course Spoken English	2014	0.8
Clinical Epidemiology	2014	0.6
Course EndNote	2014	0.1
Advanced Topics in Biostatistics	2015	2.1

ORAL PRESENTATION

Care Bundles. Development and implementation of the transfusion bundle. *6th EfCCNa Congress 2015. Expanding Horizons of Critical Care Nursing in Europe. Valencia, Spain.*	2015	0.5

POSTER PRESENTATIONS

Measurement of the Modified Early Warning Score three times daily results in enhanced implementation of a Rapid Response System. *6th EfCCNa CONGRESS 2015. Expanding Horizons of Critical Care Nursing in Europe. Valencia, Spain.*	2015	0.5

POSTER PRESENTATIONS	Year	Workload (ECTS)
Personal feedback significantly improves compliance rates. Effects of team versus personal feedback when implementing the transfusion bundle - a comparative study. *International Forum on Quality and Safety in Health Care, 21 - 24th London 2015.*	2015	0.5
INTERNATIONAL CONFERENCES		
6th EfCCNa Congress 2015. Expanding Horizons of Critical Care Nursing in Europe. Valencia, Spain.	2015	0.75
SYMPOSIA		
Symposium incidents in patient care. AMC, Amsterdam, the Netherlands.	2015	0.25
Symposium incidents in patient care. AMC, Amsterdam, the Netherlands.	2016	0.25
Research symposium. Is there a future without null hypothesis significance testing? Vrije Universiteit Amsterdam, the Netherlands.	2017	0.25
OTHER		
Journal club and Research Meetings	2012-2013	1.0
LECTURING		
Education for nurses – Internal medicine	2011-2013	1.0
Lecture on patient safety and the Rapid Response System	2013	0.25

CONTRIBUTION OF AUTHORS

Chapter 2. Ludikhuize J, Borgert MJ, Binnekade JM, Subbe C, Dongelmans DA, Goossens A. Standardized measurement of the Modified Early Warning Score results in enhanced implementation of a Rapid Response System: a quasi-experimental study. Resuscitation. 2014;85:676-682. JL and AG were responsible for conceptualization and design of the study. JL, MB, JB, AG were responsible for the conduct of the study, the statistical analysis, interpretation of the data. JL, MB were responsible for drafting and the revision of the manuscript JB, CS, DD, AG contributed to the revision of the manuscript.

Chapter 3. Borgert MJ, Goossens A, Adams R, Binnekade JM, Dongelmans DA. Emergency care within hospitals: can it be done more efficiently? British Journal of Nursing 2015:820-824. MB, DD were responsible for conceptualization and design of the study. MB, JB, RA, DA were responsible for the conduct of the study, the statistical analysis, interpretation of the data. MB was responsible for drafting the manuscript. All authors contributed to the revision of the manuscript.

Chapter 4. Borgert MJ, Binnekade JM, Paulus F, Goossens A, Dongelmans DA. A flowchart for building evidence-based care bundles in intensive care: based on a systematic review. Int J Qual Health Care 2017;1;29:163-175. MB, JB, DA, FP were responsible for conceptualization and design of the study. MB, JB, DA, FP were responsible for the conduct of the study, the statistical analysis, interpretation of the data. MB, JB, DA were responsible for drafting and the revision of the manuscript. FP, AG contributed to the revision of the manuscript.

Chapter 5. Identifying potential risk factors in the delivery of enteral nutrition in critically ill patients -arguments for introducing a nutritional care bundle. Borgert M, Binnekade JM, Tepaske R, Paulus F, Vroom MB, Goossens A, Dongelmans DA. *Submitted.* MB, JB, DA were responsible for conceptualization and design of the study, the statistical analysis, interpretation of the data, drafting and the revision of the manuscript. FP, RT, AG, MB contributed to the revision of the manuscript.

Chapter 6. Borgert MJ, Goossens A, Dongelmans DA. What are effective strategies for the implementation of care bundles on ICUs: a systematic review. Implementation Science 2015;10:119. MB was responsible for conceptualization and design of the study, the statistical analysis, interpretation of the data, drafting and the revision of the manuscript. AG, DA were responsible for conceptualization and design of the study interpretation of the data, and revision of the manuscript.

Chapter 7. Borgert MJ, Binnekade JM, Paulus F, Goossens A, Vroom MB, Dongelmans DA. Timely individual audit and feedback significantly improves transfusion bundle compliance - a comparative study. Int J Qual Health Care 2016;28:601-607. MB, JB, DA, FP, AG were responsible for conceptualization and design of the study, the conduct of the study, JB, MB were responsible for the statistical analysis and interpretation of the data. MB, JB, DA were responsible for drafting and the revision of the manuscript. FP, AG, MB contributed to the revision of the manuscript.

Chapter 8. Borgert MJ, Binnekade JM, Paulus F, Vroom MB, Vlaar APJ, Goossens A, Dongelmans DA. Implementation of a transfusion bundle reduces inappropriate red blood cell transfusions in intensive care - a before and after study. Transfus Med. 2016;26:432-439. MB, JB, DA, FP were responsible for conceptualization and design of the study. JB, MB were responsible for the statistical analysis and interpretation of the data. MB, JB, DA were responsible for drafting and the revision of the manuscript. FP, AV, AG, MB contributed to the revision of the manuscript.

PUBLICATIONS

International publications

Laan BJ, Spijkerman IJ, Godfried MH, Pasmooij BC, Maaskant JM, Borgert MJ, Opmeer BC, Vos MC, Geerlings SE. De-implementation strategy to Reduce the Inappropriate use of urinary and intravenous CATheters: study protocol for the RICAT-study. *BMC Infect Dis.* 2017;17:53.

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DANKWOORD

Het is gelukt! Jarenlang heb ik de confronterende vraag 'wanneer ga je promoveren?' proberen te vermijden of gepareerd met verbloemende antwoorden. Maar nu kan ik opgelucht zeggen: '3 november'. Graag wil ik iedereen bedanken die heeft bijgedragen aan de totstandkoming van dit proefschrift en een aantal mensen in het bijzonder.

Allereerst wil ik bedanken mijn promotor prof. dr. M.B. Vroom (Margreeth), copromotor dr. D.A. Dongelmans (Dave) en copromotor dr. A. Goossens (Astrid).

Beste Margreeth, graag wil ik je heel hartelijk danken voor de mogelijkheden die je mij hebt geboden om dit promotietraject te mogen uitvoeren. Zeker de afgelopen maanden kon ik altijd bij je terecht met vragen of andere regelzaken, ondanks je enorm volle agenda.

Beste Dave, jij hebt mij de kans geboden om onderzoek te doen op de IC. Hier ben ik je dan ook erg dankbaar voor. Ik wil je hierbij ook bedanken voor je eindeloze geduld, betrokkenheid en voor de vele leerzame discussies over de onderzoeken, strategiebepalingen of kwaliteit gerelateerde zaken. En niet te vergeten voor het feit dat je echt altijd bereikbaar was voor overleg. Menig vakantie, congres, bespreking, dienst, compensatie, diner, familiebezoek (en ga zo maar door) heb ik dan ook verstoord, omdat ik dan toevallig nèt weer die ene vraag had die niet kon wachten. Ik heb al deze jaren erg prettig en met veel plezier met je samengewerkt. Ook hoop ik dat wij in de toekomst samen mogen blijven werken aan andere kwaliteitsverbeteringsinitiatieven in het AMC.

Beste Astrid, ik ben je nog steeds enorm dankbaar dat jij mij hebt aangenomen in het AMC. Ik had toen niet durven dromen dat ik nu hier zou staan! Dit heb ik mede aan jou te danken en ik ben je daar dan ook ontzettend dankbaar voor! Jij bent een erg fijn en open persoon. Het was dan ook erg plezierig om met jou samen te werken. Ik heb erg veel van jou geleerd, met name van jouw methodologische kennis en van je altijd kritische vragen. Ik heb enorm veel bewondering voor hoe jij alle ballen in de lucht houdt, met een fulltime baan, opleiding, groot gezin, een verbouwing, bedrijf en ga zo maar door. Multitasking bestaat dus wel.

Geachte leden van de promotiecommissie, prof. dr. J.A. Romijn, prof. dr. D.A. Legemate, prof. dr. D. van Dijk, dr. M.C. de Bruijne, prof. dr. N.P. Juffermans, prof. dr. B. Preckel. Ik wil u hartelijk danken voor de inhoudelijke beoordeling van mijn proefschrift en uw bereidheid hierover met mij van gedachten te wisselen tijdens de openbare verdediging.

Beste Jan en Frederique, wat was het fijn samenwerken met jullie! Ik mis jullie dan ook nog steeds. Jan, je altijd kritische blik, je enorme kennis over onderzoek en statistiek en je creatieve geest, leidden altijd weer tot nieuwe inzichten of grootse plannen. De discussies die volgden waren voor mij erg leerzaam en waardevol. Ik ben je dan ook erg dankbaar dat wij zoveel onderzoek samen hebben mogen uitvoeren. Jij begreep als geen ander hoe blij ik was als een 'R-code' toch werkte en ik was stiekem zó blij als jij jouw ingewikkelde code weer met mij wilde delen. Ik hoop dat ik in de toekomst nog meer van je mag leren. Frederique, ik heb het woord 'multitasking' al eerder genoemd, maar dit is ook zeker op jou van toepassing. Ik bewonder het enorm hoe jij je enerverende onderzoeks- en kwaliteitsbaan samen met de intensieve opleiding combineert met je drukke gezinsleven. Jij vervult hierin absoluut een voorbeeldrol voor mij. Op zowel onderzoeks- als kwaliteitsgebied heb ik veel van jou geleerd. Ontzettend veel dank daarvoor. En natuurlijk ook voor de nodige gesprekken en gezelligheid op de vrijdagen. Ik hoop in de toekomst nog vaak met je samen te mogen werken.

Mijn lieve paranimfen en allerliefste nichtjes Mirjam en Maartje. Wat vind ik het bijzonder dat jullie op deze dag aan mijn zijde willen staan. Ik ken jullie natuurlijk al zo ontzettend lang en daarnaast begrijpen jullie het ziekenhuis- en onderzoekswereldje als geen ander. Ontzettend bedankt voor jullie oprechte interesse, vertrouwen en steun de afgelopen jaren en natuurlijk ook voor de nodige afleiding in de vorm van gezellige borrels en etentjes.

Graag wil ik alle verpleegkundigen en artsen uit het AMC bedanken en met name de IC verpleegkundigen en IC staf. Zonder jullie hulp had ik dit natuurlijk nooit kunnen doen. In het bijzonder wil ik Mark en Rob bedanken. Jullie hulp bij verschillende studies was onmisbaar. Erica, veel dank voor alle hulp die je mij hebt geboden. Voor vragen kon ik altijd bij jou terecht. Natuurlijk wil ik ook alle collega's van de IC-onderzoeksgroep bedanken, in het bijzonder Sophia, Gerie, Roosmarijn, Marleen, Esther, Laura, Fabiënne, Anna-Linda, Maike, Marjolein, Margit, Hemmik, Frank, Matt, Rianne, Tineke en Annelou.

En natuurlijk Jeroen. Ook mede dankzij jou ben ik in het AMC terecht gekomen. Daar ben ik je nog steeds dankbaar voor. En door jou ben ik nòg enthousiaster geworden over onderzoek, gek genoeg;) Want wat een hectisch en intensief eerste jaar was het! Dat was een goede introductie in de onderzoekswereld. Ik heb er bewondering voor hoe hard je hebt gewerkt en hoe ver je inmiddels al bent gekomen.

Alle oud-collega's/onderzoekers bij KPI, in het bijzonder Linda, Heleen, Ronald, Ferry, Stephan, Delphine, Aleida, Hannah, Agnès, Marjan, Jolanda, Patty, Sjaak, Henk, Niki, Jan, Hester, Dirk, Anne, Catharina, Fleur, Katrien. Ik heb altijd met veel plezier met jullie samengewerkt en dank voor de gezellige lunches, taartmomenten, borrels en fanatieke hardloopwedstrijden.

Kamergenoten van F5-151: niet veel mensen zouden het gezamenlijk zo goed met elkaar uit kunnen houden in zo'n kleine ruimte, maar dat doen wij toch goed. Ik ben erg blij met jullie als collega's. Ik hoop nog lang met jullie samen te mogen werken.

Lieve vrienden en vriendinnen, promoveren en vrije tijd vond ik lastig te combineren. De afgelopen jaren heb ik onze contacten dan ook, tegen mijn principes in, meer verwaarloosd dan dat ik wilde. Toch heb ik altijd genoten van de gezellige lunches, etentjes, borrels en weekendjes weg. Ik hoop dat er straks weer vele gezellige momenten gaan volgen.

Lieve oom Koop en tante Truus, toen ik aan dit traject begon had ik het dankwoord aan jullie gericht al in mijn hoofd. Ik had alleen nooit kunnen bedenken dat jullie beiden deze dag niet meer mee zouden maken. Toch wil ik nog het volgende zeggen: enorm veel dank voor alles wat jullie voor mij (en ons) hebben gedaan en voor jullie onvoorwaardelijke steun en vertrouwen in mij. Jullie zijn enorm belangrijk voor mij en zullen dat ook altijd blijven. Lieve Jan, Joke, Konnie, Richard, Aart, Marianne en kids, jullie zijn heel bijzonder voor mij.

Lieve Wim en Anneke, een betere schoonfamilie had ik mij niet kunnen wensen. Redders in nood als het ging om oppas en daarnaast de gezellige etentjes en borrels als zeer welkome afleiding. Ontzettend veel dank voor alles wat jullie voor mij en voor ons hebben gedaan de afgelopen jaren.

Lieve Jelleke, Dennis, Josephine en Philippe, dank voor jullie steun en betrokkenheid, maar zeker ook voor de gezellige uitjes tussendoor!

Lieve pap en mam, hoe ouder ik word, hoe meer bewondering ik voor jullie krijg. Ik heb dan ook ontzettend veel waardering voor hoe jullie ons als gezin hebben op laten groeien. Erg veel dank voor het vertrouwen dat jullie mij hebben gegeven en dat jullie er altijd voor ons zijn.

Lieve Jan & Lianne, Elsbeth & Arjen, Wichor & Saskia en alle neefjes en nichtjes, hierbij wil ik jullie bedanken voor jullie support in welke vorm dan ook. Van de gezelligheid tijdens wintersport tot aan het mij ontzien van het 'kerst-koken' als ik daar weer eens geen tijd voor had.

Maar boven alles en iedereen:

Lieve Stijn, jij bent waar het leven echt om draait! Vanaf het begin af aan heb jij je al voorbeeldig gedragen. Tot op de dag van vandaag heb ik dan ook dankbaar gebruik gemaakt van je vele en lange slaapjes. Dat hoeft vanaf nu niet meer, we gaan alleen nog maar leuke dingen doen.

Lieve Hans, ik weet dat ik de afgelopen jaren ontzettend veel van je heb gevraagd. Geen vakantie zonder laptop en werk had altijd prioriteit. Daar gaat vanaf nu hopelijk verandering in komen. Ontzettend veel dank voor je onvoorwaardelijke steun, je geduld en vooral voor je dosis humor op de momenten dat ik dat nodig had. Vanaf nu gaan we weer samen mooie dingen beleven.