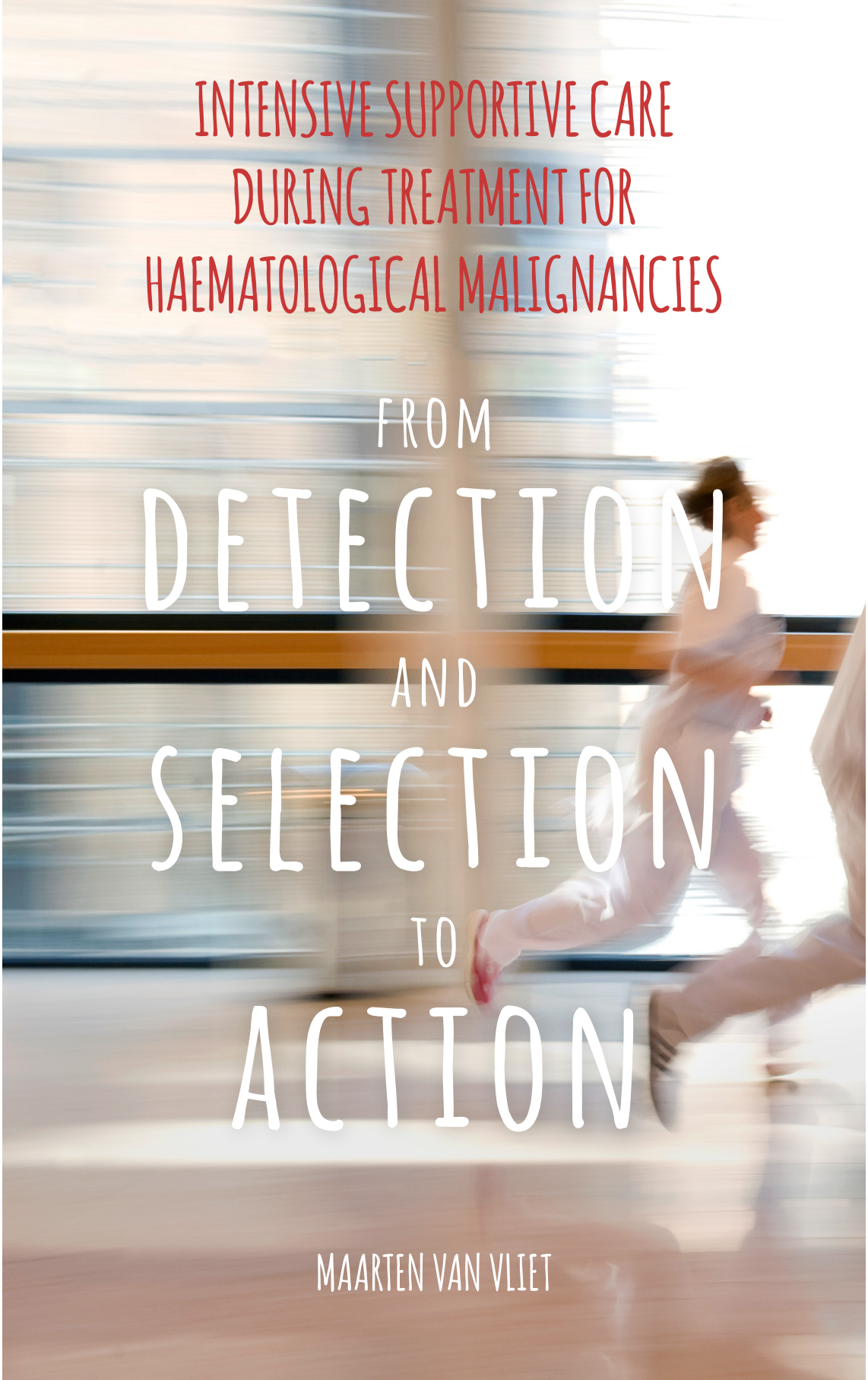
INTENSIVE SUPPORTIVE CARE
DURING TREATMENT FOR
HAEMATOLOGICAL MALIGNANCIES
FROM
DETECTION
AND
SELECTION
TO
ACTION
MAARTEN VAN VLIET

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Prof. dr. W.R. Gerritsen

'Death is not the enemy but occasionally needs help with timing'

Peter's Laws for the Navigation of Life

CONTENTS

1

General introduction and outline of the thesis

BACKGROUND

Haematological diseases account for approximately 8% of all malignant tumours that are diagnosed each year in the Netherlands. Between 2006 and 2011 the number of new adult patients with haematological malignancies increased from 7,000 to 8,200 per year. Most of these patients were aged between 60 and 75 years [1].

Haematological malignancies originate in the bone marrow and lymph nodes and include leukaemia, lymphoma and myeloma. Mature B-cell malignancies affect by far the largest group of patients, with non-Hodgkin lymphoma being the most common, followed by multiple myeloma and chronic lymphocytic leukaemia [1]. Just fifty years ago there was no cure for disseminated malignant disease. The first successes for chemotherapy were made in the 1960s and further escalation of the dosage and intensity of the cytostatic drugs led to better results. In fact, chemotherapy is still the most important modality for treating haematological cancers.

TREATMENT OF HAEMATOLOGICAL MALIGNANCIES

Several cycles of treatment with chemotherapy are necessary to obtain remission from haematological malignancies as only a certain proportion of cancer cells will be killed with each successive cycle. The first cycle of treatment of acute myeloid leukaemia is referred to as remission-induction therapy and aims to destroy leukaemic cells. As remission-induction seldom destroys all the leukaemic cells, consolidation treatment is necessary to reduce the risk of the disease recurring.

Once remission is achieved, haematopoietic stem cell transplantation (HSCT) is frequently the way to achieve the best long-term outcome. This HSCT requires a conditioning regimen consisting of high doses of chemotherapy, with or without total body irradiation (TBI), to eliminate residual bone marrow stem cells. This regimen is then followed by either an allogeneic (from a related or unrelated donor) or autologous (patient's own) stem cell transplant to restore blood stem cell production and immune defences.

Allogeneic HSCT is highly effective, resulting in increased definitive cure rates and extended disease-free survival in various high-risk haematological diseases [2]. Allogeneic HSCT relies on immune-mediated effects to control the underlying malignant disease. The rationale for using immunotherapy to prevent and/or treat the re-emergence of malignancy is based upon the observations that graft-versus-tumour (GVT) effect plays a major role in reducing the risk of relapse following an allogeneic HSCT. The importance of a graft-versus-tumour effect has encouraged the use of various strategies which optimise an immunologically-mediated anti tumour effect [3].

CHEMOTHERAPY-INDUCED TOXICITY

The efficacy of chemotherapy comes at a price. Several side-effects are known and can be as severe and life-threatening as the haematological disease itself.

— *Haematological toxicity*

Administration of chemotherapy is associated with haematological toxicity such as anaemia, leukopenia and thrombocytopenia. In addition, the cytotoxic drugs suppress not only the haematopoiesis system, but impair other host defences as well. This can limit the amount of chemotherapy that can be tolerated and may result in necessary dose reductions or even postpone further therapy, thereby compromising patient outcome.

Neutrophils are white blood cells that play a crucial role in the killing of micro-organisms. A low neutrophil count, called neutropenia, is defined by absolute neutrophil count (ANC) as being mild (ANC = 1.0-1.5x10^9/L), moderate (ANC = 0.5-1.0x10^9/L) or severe (ANC <0.5x10^9/L) and is the most serious haematological toxicity as it increases the risk of life-threatening infections. Neutropenia blunts the inflammatory response to nascent infections, allowing bacterial multiplication and tissue invasion. The risk of infection also corresponds with the depth and duration of neutropenia [4].

Because neutropenia attenuates most of the signs and symptoms of infection, patients with neutropenia often present with fever as the only sign of infection. Fever that develops during neutropenia is referred to as 'febrile neutropenia' (FN), and requires prompt treatment with broad-spectrum antibiotics and hospitalization, because the risk of death from rapidly spreading uncontrolled infection is high. The definition of febrile neutropenia varies, but is generally accepted as the presence of fever during severe neutropenia.

— *Mucosal barrier injury*

The mucosal barriers of the gut and lung are also injured by high-dose chemotherapy. The mucous membranes in the human body form a natural barrier that protects the body against the penetration of harmful substances as well as bacteria and fungi. Mucosal damage caused by chemotherapy or radiation is visible only in the mouth, but actually extends along the whole gastro-intestinal tract. Patients undergoing a myeloablative stem cell transplantation are particular vulnerable to mucosal damage because their conditioning consists of high-dose chemotherapy, sometimes in combination with total body irradiation.

Chemotherapeutic drugs and irradiation activate the important common transcription factor: nuclear factor-kappaB (NF-kB), found in epithelial and endothelial cells. Apart from an infection, this factor also initiates the production and release of pro-inflammatory

cytokines and chemokines. The mucosa may be damaged or ulcerated to such extent that bacteria and fungi can no longer be prevented from entering the bloodstream, which can lead to life-threatening infections. The degree of mucosal damage after intensive chemotherapy is mainly determined by the inflammatory response in general and that of cells of the intestinal mucosa in particular. The peak of mucosal damage typically coincides with the nadir of neutropenia both jeopardizing the patient at the same time. The tissue damage inflicted by cytotoxic therapy contributes to uncontrolled inflammation increasing the risk for critical illness which cannot be prevented by antimicrobial therapy. The net result is fever of unknown origin accompanying mucositis and elevated C-reactive protein (CRP) levels [5,6] (figure 1).

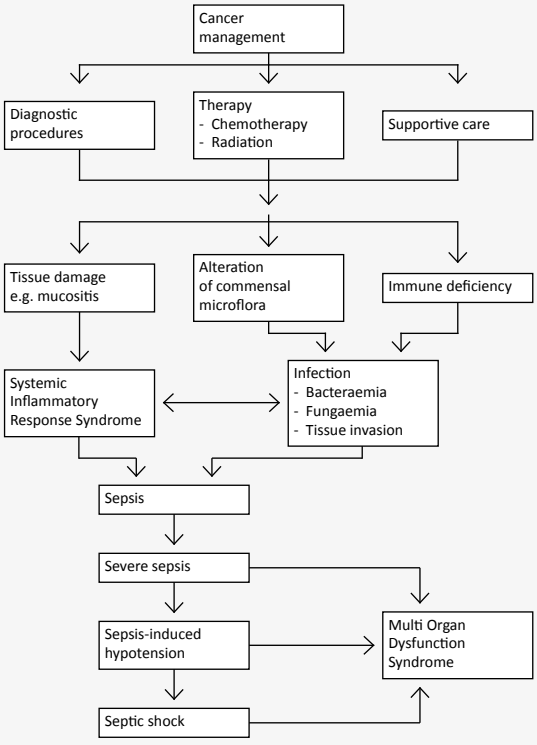

Figure 1 From cancer to critical illness (partly adapted from Viscoli et al. [7])

NEUTROPENIC FEVER: INFLAMMATION OR INFECTION?

Fever occurs when pyrogenic factors (exogenous or endogenous toxins, such as cell wall components of bacteria) induce the white blood cells to release pyrogenic cytokines (such as interleukin 1 and 6, Tumour Necrosis Factor and Interferon). These cytokines stimulate the

hypothalamus to the release of prostaglandin E2 through which the temperature set-point of the hypothalamus increases. In response, the body will have an increased heat production and heat retention resulting in an elevated core temperature. The hypothalamus is the thermoregulation centre of the body and is innervated by peripheral nerves that communicate with heat and cold receptors. In addition, it registers the core body temperature by measuring the temperature of the blood. These two signals are integrated in order to maintain a normal temperature and the body is able to provide additional warmth by shivering and increasing metabolic activity and vasoconstriction or lose heat by vasodilation and sweating when necessary.

In fact, only 30-50% of the febrile episodes in patients treated with high dose chemotherapy can be explained by proven infections, mostly bacteraemia, with the majority remaining unexplained [8]. Unexplained (culture-negative) fever is also often referred to as 'fever of unknown origin' and may be well related to chemotherapy-induced mucositis [5]. Fever can also develop from non-infectious causes including drug-induced side effects and transfusion reactions.

TREATMENT-INDUCED TOXICITY LEADING TO INFLAMMATION

Cancer and its therapy perturb a wide range of healthy tissues including both the innate and adaptive immune system increasing the risk of potentially dangerous infections that can result in critical illness. The barrier function of the oral and intestinal mucosa is extremely effective, especially when one realizes that the human body hosts more than 10^{14} micro-organisms. This symbiosis is normally beneficial, but it requires strict control by the immune system. Innate immunity plays a crucial role in maintaining this delicate homeostasis. Important elements of the innate immune system that play a crucial role in initiating inflammation are the pattern recognition receptors (PRR) such as the Toll-like, Nod-like and C-type lectin receptors that are involved in the recognition of pathogen-associated molecular patterns (PAMP's) and danger-associated molecular patterns (DAMP's) [9]. PRR's are expressed on epithelial cells, endothelial cells and immune cells, mainly antigen presenting cells such as macrophages and dendritic cells. When the interaction of host and microbes dysfunctions in the presence of tissue damage the PAMP's and DAMP's contribute to the development of uncontrolled inflammation. Chemotherapy-induced disruption of the mucosal innate immunity also plays a major role in the development of clinical inflammation manifested in mucositis and Graft-versus-Host disease [10, 11].

TREATMENT TOXICITY LEADING TO INFECTION

Microorganisms that may cause infection of patients with cancer include bacteria, viruses, fungi and protozoa. Importantly, infections by microorganisms with low virulence can result in significant morbidity and mortality in immunocompromised patients with cancer [12].

Clinically documented infection (CDI) involves a site of infection identified either by physical examination or by imaging, but without a potential pathogen being detected. Microbiologically documented infection (MDI) indicates that an opportunistic pathogen has been identified by cultures, microscopy or indirectly by the detection of antigens or nucleic acids. Fever of unknown origin (FUO) indicates fever without any documentation of either a clinically or microbiologically documented infection [13].

Since the 1990s, Gram-positive bacteria outnumber Gram-negative organisms as infectious pathogens, at least in part due to the widespread use of intravascular catheters. Fungi, mainly *Candida* species and *Aspergillus fumigatus* also cause infections in neutropenic patients, especially in those who are receiving broad-spectrum antibiotics. Other risk factors for fungal infections include prior use of steroids, advanced age, intensity of chemotherapy and the presence of an indwelling central venous catheter (figure 2) [14]. The six week mortality rate associated with fungal infections is about 1 out of 5 for HSCT recipients [15] and about 1 out of 4 for patients with acute myeloid leukaemia [16]. The use of central vascular catheters (CVC) is an important risk factor for infections due to coagulase-negative staphylococci, S*taphylococcus aureus*, aerobic Gram-negative bacilli and *Candida albicans* [14]. Besides infection, the use of CVCs can also be complicated by thrombosis, that, in turn, can become infected. Septic thrombosis is a serious condition frequently associated with persistent bacteraemia or fungaemia.

TREATMENT TOXICITY MIGHT ESCALATE FROM SIRS TO SEVERE SEPSIS AND SEPTIC SHOCK

The most severe clinical manifestation of infection is sepsis, defined as the systemic inflammatory response of the host to invading pathogens. Patients with cancer are ten times more likely to develop sepsis than those who do not have cancer. Cancer is also associated with a 30% higher risk for death from sepsis and, moreover, sepsis is responsible for approximately one in ten of all deaths due to cancer [17]. Haematological malignancies are more frequently associated with severe sepsis than are solid tumours and show higher mortality rates [18]. Neutropenic patients are unable to mount robust inflammatory responses so serious infection may be present with minimal symptoms and signs. Consequently, fever is often the first, and frequently the only, sign of infection [19] and therefore, fever is a critical factor in recognizing the systemic inflammatory response syndrome (SIRS), a complex of symptoms indicating systemic activation of the immune system which may result in sepsis, depending on the presence or absence of infection [20].

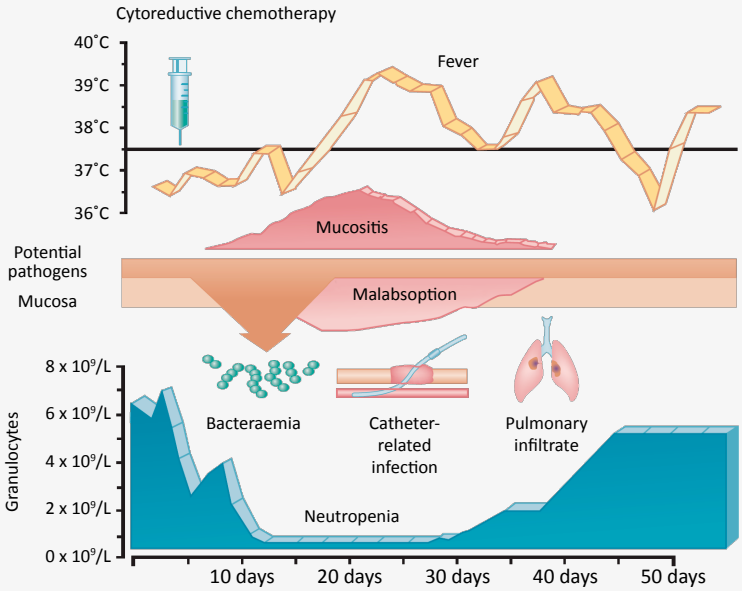

Figure 2 Timing of neutropenia, mucosal barrier damage, infection and fever in haematological patients treated with cytotoxic therapy. In this figure the relation and timeframe is depicted wherein treatment toxicity and neutropenia such as mucositis as well as fever, as a sign of inflammation or infection, appear in patients treated with intensive chemotherapy for haematological malignancies. Day 0 indicates start of chemotherapy.

Sepsis is the systemic immune response to infection and is initiated by invading micro-organisms. The inflammatory response, that persists after the elimination of the infection, is also associated with an increased mortality [21] and determines even more the prognosis of the patient than does the initial infection. Severe sepsis is defined as sepsis resulting in sepsis-induced organ dysfunction or signs of tissue hypoperfusion. Septic shock is defined as sepsis-induced hypotension that persists despite adequate fluid resuscitation [22]. Organ dysfunction results from the direct toxic effects of microbial toxins as well as from dysregulation of the circulation, oxygen transport and tissue oxygenation. Restriction of global oxygen transport (respiratory failure, decrease in cardiac output and anaemia), and inadequate regional oxygen supply due to perfusion mismatch are also critical factors [23] (figure 3).

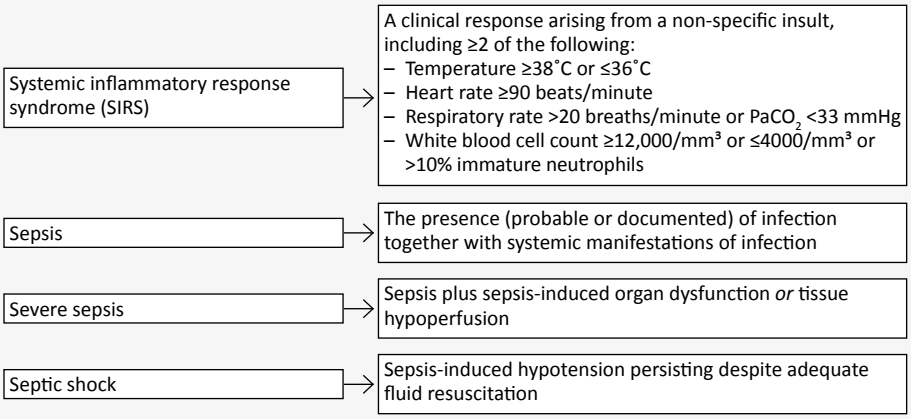

Figure 3 Definition of sepsis and related syndromes (adapted from Dellinger et al. [22])

PREVENTION AND TREATMENT OF SEPSIS

Early recognition and immediate treatment of sepsis is critically important and, since fever is likely to be the first sign, current guidelines recommend prompt treatment with antibacterials targeted against Gram-negative bacilli such as *Escherichia coli* at the onset of fever to prevent the occurrence of sepsis and septic shock in haematological patients.

In 2004 an international group of experts in the diagnosis and management of infection and sepsis, representing eleven scientific organizations, published the first internationally accepted guideline for use at the bedside to improve outcomes in severe sepsis and septic shock [24]. The Surviving Sepsis Campaign uses bundles to simplify the complex processes of caring for patients with severe sepsis. A bundle is a selected set of elements of care distilled from evidence-based practice guidelines that, when implemented as a group, are thought to be more effective than the individual elements alone. Key recommendations include measuring the lactate level, obtaining blood cultures before initiating treatment with broad spectrum antibiotics and administering crystalloid for hypotension or lactate ≥4mmol/L. These items have to be completed within three hours. Several other treatments have to be completed within six hours.

MANAGING THE CRITICALLY ILL FEBRILE NEUTROPENIC PATIENT

— *Detection*

Adequate interventions at an early stage offers the best chance of preventing sepsis to develop any further. Especially in neutropenic patients infections can progress rapidly, leading to hypotension or other life-threatening complications within minutes to hours. It is critical to recognize neutropenic fever as early as possible to allow prompt initiation of empirical systemic antibacterial therapy in order to avert progression to severe sepsis and septic shock, and possibly death [25]. The efficacy of the treatment of patients with neutropenic fever syndromes has improved greatly as is shown by a progressive decline in mortality rates since the practice was implemented in the 1970s [26, 27]. This has been recently confirmed by the results of the international Surviving Sepsis Campaign showing that increased compliance with sepsis performance bundles was associated with 25% relative risk reduction in mortality rate [28]. Comparable outcomes were found for participating hospitals in the Netherlands [29] demonstrating clearly that mortality reduction can be achieved by increased protocol compliance.

A complicating factor in the detection of fever is that it presents mostly outside of office hours and that the definition and methods to estimate body core temperature vary [30]. Thresholds for defining fever are a peripheral body temperature of 37.5 - 38.5°C measured in the oral cavity, in the ear, under the axilla, rectally or on the surface of the skin. All these methods have their limitations when the aim is to reliably determine the body's core temperature [31].

For those presenting with hypothermia or those developing less pronounced or delayed fever (e.g. when antipyretics or steroids are given), reliance is placed on other vital signs including respiratory and heart rate, blood pressure and oxygen saturation because changes in these signs might be the consequence of a systemic inflammatory response. Recognition of the systemic inflammatory response syndrome is the first step to the early recognition of patients with sepsis. That this is far from easy in daily practice was shown by the fact that, even after an effective sepsis training programme, only half to two-thirds of the physicians could define severe sepsis and septic shock, respectively [32, 33]. Nurses also experience difficulties in recognising patients with sepsis due mainly to a lack of detailed knowledge [34]. Moreover, the applicability of Surviving Sepsis Campaign definitions for inflammation in clinical practice can be questioned as the immune response of haematological patients is different from that of other patients. A window of three hours to initiate antibacterial treatment for febrile neutropenia, as advocated in the surviving sepsis guidelines, is also unlikely to be appropriate for the haematological population.

— *Selection*

Sepsis is a serious condition caused by an overwhelming immune response to infection. Immune chemicals released into the blood to combat the infection trigger widespread inflammation, which leads to blood clots and increased capillary permeability. This results in impaired blood flow, which damages the body's organs by depriving them of nutrients and oxygen. In severe cases, one or more organs fail. In the worst cases, blood pressure drops, the heart fails and the patient spirals toward septic shock. Once this happens, multiple organ failure may occur and the patient is likely to die.

One might argue that these patients need intensive care treatment. However, treating groups of patients with conditions associated with high mortality rates on an Intensive Care Unit (ICU) poses significant ethical difficulties. Intensive care treatment is a burden for the patient and her/his relatives because of the discomfort associated with it and is becoming increasingly burdensome to health care systems. These issues become more important when high mortality is anticipated [35, 36]. Clearly, ICU survival strongly depends on the selection of patients who are actually offered ICU treatment. Therefore, the decision to admit these patients to the intensive care is challenging since subjecting every patient will lead to futile treatment and prolonged suffering for patients and their families. On the other hand, if the selection of patients is too strict and based solely on the level of risk, it will inevitably lead to inadequate treatment and unnecessary deaths. Optimal selection of suitable candidates for the ICU is also hampered by the fact that there is no standard for objectively assessing prognosis. Hence we need to select which patients are not eligible for ICU admission and determine triggers to initiate in a timely manner an adequate level of intensive supportive care for those who are.

— *Action*

Time is of the essence for patients with severe sepsis or septic shock, since they have better chance of survival if sepsis is treated adequately at an earlier stage to prevent progression from sepsis to severe sepsis and septic shock [22]. Besides reduction in mortality, optimal guideline based treatment of sepsis might also lead to fewer days with fever, reduction of antibiotic use, a shorter length of hospital stay, less aggressive supportive care and less infection-related costs. However, the identification of patients with sepsis can be difficult in daily practice as the signs of systemic inflammation response syndrome are not specific [37]. Antibacterial therapy is the most important treatment for sepsis. The choice of antibacterial therapy mainly depends on the suspected site of infection and the antimicrobial susceptibility of the expected pathogens, so therapy with broad-spectrum antibiotics is initiated empirically [38].

Considering the role of inflammation due to tissue damage and disrupted innate immunity there might be a place for anti-inflammatory therapies in the care of critically ill haematology patients. Data are however scarce and there remains a general concern regarding the risk of worsening infectious complications when embracing such an approach. Nevertheless, the use of corticosteroids has already shown beneficial in specific situations, including acute respiratory distress syndrome (ARDS) during streptococcal bacteraemia, *Pneumocystis jirovecii* pneumonia and immune reconstitution inflammatory syndrome (IRIS).

MANAGEMENT OF THE CRITICALLY ILL HAEMATOLOGICAL PATIENT

The decision to admit haematological patients to an ICU for continuous monitoring of the vital functions or for intensified supportive care treatment including organ support often presents difficult ethical issues as high mortality rates underlie a reticent attitude among both haematologists and intensivists [39]. A taskforce of the American College of Critical Care Medicine concluded less than two decades ago that patients with haematological malignancies were poor candidates for ICU admission [40]. In the last decade, the body of evidence has grown that survival of patients with haematological malignancies is improved when they are admitted to the ICU, which has led to an improved awareness of the benefits of early admission to an ICU [41]. However, there are still considerable inter- and intraregional disparities regarding the ICU admission policy of haemato-oncological patients in the Netherlands. A survey, entitled 'the vision of the Dutch haematologist on the role of intensive care in the care of haematological patients' was conducted in February 2012 and consisted of a web-based questionnaire that was distributed through the Haemato-Oncology Foundation for Adults in the Netherlands (HOVON) mailing list (unpublished). Briefly, 23 hospitals (7 university medical centres (HOVON level A) and 16 general hospitals (7x level C and 9x level D)) have responded. A 'no-ICU' policy was based primarily on the haematological prognosis (17x). Three hospitals registered the numbers of ICU transfers but thirteen hospitals reported an increase and seven reported a constant number of ICU transfers. The majority of hospitals mentioned the use of predefined criteria for consultation with an intensivist and ICU transfer. In seven hospitals there was no medical emergency intervention team available. In general, although there was a greater willingness among intensivists to admit haematological patients, important differences between centres concerning ICU admission policies exist. Consequently, more evidence is needed to show that ICU treatment of this specific transplant group may not be futile.

To conclude, treatment for patients with haematological malignancies has improved over the recent years, which has led to increased survival rates. Nevertheless, side-effects of these intensive chemotherapy regimens frequently occur. Supportive care aimed to manage the inevitable inflammatory complications of these intensive treatments is no longer restricted to haematological wards. However, we need to learn more about the optimal detection of

sepsis, the selection of patients who should be offered ICU treatment, and the timeframes within which appropriate action should be taken to attain optimal survival while preserving an acceptable quality of life.

With this thesis we address the following questions:

1. Can we further improve our standards of care in the management of fever in neutropenic haematological patients?
2. What are the trends in ICU admissions of critically ill haematological patients and what is their outcome?

AIMS AND OUTLINE OF THE THESIS

The thesis consists of two complementary parts addressing the management of the critically ill neutropenic haematological patient. The overall objective of the research presented in this thesis was to obtain insight in characteristics of patients during treatment for a haematological malignancy who are at risk for inflammatory complications and to investigate the trends in ICU admissions of critically ill haematological patients and their outcome.

The first part of the thesis focuses on improving our standards of care in the management of fever among neutropenic patients. Which factors in the detection of fever and instituting adequate action can be improved? With fever being the most common early manifestation of sepsis, clinical practice guidelines emphasise the prompt institution of empirical broad-spectrum antibacterial therapy at the onset of fever as this has been shown to be crucial to patient survival. In **Chapter 2** we assess the feasibility and validity of a method for continuously monitoring the skin temperature of adults, admitted to the haematology ward for an HSCT, in order to detect fever at its onset. Subsequently, **Chapter 3** focuses on interventions to avoid delay in initiating empirical antibacterial treatment at the onset of fever, as this is the cornerstone for preventing sepsis during neutropenia. In **Chapter 4** we explore the value of two instruments, SIRS and R-MEWS to recognise the changes in vital signs associated with systemic inflammation. We also investigated whether chemotherapy treatment was related to persistent fever in patients treated for haematological malignancies. Since central venous catheters (CVCs) are widely used in the management of patients receiving intensive chemotherapy, with some being related to infection and thrombosis, we present in **Chapter 5** a retrospective analysis to investigate the risk factors for persistent coagulase-negative staphylococci bacteraemia and central venous catheter related thrombosis and their relationship to each other.

The second part of the thesis focuses on the critically ill patient and the trends over time in ICU admission policies and clinical outcomes. In **Chapter 6** we investigate the changes over time in the ICU and hospital mortality as well as the 100 day post-HSCT mortality for three cohorts of HSCT recipients admitted to our ICU, compared to those who were not. In **Chapter 7**, we explored trends over time in admission prevalence and outcome of 1,741 critically ill haematological patients in the Netherlands by using the National Intensive Care Evaluation database. In **Chapter 8** we describe the long-term self reported health related quality of life, including fatigue, cognitive functioning and anxiety and depression, of patients being treated for a haematological disease who received intensive care treatment compared to those who did not. We also included a group of non-haematological general medical ICU patients as a control group. **Chapter 9** contains the summary of the thesis as well as a general discussion and future perspectives.

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PT 1

Management of the febrile neutropenic haematological patient

2

Continuous non-invasive monitoring of the skin temperature of HSCT recipients

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ABSTRACT

GOALS OF WORK

Empirical antibiotic therapy is usually started in patients who are neutropenic following treatment with cytostatic chemotherapy for a haematological malignancy as soon as fever develops to forestall fulminant sepsis. Hence, accurate and timely detection of fever is crucial to the successful management of infectious complications in these patients. We report an investigation of the feasibility and validity of continuous non-invasive body temperature measurement.

PATIENTS AND METHODS

The feasibility of non-invasive continuous measurement of the skin temperature was investigated using the Propaq® device in a cohort of 33 patients receiving an allogeneic HSCT who were all at risk of developing a febrile episode. Non-invasive continuous measurement of the skin temperature (CST) was compared with a standard episodic axillary temperature measurement (EAT) five times daily using a Terumo® device. The study period entailed monitoring during the ten or twelve days that profound neutropenia was expected to be present.

MAIN RESULTS

Measuring the skin temperature continuously and accurately by using the Propaq® was feasible. The CST correlated well with the EAT measurements (Pearson r=0.782). Compared to EAT, the start of empirical therapy could be started 2.5 h earlier when relying on continuous measurements than was possible with EAT.

CONCLUSION

Continuous skin temperature measurements are feasible and valid compared to the conventional temperature measurement and may improve the management of infections by earlier detection of fever in neutropenic patients.

INTRODUCTION

Approximately 90% of cycles of intensive chemotherapy used to treat acute leukaemia are complicated by prolonged and profound neutropenia that is usually accompanied by fever and infections [1]. Neutropenic patients who are febrile are at high risk for developing sepsis, which often necessitates acute admission to the Intensive Care Unit (ICU) and is associated with a high mortality [2]. Fever is usually the most obvious sign of a systemic inflammatory response [3], so measuring the body temperature is one of the most important nursing tasks. Instituting empirical broad-spectrum antimicrobial therapy promptly at the first sign of fever has been shown crucial to patient survival and remains the cornerstone of infection management [4-6]. Mortality associated with fever and neutropenia has dramatically decreased over the last three decades and is, in no small measure, the result of general adherence to the concept of giving empirical therapy with broad-spectrum antibiotics promptly at the onset of fever [7]. Needless to say this approach hinges upon the early detection of fever by measuring the body temperature.

A variety of methods are used to measure body temperature, involving different sites, instruments and techniques. The core temperature is best measured in the pulmonary artery using a Swan-Ganz catheter [8, 9], but this is impossible to employ on a haematology ward in daily clinical practice. Mercury thermometers are now obsolete and have been replaced by electronic devices. These thermometers accurately predict temperature and can be adapted for use at different body sites to measure temperature orally, axillary, tympanically or rectally [10]. However, the choice of sites for adults on a haematology ward is limited. Temperature is most often measured orally although oral mucositis results in erroneous measurements [11]. Rectal measurement during thrombocytopenia is too dangerous because of the risk of rectal bleeding. There are convincing data to show that tympanic temperature measurement is reliable, but the results are more variable than found with rectal or oral readings [12]. For these reasons, we have continued to measure the axillary temperature for our adult population [13].

For continuous measurements, a temperature sensor connected to the Welch-Allyn® Propaq monitor was used. This device is able to measure temperature continuously. In this audit, 24 h non-invasive measurement of skin temperature was explored. The goals were:

1. To assess the feasibility of continuously monitoring the skin temperature of adults admitted to the haematology ward for an HSCT.
2. To assess the validity of the data by calculating the correlation between the values measured by the continuous device and the axillary measurements.

PATIENTS AND METHODS

PATIENT POPULATION

The audit was carried out on the haematology ward of the Radboud University Nijmegen Medical Centre where 33 patients admitted to receive an HLA compatible allogeneic haematopoietic stem cell transplant (HSCT) from a sibling or a voluntary unrelated donor, consented verbally to participate. Ethics Committee approval was not required. Both myeloablative or non-myeloablative conditioning was used for prepatory regimen. Demographic data of the patients are shown in table 1.

PROCEDURE

Participating patients had their body temperature measured simultaneously by two different instruments. This period was defined as the first ten days post-transplant or, in the case of idarubicin, two days before HSCT until ten days post-transplant as this drug was given two weeks before transplant whilst others were given within a week. Temperature was scheduled to be registered five times daily at fixed times: 03:00, 08:00, 13:00, 18:00 and 22:00. The maximum interval between two measurements was 5 h.

Table 1 Demographic data

Gender	14 Male
	19 Female
Age	Mean 48.0 years and range 22-64 years
Type of transplant	17 Sibling HSCT
	16 Voluntary Unrelated Donor HSCT
Underlying disease	10 Acute Myeloid Leukaemia
	5 Myelodysplastic syndrome
	4 Severe aplastic anaemia
	3 Chronic lymphocytic leukaemia
	4 Non-Hodgkin's lymphoma
	3 Acute lymphocytic leukaemia
	1 Multiple myeloma
	1 Chronic myeloid leukaemia
	1 Myelofibrosis
	1 Acute basophile leukaemia
Conditioning regimen	Myeloablative
	– 9 Idarubicin-cyclophosphamide-total body irradiation (TBI)
	– 11 ATG-cyclophosphamide-TBI
	– 4 ATG-cyclophosphamide-fludarabine
	– 1 Idarubicin-busilvex-cyclophosphamide
	Nonmyeloablative
	– 2 Cyclophosphamide-fludarabine-TBI
	– 3 Cyclophosphamide-TBI
	– 2 Cyclophosphamide-fludarabine
	– 1 Cyclophosphamide-TLI

INSTRUMENTS

— *EAT*

We used a Terumo® axillary thermometer, type C202, to measure axillary temperature. The device was calibrated for the range of 32.0–42.0°C, in steps of 0.5°, by means of a warm water bath. The maximum deviation after 90 s was 0.02°, as was internally validated by the technical service (data not shown). The Terumo thermometer predicts the axillary temperature after approximately 60 seconds.

— *CST*

Continuous measurement was achieved by using a temperature sensor connected to the Welch-Allyn® Propaq monitor. This device measures temperature continuously preferably in a body cavity that is least exposed to ambient air. Patients were asked to carry the sensor either in their groin or axilla, though the former was preferred as it is least influenced by the patient's movements.

SUPPORTIVE CARE

Empirical therapy was started once when the axillary temperature as measured by episodic axillary temperature (EAT) was equal to, or exceeded, 38.5°C. When continuously measured skin temperature (CST) indicated T≥ 38.3°C axillary measurement was performed to see if EAT confirmed this. At the onset of fever, blood was obtained for cultures, ceftazidime was administered empirically, and the attending physician was alerted. A blood culture was considered positive if one or more cultures yielded a microorganism, except for coagulase-negative staphylococci, for which two separate positive blood cultures yielding the same strain were required to be considered to represent bacteraemia [14].

AUDIT

Feasibility was tested in the first six patients, and a go/no-go decision to continue the audit was made. Carrying the device was found feasible when five of the six patients could bear the sensor during the day, and the monitor reflected the body temperature. Patients were interviewed to assess the feasibility of carrying a temperature device on the body during the day. The validity of the continuous measurements was assessed by comparing pairs of simultaneously measured values and calculating the correlation and regression between them.

DATA ANALYSIS

Data on the validity of the measurements were collected by the nurses of the ward. A registration form was specially developed to record the data. All temperature measurements were recorded during ten or twelve days of observation.

Data were imported in SPSS version 14.0 for data analysis. Correlation and regression analysis were performed to assess validity of the experimental measurements. The outliers in temperature difference, defined as a 0.5° difference (ΔT) or more between the two simultaneously used methods were analysed on possibly confounding factors age, BMI and gender.

RESULTS

FEASIBILITY

Feasibility was assessed after the first six patients had been observed, and the decision was made to continue when five patients had been shown to have no problems carrying the CST device. A total of 33 patients were included and 29 completed the observation period successfully. Each patient could move around freely as the sensor was not attached to their body and could easily be disconnected temporally when desired. During the audit, one patient was uncomfortable carrying the device during the day and withdrew from the study for that reason. Three patients complained about the sensor and considered abandoning the study but decided to continue. The CST did not reflect the body temperature in one case as the patient's physique did not permit sufficient isolation from ambient air.

VALIDITY OF THE CST RELATED TO THE EAT

Regarding the difference in the simultaneously measured body temperature between the EAT and the CST (ΔT), 1,409 values were valid for evaluation as missing values were not properly recorded on the registration form. As shown in figure 1, 90% of the differences in measurements are located in a range of –0.5°C to 0.9°C. The CST measured both higher and lower temperatures than was recorded for EAT and frequency, the values of both were distributed in a Gaussian fashion though EAT was on average 0.23° higher (figure 1).

There was a good correlation between the two methods (figure 2; Pearson correlation of 0.782, p ≤0.01). Regression analysis yielded an R^2 of 0.612 and the intercept and slope indicated that ΔT was most pronounced at higher values: y=0.934*x+2.259. For an axillary temperature of 36°C, the mean deviation of the CST was 0.12°; for an axillary temperature of 40.5°C, the mean deviation of the CST was 0.41°.

ΔT was 0.5 or more in 29.5% of all cases. Per patient, a ΔT≥0.5 was found in 2% to 69% of the total number of measurements suggesting that patient characteristics played a considerable role. Analysis of 'gender' and 'ΔT≥0.5' showed no significant difference between the groups (p=0.309), and there was no influence of either BMI (p=0.227) or age (p=0.614).

In 78% of patients, bacteraemia was detected during the initial febrile episode during neutropenia justifying the decision to start broad-spectrum antibiotic treatment.

Although it was not the primary object of the study, we noted that antibiotics were started over 2.5 hours earlier for twelve out of fourteen evaluable patients as a result of earlier detection of fever by continuous measurements.

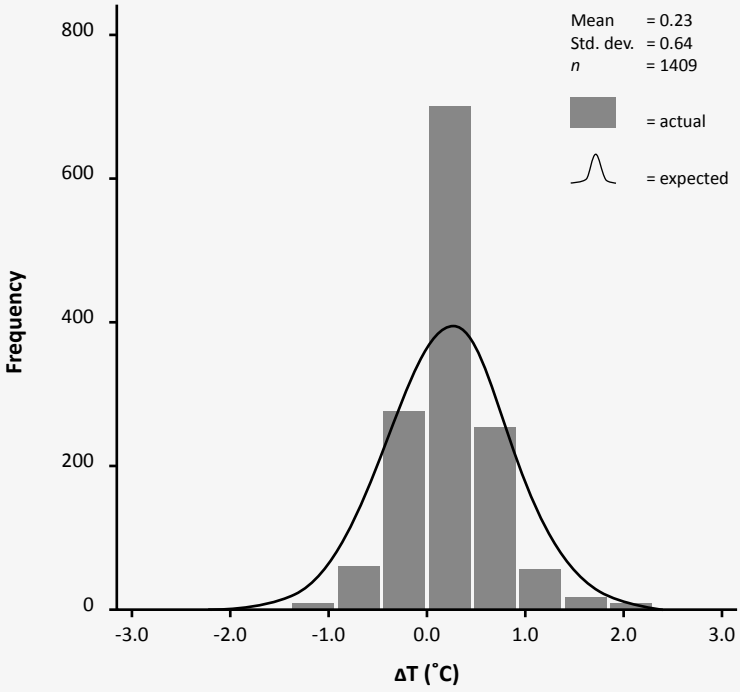

Figure 1 Histogram on the difference (EAT minus CST) in simultaneously measured temperature by two different methods (outliers are left out)

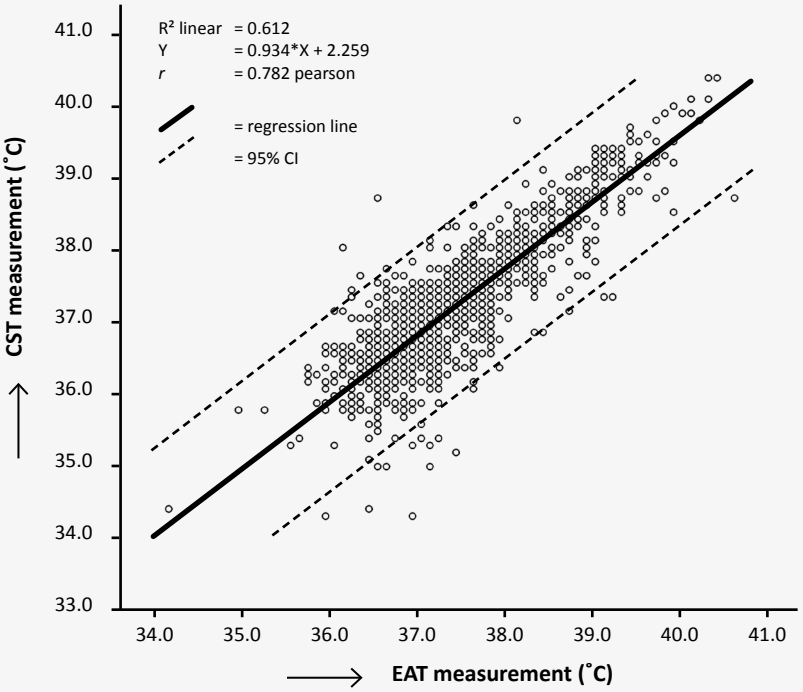

Figure 2 Scattergram with regression line on the correlation of two independent measurements of body temperature

DISCUSSION

Fever is regarded as the most important means of identifying an inflammatory process in neutropenic patients, but there is reason for concern as the reliability of the common methods of temperature measurement all appears to have limitations. A high frequency of recording vital signs should be adopted with in every haematology ward's daily practice where early detection of fever can be lifesaving. Surprisingly, no published data were available on non-invasive continuous body temperature measurement in oncology patients.

The goals of this audit were to assess feasibility and validity of continuous skin temperature measurement (CST). This audit found that CST is feasible in clinical haematology patients and is valid compared to the traditional measurements except when a patient is physically incapable of carrying the sensor where it can remain sufficiently isolated.

The extreme values observed ($\Delta T \geq 0.5$) were likely explained by the malpositioning of either of the instruments. The relationships between the distribution of $\Delta T \geq 0.5$ and factors of the human physical composition such as gender, BMI and age were explored but these did not explain the findings. Both the standard instructions with the Terumo (proper placement and drying the axilla previous to the measurement) and the continuous device (isolation from outside air is necessary for reliable values) are sensitive to erroneous measurement. Also, the positioning of the device could account for this when done by the patients themselves. Alternatively this may reflect a common problem, namely inconsistency in the use of thermometry in daily practice.

Early detection of fever is a challenge during cycles of chemotherapy where the start of empirical antibiotic therapy can be life-saving during neutropenia. All guidelines emphasise the immediate start of empirical therapy at the onset of fever so it makes sense to increase the frequency of measurements to increase the chance that the onset of fever is detected promptly. This is not the case when the temperature is only measured every 4–6 hours, but reliable continuous measurements allow the onset of fever to be caught in the act so to speak.

The fact that 78% of the patients actually had bacteraemia during the first episode of fever sufficiently justifies the start of broad-spectrum antibiotic treatment as soon as fever occurs. Hence, it could be argued that the lack of a rapid, reliable and continuous means of temperature monitoring may increase the risk for developing a systematic inflammatory response syndrome (SIRS), sepsis, shock and even death.

Although the concept of fever is familiar to nurse, the precise definition we should adopt for optimal patient outcomes is far from clear as a variety of thresholds varying between

37.5 and 38.5 are employed, and the temperature is measured in several different ways. For instance, the 2002 IDSA guidelines recommends using a definition of fever as a single measured oral temperature of ≥38.3 or a temperature of ≥38.0 for ≥1 h [15], despite the influence of oral mucositis on oral thermometry [11]. Clearly, there is still much to be done.

CONCLUSION

Continuous temperature measurement makes it possible to monitor patients intensively during round the clock without involving extra personnel. Continuous body temperature measurement is commonly used in the ICU but is alien to haematology wards. Earlier detection of the onset of fever and SIRS makes earlier initiation of empirical therapy possible which might lead to fewer days with fever, reduce antibiotic usage, the length of stay and mortality and allow better deployment of nursing staff.

FUTURE DIRECTIONS

Neither CST and EAT are considered to be the Gold standard for estimating the core temperature. Ideally, a valid means of continuously measuring temperature needs to be developed that is more reliably correlated to core temperature. However, it will be a challenge to find a method of reliably achieving this while being economic and userfriendly. In the meantime, further research should be done on a larger group of neutropenic patients exploring the consequences of earlier detection of fever on outcomes such as length of stay, costs and amount of antibiotics and survival.

ACKNOWLEDGEMENT

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3

How prompt is prompt in daily practice?

Earlier initiation of empirical antibacterial therapy for the febrile neutropenic patient

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ABSTRACT

With fever being the most common manifestation of early sepsis, clinical practice guidelines emphasise the prompt institution of broad-spectrum antibacterial therapy at its onset. An audit was performed on the haematology ward to determine whether there was any delay in starting antibiotic treatment during neutropenia in clinical patients and to define the main reasons for this. Strategies were developed, implemented and evaluated on short- and long-term implications on the delay in the start of antibacterial therapy. The procedures specified in the protocol for starting empirical antibacterial therapy were audited to assess whether the target for starting therapy within 30 min of fever was achieved. Initial results indicated that two major changes to the protocol were necessary to achieve a reduction in the delay between detection of fever and starting antibacterial therapy. This modified protocol was evaluated four months after implementation by means of a consecutive audit. After three years, a third audit was performed to determine the long-term implications of the improved protocol. In the initial audit, the mean time interval between the onset of fever and the administration of antibacterial therapy was 75 minutes. With the modified protocol, the mean time to starting therapy was shortened to 32 minutes ($p<0.05$). Changing the protocol for starting antibacterial therapy allowed nurses to administer the first dose of antibiotic significantly earlier.

INTRODUCTION

Patients who are clinically treated for haematological malignancies with high-dose chemotherapy or who are given myeloablative conditioning to prepare them for a haematopoietic stem cell transplant (HSCT) are expected to be profoundly neutropenic for at least ten days. Consequently, they are at high risk for developing sepsis that may require admission to the intensive care unit and is associated with a high mortality [1]. Where sepsis is defined as a clinical response arising from confirmed infection, it will always be preceded by signs of a systemic inflammatory response syndrome (SIRS) because confirmation of infection by means of blood cultures needs time [2]. Sepsis is hard to recognise in the beginning so treatment often starts late. With fever being the most common manifestation of early sepsis, clinical practice guidelines emphasise the prompt institution of empirical broad-spectrum antibacterial therapy promptly at the onset of fever as this has been shown to be crucial to patient survival [3-5], because the progression of infection can be rapid, and cannot be reliably distinguished from fever due to other causes. The justification for prompt empirical therapy is motivated in the 2002 Infectious Diseases Society of America (IDSA) guideline [6]. The nurse plays a vital role in detecting the early signs of SIRS predicting sepsis as she or he is responsible for round-the-clock monitoring of the vital signs including body temperature, pulse, blood pressure and respiratory rate. The optimal frequency for measuring body temperature has been discussed earlier [7], but experience suggests there is room for improvement in minimising the delay between the onset of fever and the administration of the first dose of an antibacterial agent [8] as the success of empirical antibacterial therapy depends not only on the correct choice and dosage of the drug but also on its prompt administration [6]. However, delays can and do occur in daily practice. For example, the attending physician may be occupied elsewhere, obtaining venous access may prove difficult and even the day of the week can matter [8-10]. Apart from providing a better chance of survival, there may also be a measurable benefit from prompt antibacterial treatment by shortening the length of stay [11]. Our ward set itself the goal of starting antibiotics within 30 minutes after detecting fever in order to secure adequate treatment well within the 60 minutes proposed by the international Surviving Sepsis Campaign [12].

The aims of the audit were:

- to collect information on the procedures on the ward leading up to starting empirical antibacterial treatment during neutropenia;
- to determine the reasons for any delay in these procedures;
- to develop and implement strategies for improvement;
- to evaluate the short- and long-term effects of these strategies on the quality of procedures on the ward for starting empirical antibacterial treatment during neutropenia in a timely fashion.

PATIENTS AND METHODS

PATIENTS

Three groups of adults, consecutively admitted to the haematology ward, participated in the audit and were considered to be immunocompromised because of their underlying disease or its treatment with chemotherapy. Informed consent was not required because the usual standard of care was provided at all times. Furthermore, the data were analysed anonymously, and did not breach patient privacy.

SUPPORTIVE CARE

All patients were housed in single- or double-bed rooms furnished with high-efficiency particulate air (HEPA) filtered air to create positive pressure. Ciprofloxacin alone or co-trimoxazole plus colistin were given as prophylaxis to prevent infections due to Gram-negative bacilli such as *Escherichia coli*. Stem cell transplant recipients were managed using a central venous catheter for parenteral nutrition, blood drawing and for administering fluids, medication and transfusion products. Allogeneic stem cell transplant recipients were given cyclosporine as prophylaxis against graft-versus-host disease. All patients were monitored daily for the presence of oral mucositis and received continuously intravenous morphine on demand to control severe mucositis-related pain. Erythrocyte transfusions were given when the haemoglobin level was less than 5.5 mmol/L and platelets were transfused when bleeding occurred and when platelet counts fell below 10 x 10^9/L.

PROCEDURES

The routine protocol required the patients' axillary temperature to be measured four times daily (8:00 h, 13:00 h, 18:00 h and 22:00 h). An additional measurement was done at 3:00 h for HSCT recipients during the period of highest risk from the day of transplantation (or two days before if idarubicin was given as part of the conditioning regimen), until ten days after transplantation. Fever was defined as a single axillary body temperature measurement of 38.5°C or more. When fever was registered, three steps were taken: (1) The physician on duty was contacted to conduct a thorough comprehensive physical examination. (2) Ten millilitres of blood was drawn for culture by venepuncture for an aerobic and an anaerobic blood culture bottle (BACTEC 9000; BD Diagnostics). A second set of blood cultures was drawn by venepuncture 15–30 min later. (3) Ceftazidime or meropenem were ordered by the physician and drawn from the stock kept on the ward so that the nurse could administer the first dose as soon as possible. These beta-lactam antibiotics have been the mainstay of our empirical antibacterial therapy since their introduction [12-18]. These standard procedures were known to the staff and available online.

AUDIT

The key component of clinical audit is that performance is reviewed to ensure that what *should* be done is *being* done, and, if not, it provides a framework to enable improvements to be made. To attain this, the following steps were carried out (figure 1).

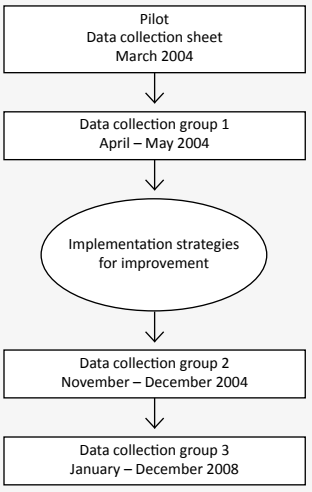

Figure 1 Flow chart of the audit's timeline

REGISTRATION

The data collection sheet was designed by the researcher, and was piloted for one month. The following data were recorded by the nurse when the patient developed fever for the first time: (1) the time of detection of fever; (2) the time blood cultures were drawn; (3) the time the physical examination was done; and (4) the time the first dose of antibiotic was given. The time between the detection of fever and blood culture collection was calculated (2-1), as were the time between detection of fever and physical examination (3-1) and the time between detection of fever and administration of the first dose of medication (4-1). Patients' demographic data were documented on the form and there was also room allowed for remarks. Data were collected in three groups of patients. Data from the first group were collected after the pilot period. Registration was done during two months on the assumption that the results from 25 episodes of fever would be sufficient to evaluate the protocol.

The results were analysed to identify those factors that led to any delay and were subsequently used to develop strategies for improvement. The modified protocol was then implemented and monitored for four months after which a registration was done on the second

group exactly as had been conducted for the first group using the same data collection sheet.

Three years after implementation of the improved protocol, a similar exercise was carried out once again to determine long-term compliance. The time of detection of fever and the time of administration of the first dose of empirical antibacterial therapy were noted for all consecutive patients who had received chemotherapy in hospital in 2008. This formed the third group that was audited.

ANALYSIS

Descriptive statistics were calculated using SPSS version 15.0 (SPSS Benelux BV). Three registration periods were compared to determine the differences in the delay of starting empirical therapy. The Student *t*-test for independent samples was used to compare the three groups. The data were presented using Box plots.

RESULTS

Patients' demographics are shown in table 1.

GROUP 1

During registration, a total of 23 clinical patients experienced 43 episodes of fever. Twelve episodes were excluded from further analyses because of incomplete data. In total, 31 episodes were analysed with 24 (77%) happened outside office hours between 17:00 h and 8:00 h the following morning. Seventeen different nurses took care of the patients and eight different physicians were involved. The mean time between the detection of fever and administration of the first dose of antibiotic was 75.1 min (±SD 46.1, range 30–210 min). The mean time between detection of fever and blood culture collection was 22.9 min (±SD 15.4, range 5–60 min), and the mean time between detection of fever and physical examination was 44.2 min (±SD 24.2, range 0–75 min). There was a striking difference between office hours and shifts: during shifts the mean time between the detection of fever and the physical examination was 48.5 min, whereas this was 27 min during the day.

STRATEGIES FOR IMPROVEMENT

The results of the baseline registration showed that waiting for the physician to conduct a physical examination was the main reason for a delay in starting antibacterial therapy, especially out of hours. To circumvent this, we instituted a standing order that allowed the nurse to administer the first dose of antibacterial therapy immediately after taking blood cultures and before calling the physician. This required the prescription to be already written. To further reduce the delay, the two sets of blood cultures were collected at the same time by a single venepuncture to allow 30–40 mL of blood to be cultured. This was to ensure that the sensitivity of blood cultures remained the same by requiring the same volume of blood as before.

GROUP 2

During registration, 25 patients experienced 39 episodes of fever. Eleven episodes were excluded from further analyses because of incomplete data. In total, 28 episodes are analysed and fourteen nurses and eight physicians were involved. The mean time between the detection of fever and administration of the first dose of antibiotics was 32.0 min (±SD 17.6 min, $p<0.05$, figure 2). The mean time between detection of fever and blood culture collection was 12.7 min (±SD 11.0 min, $p>0.05$), and the mean time between detection of fever and physical examination was 55.4 min (±SD 53.7 min, $p>0.05$).

Table 1 Demographic data

Characteristics	Group 1 (*n*=23)	Group 2 (*n*=25)	Group 3 (*n*=119)
Gender, male (%)	14 (61)	15 (60)	76 (64)
Age, mean and range (years)	48, 21-77	50, 17-65	51, 17-73
Episodes of fever reported	43	39	156
Evaluable episodes of fever	31	28	128
Episodes of fever	Group 1 (*n*=31)	Group 2 (*n*=28)	Group 3 (*n*=128)
Underlying disease, *n* (%)			
– Acute myeloid leukaemia	13 (42)	8 (29)	46 (36)
– Multiple myeloma	5 (16)	9 (32)	23 (18)
– Non-Hodgkin lymphoma	5 (16)	6 (21)	20 (16)
– Myelodysplastic syndrome	5 (16)	1 (4)	5 (4)
– Acute lymphoblastic leukaemia	1 (3)	-	8 (6)
– Aplastic anaemia	1 (3)	2 (7)	2 (2)
– Chronic myeloid leukaemia	-	2 (7)	4 (3)
– Other	1 (3)	-	20 (16)
Type of treatment, *n* (%)			
– Non-transplant regimen	15 (48)	9 (32)	33 (26)
– SIB HSCT			
- Ida-Cyclo-TBI	2 (6)	4 (14)	13 (10)
- Other	2 (6)	1 (4)	10 (8)
– VUD HSCT			
- ATG-Cyclo-TBI	1 (3)	4 (14)	6 (5)
- Other	-	1 (4)	8 (6)
– Autologous HSCT			
- High dose melphalan	5 (16)	8 (29)	16 (13)
- BEAM	-	-	14 (11)
- Other	1 (3)	-	3 (2)
– No therapy preceding fever	2 (6)	1 (4)	8 (6)
– Unknown	3 (10)	-	17 (13)

SIB Sibling donor
Ida Idarubicine
Cyclo Cyclofosfamide
HSCT Hematopoietic stem cell transplantation
TBI Total body irradiation
VUD Volunteer unrelated donor
ATG Anti thymocyte globuline
BEAM Carmustine, etoposide, cytarabine and melphalan

GROUP 3

In the period between 1 January and 31 December of 2008, episodes of fever of all consecutive patients are reported by the nurses of the ward. One hundred and nineteen different patients experienced 156 episodes of fever. In total, 128 episodes were analysed because 28 episodes had to be excluded because of missing data. The mean time between detection of fever and administration of the first dose of antibacterial therapy was 35.0 min (±SD 26.4 min, $p<0.05$, figure 2).

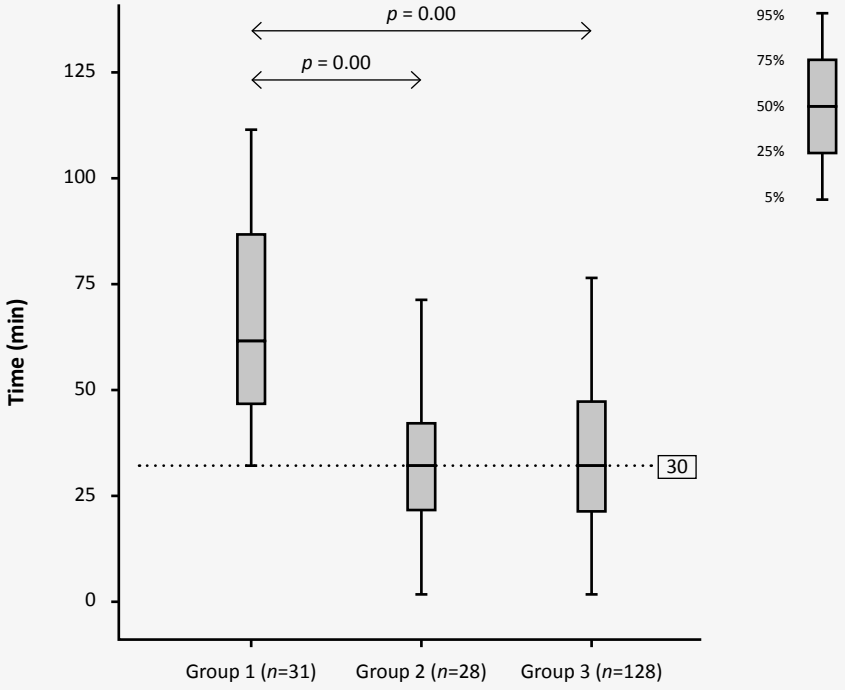

Figure 2 Effect of antibiotic prescription in advance and simplified culture regimen on delay in starting empirical antibacterial therapy

DISCUSSION

In this audit, we defined the level of promptness on our haematology ward and identified the main reason for the delay in starting empirical antibacterial therapy, especially out of hours, was the necessity of waiting until the duty physician arrived. Even during office hours when the duty physicians are on the ward, a mean 27 min were needed to examine the patient. Hence, physical examination that precedes the prescription of antibiotics causes a considerable delay although it has no influence on the choice and dosage of the antibiotics given for empirical therapy. Bishara *et al*. reported a similar experience on an emergency department during weekends [9] and other studies have also noted considerable delay in daily practice [8]. Consequently, the first significant improvement we found was allowing prescription of the antibiotic in advance at the moment the conditioning regimen was started.

Patients receiving high-dosed chemotherapy to treat a haematological malignancy or myeloablative conditioning therapy for an HSCT become profoundly neutropenic and most develop fever in a predictable fashion. Moreover, episodes of bacteraemia associated with the first fever were due to coagulase-negative staphylococci and viridans streptococci, and such infections are usually less severe than those due to Gram-negative bacilli [14, 16]. The second significant improvement was the time gained by simplifying the culturing regimen, by omitting the 15 to 30 min interval between two sets of cultures. This was justified by the need for prompt administration of antibacterial therapy when blood cultures should be obtained simultaneously [19]. These improvements allowed antibiotics to be administered within 30 min after fever was first detected. Thereafter, the protocol was modified accordingly and the third audit confirmed that the changes made shortened the time taken.

The prescription in advance had important implications for the role of the physician especially out of hours. One untoward effect of the standing order was that physicians allowed themselves even more time to come and assess the patient because it was no longer necessary before administration of antibiotics. This finding was unexpected and suggests that physicians rely so much on the protocol that they no longer consider the need for physical examination urgent since appropriate medication was already started by the nurses anyway. However, thorough physical examination directly at the onset of fever is still required in every new case of fever to determine whether an infectious focus is present such as pneumonia for which additional diagnostic tests or treatment are essential. Also, optimal supportive care needs to be guaranteed at all times.

The method of temperature measurement is controversial as is the definition of fever which is defined by the IDSA as a single oral temperature of ≥38.5°C or a temperature of ≥38.0°C

during ≥1 h [6] despite the influence of oral mucositis on oral thermometry [20]. The IDSA itself, in cooperation with the American College of Critical Care medicine, indicate that the definition of fever is arbitrary and depends on the purpose for which it is defined [18]. The vulnerable neutropenic patient, for whom timely detection of fever and adequate administration of antibacterial therapy is of vital importance, needs a more consistent and logical approach.

IMPLICATIONS FOR DAILY PRACTICE

Our earlier assumption that a first dose of empirical therapy was often delayed due to absence of a physician was confirmed. Nurses play a critical role in monitoring the whole procedure because they observe and interpret the patient's temperature and initiate further action round the clock and neither task requires intervention by the physician. Hence, reducing any delay in starting antibacterial therapy is primarily down to the nurse on duty who plays a key role in instituting the correct measures required to prevent SIRS evolving into sepsis.

The speed with which procedures were carried out could also be markedly improved by implementing relatively simple interventions such as preparing a written prescription in advance and simplifying the culture regimen. This enabled nurses to achieve the stated goal of administering the first dose of antibiotic therapy within 30 min after the onset of fever.

FUTURE RECOMMENDATIONS

A protocol is needed that guarantees starting antibiotics empirically as soon as fever develops during neutropenia as this remains the cornerstone for preventing sepsis during neutropenia. Further research needs to be done to investigate the optimal frequency, site and method for monitoring the body temperature of these patients. The impact of the nurse's awareness of the key role he or she plays in sepsis prevention should also be examined. Further study should also assess the extent to which the current results represent the whole group of neutropenic patients and the impact of reduced delay on outcome, length of hospital stay and cost-effectiveness.

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4

Persistent fever during neutropenia; risk factors and use of early warning scores for clinical monitoring

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ABSTRACT

OBJECTIVE

The aim of the study was to explore the value of two instruments, SIRS and R-MEWS, in recognition of the changes in vital signs associated with systemic inflammation. We also investigated whether chemotherapy treatment was related to persistent fever, in patients treated for haematological malignancies.

METHODS

A retrospective study was conducted in patients experiencing febrile neutropenia following intensive chemotherapy for treating haematological malignancies or to prepare for a stem cell transplant. Fever during neutropenia was considered due to either microbiologically or clinically defined infection or unknown origin. The incidence of persistent fever and the risk factors associated with it were assessed. Clinical manifestations of inflammation were graded using the Radboudumc modified early warning score (R-MEWS) and the systemic inflammatory response syndrome (SIRS) criteria at two time points: the onset of fever (t_1) and the fourth day of fever (t_4).

RESULTS

Fever persisted in 25 of the 113 (22%) consecutive patients for four days or more. Persistent fever was related to the nature of the chemotherapeutic regimens used (p=0.01) but was independent of the presence of a microbiologically defined infection or clinically defined infection at the onset of fever (p=0.47). More SIRS criteria were met and a higher R-MEWS was found at t_4 for patients with persistent fever compared to those without (both p<0.01).

CONCLUSION

R-MEWS looks promising as a tool for determining clinical deterioration due to treatment related systemic inflammation in patients being treated with intensive chemotherapy.

INTRODUCTION

Neutropenic sepsis is still the most common complication of intensive chemotherapy used to treat patients for haematological malignancies or to prepare for a stem cell transplant. This complication typically occurs during the period of profound neutropenia approximately ten days following the start of chemotherapy [1-3].

Sepsis is defined as the presence (probable or documented) of infection together with systemic manifestations of infection [4] and is associated with increased mortality, prolonged hospital admission, possible admission to the intensive care unit and decreased quality of life [5, 6]. Fever is likely to be the first sign of sepsis so current guidelines still recommend immediate antibacterial treatment, within an hour after the onset of fever, to prevent patients from developing sepsis and septic shock [4, 7].

Only 30-50% of the febrile episodes in patients treated with high dose chemotherapy meet consensus definitions of the Immunocompromised Host Society of either microbiologically or clinically defined infections [8]. The majority of febrile episodes remain unexplained [9] but may be related to chemotherapy-induced mucositis [10] or non-infectious causes including drug side effects and transfusion reactions.

Early recognition of infection and selection of those at risk for escalating from sepsis to severe sepsis and septic shock, followed by prompt and adequate action, has the potential to reduce mortality, morbidity, hospital length of stay and costs [11]. The criteria for systemic inflammatory response syndrome (SIRS) assume that the progressive pathophysiological derangement as seen in severe sepsis can also occur in the absence of infection [12]. SIRS allows the level of inflammation to be determined using four dichotomous clinical criteria for body dysfunction [13]. An alternative approach is to employ an early warning score based on the vital signs heart rate, respiratory rate and systolic blood pressure as well as oxygen saturation, amount of inspired oxygen needed and level of consciousness [14]. A modified early warning score has recently been adopted by the Radboud university medical center (R-MEWS) and is being used as a track-and-trigger system on the haematology ward [15] in order to recognize potential clinical deterioration.

The main aim of this study was to explore the value of two instruments, SIRS and R-MEWS, in recognition of the changes in vital signs associated with systemic inflammation, in patients treated for haematological malignancies. We also investigated whether chemotherapy treatment was related to persistent fever.

METHODS

STUDY POPULATION

A retrospective cohort study was conducted on the 28-bed haematology ward of the Radboud university medical center. All consecutive patients admitted for intensive chemotherapy for the treatment of a haematological malignancy or to prepare for a haematopoietic stem cell transplant (HSCT) between April 2007 and May 2009 were eligible for the study. Patients were included at the first onset of fever (a single measured axillary temperature of ≥38.5°C) and defined as severely neutropenic as their neutrophil count was <0.5x10^9/L. Patients who developed fever as an immediate (the same day) response to medication or irradiation as happens frequently after total body irradiation (TBI) or medication like anti-thymocyte globulins (ATG) were excluded. The period of investigation ranged from two days before the onset of fever until six days after.

ETHICS STATEMENT

The Committee on Research Involving Human Subjects (Arnhem-Nijmegen region CMO) approved the study (study number 2014/164).

SUPPORTIVE CARE

All patients were accommodated in single or double bed rooms equipped with HEPA filtered air to create positive pressure. Gut decontamination is largely used in the prophylaxis of bacterial infections in departments treating neutropenic patients, in particular those patients subject to profound and prolonged neutropenia, such as patients undergoing haematopoietic stem cell transplant or induction chemotherapy for acute leukaemia. Ciprofloxacin was given as prophylaxis to recipients of a haematopoietic stem cell transplant (HSCT) to prevent infections due to Gram-negative bacilli such as *Escherichia coli* whereas co-trimoxazole combined with colistin was given to patients undergoing treatment for leukaemia [16]. HSCT recipients were managed using a central venous catheter for parenteral nutrition, drawing of blood samples and for administering fluids, medication and transfusion products. Erythrocyte transfusions were given when the haemoglobin level was less than 5.5 mmol/L and platelets were transfused when bleeding occurred and when platelet counts fell below 10x10^9/L. No mould active prophylaxis was given. Growth factors are not being used. A preventive approach for reducing the length of the period of neutropenia by the use of growth-factors, which indeed shortens the period of vulnerability for bacteraemia, is contraindicated for the haematological population after highly dosed chemotherapeutic regimens because growth-factors also stimulate cancer cells to multiply.

INITIATION OF EMPIRICAL ANTIBACTERIAL THERAPY AT THE ONSET OF FEVER

The protocol required the patient's axillary temperature to be routinely measured four times daily (8am, 1pm, 6pm and 10pm). An additional overnight measurement was done at 3am during the risk period for infectious complications i.e. between day 0 and 10 of HSCT or when nocturnal body temperature was between 37.5°C - 38.5°C. In case of fever, the physician on duty was called to conduct a thorough comprehensive physical examination. The nurse obtained blood for cultures by venepuncture and through the central venous catheter for aerobic and anaerobic cultures (BACTEC 9000, BD Diagnostics). Empirical therapy was then started with ceftazidime 2g IV or meropenem 1g IV when there had been a previous infection due to resistant Gram-negative bacilli. Each drug was given three times a day and was ordered in advance by the physician and drawn from the stock kept on the ward so that the nurse could administer the first dose as soon as possible [17]. Blood cultures were repeated on the fourth day of treatment to evaluate efficacy and additional diagnostic tests were ordered if required.

DATA COLLECTION

Age, gender, underlying disease, type of treatment, relevant laboratory results and microbiological data were extracted from medical files. The aetiology of fever was assigned once the results of the microbiological investigations were known and episodes were classified as due to either a microbiologically defined infection (MDI) when cultures yield an organism or clinically defined infection (CDI) when there was a focal site of infection without microbiological confirmation. All other episodes were classified as unexplained fever [8]. Bacteraemia was documented when one or more blood cultures yielded a microorganism, except in the cases of coagulase-negative staphylococci, for which two separate positive blood cultures obtained at the same time and yielding the same strain were required [18].

Vital signs registration included body temperature, heart rate, systolic blood pressure, respiratory rate and oxygen saturation and were recorded at the onset of fever (t1). SIRS criteria are dichotomous (yes or no) and allow a score of 0-4. R-MEWS rates five physiological parameters on a scale from 0-3 and has a calculated range of 0-15. R-MEWS was calculated (after omitting of the value for consciousness and amount of inspired O^2) and the number of SIRS criteria were determined (table 1). The time of fever onset and the time the initial dose of antibiotics was given were also recorded. On the morning of the fourth day (t4) an identical set of vital signs was registered and SIRS and R-MEWS were assessed in the same way. Fever that was still present at t4 was defined as persistent fever.

Table 1 Systemic Inflammatory Response Syndrome (SIRS) and the Radboudumc Modified Early Warning Score (R-MEWS) criteria. SIRS criteria are dichotomous (yes or no) and allow a score of 0-4. R-MEWS rates physiological parameters on a scale from 0-3 and has a calculated range of 0-15.

SIRS	R-MEWS							
1	**Score**	**3**	**2**	**1**	**0**	**1**	**2**	**3**
	Oxygen saturation (%)	≤91	92-93	94-95	≥96			
>20	Respiratory rate (breaths/minute)	≤8		9-11	12-20		21-24	≥25
>90	Heart rate (beats/minute)	≤40		41-50	51-90	91-110	111-130	≥131
	Blood pressure systolic (mm Hg)	≤90	91-100	101-110	111-219			≥220
	Consciousness*				alert		delirious	verbal / pain /unresponsive
	Inspired O_2*				air	<5l/min	≥5l/min	
>38 or <36	Body temperature (˚C)	≤35.0		35.1-36.0	36.1-38.0	38.1-39.0	≥39.1	
<4.0 or >12.0	White blood cell count (10^9/L)							

* Consciousness and inspired O2 were not considered for the study

STATISTICAL ANALYSIS

The underlying diagnoses were divided into two groups: acute leukaemia (AML, ALL and MDS) and other haematological malignancies (e.g. lymphoma, multiple myeloma, chronic leukaemia). Therapeutic procedures were categorized into three groups: autologous HSCT, myeloablative allogeneic HSCT and chemotherapy. Continuous variables were summarized by mean values and standard deviations (SD) or by median values and interquartile range [IQR] if the data were not normally distributed. To test differences between groups we applied the independent *t*-test or Mann-Whitney-U test for continuous variables and Fisher's exact test for categorical variables. Values for SIRS and R-MEWS were calculated both with and without including the value for body temperature. Spearman's correlation was used to compare the number of SIRS criteria with the R-MEWS score. Two-tailed *p*-values ‹0.05 were considered to indicate statistical significance. Statistical analyses were performed by use of IBM SPSS Statistics version 20.

RESULTS

STUDY POPULATION

Initially, 155 patients were screened of which 42 had to be excluded because of missing microbiological data at t1 (*n*=10) or missing values for body temperature at t4 (*n*=32), resulting in a cohort of 113 patients. Demographic data are depicted in table 2. The main reason for admission was autologous HSCT (*n*=50, 44%) followed by allogeneic HSCT (29%) and chemotherapy (27%). All patients were severely neutropenic (neutrophil count ‹0.5x10^9/L) at the onset of fever. Complete data to compare the number of SIRS criteria with the value of R-MEWS was available for only 50 patients. The only statistically significant difference between those with completed R-MEWS and those with incomplete R-MEWS was that completion rates for the R-MEWS scores was significantly higher for those patients with persistent fever (17/50=34%) than for those with incomplete scores (8/63=13%) (table 2).

ONSET OF FEVER AND EMPIRICAL ANTIBACTERIAL THERAPY

Fever developed 13 days (SD±7) after the start of chemotherapy. For HSCT recipients (*n*=83) this was four days (SD±4) following stem cell infusion. Antibacterial treatment was started in every case at the onset of fever according to the protocol. The time between fever and the first dose of antibiotics was median 25 minutes [IQR 20-30] and most patients were initially treated with ceftazidime (*n*=106, 94%), with the remainder receiving meropenem. The time fever was first recorded was distributed over the whole day though only 23% occurred within office hours (9-5 pm).

HSCT Haematopoietic stem cell transplant

a Independent T-test
b Fisher's exact test

Table 2 Demographic data for the complete sample (*n*=113) and the subgroups with (*n*=50) and without (*n*=63) completed Radboudumc Modified Early Warning Scores (R-MEWS)

	Sample *n*=113	Completed R-MEWS *n*=50	Uncompleted R-MEWS *n*=63	*p*-value
Demographics				
Age (years, mean and sd)	51 (±14)	53 (±13)	49 (±15)	0.24[a]
Male gender	68 (60%)	29 (58%)	39 (62%)	0.70[b]
Diagnosis				0.60[b]
– Acute myeloid leukaemia	46 (41%)	18 (36%)	28 (44%)	
– Acute lymphoblastic leukaemia	7 (6%)	3 (6%)	4 (6%)	
– Myelodysplastic syndrome	5 (4%)	3 (6%)	2 (3%)	
– Multiple myeloma	24 (21%)	14 (28%)	10 (16%)	
– Non-Hodgkin's lymphoma	16 (14%)	6 (12%)	10 (16%)	
– Myelofibrosis	4 (4%)	3 (6%)	1 (2%)	
– Hodgkin's lymphoma	4 (4%)	1 (2%)	3 (5%)	
– Chronic myeloid leukaemia	2 (2%)	1 (2%)	1 (2%)	
– Other	5 (4%)	1 (2%)	3 (6%)	
Therapeutic procedure				0.73[b]
– Autologous HSCT – HDM	25 (22%)	15 (30%)	10 (16%)	
– Autologous HSCT – BEAM	16 (14%)	7 (14%)	9 (14%)	
– Autologous HSCT – other	9 (8%)	4 (8%)	5 (8%)	
– Allogeneic HSCT – Ida/cyclo/TBI	15 (13%)	5 (10%)	10 (16%)	
– Allogeneic HSCT – ATG/cyclo/TBI	12 (11%)	7 (14%)	5 (8%)	
– Allogeneic HSCT – other	6 (5%)	3 (6%)	3 (5%)	
– Non-HSCT chemotherapy	30 (27%)	9 (18%)	21 (33%)	
Origin of fever				
Infectious	79 (70%)	33 (66%)	46 (73%)	0.54[b]
– Microbiologically defined (MDI)	70 (62%)	30 (60%)	40 (64%)	0.85[b]
– Clinically defined (CDI)	37 (33%)	14 (28%)	23 (37%)	0.42[b]
Persistent fever on t4	25 (22%)	17 (34%)	8 (13%)	0.01[b]
– Autologous HSCT	17/50 (34%)			
– Allogeneic HSCT	6/33 (18%)			
– Non-HSCT chemotherapy	2/30 (7%)			

CAUSES OF FEBRILE NEUTROPENIA

Fever could be explained by an infectious event in 79 cases (70%).

— *Microbiologically defined infection (MDI)*

A microbiologically defined infection was found in 70 patients:

- *Streptococcus mitis* (*n*=27, 40%), of which three were in combination with other species; *Pseudomonas aeruginosa* (1x), *Klebsiella oxytoca* (1x), *Enterococcus casseliflavus* (1x).
- Coagulase-negative staphylococci (*n*=19, 28%), of which two in combination with other species (*Enterococcus faecalis* (1x), *Rothia mucilaginosa* (1x)).
- Combination of coagulase-negative staphylococci and *Streptococcus mitis* (n=11, 16%), of which one was also in combination with another species (*Enterococcus casseliflavus*). One patient also developed probable invasive aspergillosis.
- The remaining eleven patients (16%) had bacteraemia due to; viridans streptococci (2x), *Escherichia coli* (2x), *Enterococcus faecalis* (3x), Group G streptococcus (1x), *Pseudomonas aeruginosa* (1x), *Rothia mucilaginosa* (1x) and *Staphylococcus aureus* (1x).

Another two patients had MDI that did not involve bacteraemia: one patient had *Clostridium difficile* enteritis and the other had oral herpes infection.

— *Clinically defined infection (CDI)*

Clinically defined infection solely was reported in nine patients: a pulmonary infiltrate in seven patients (of which one in combination with sinusitis), pneumonia and sigmoiditis (both *n*=1).

In 28 (40%) of the 70 patients with a MDI, also a CDI was identified: pulmonary infiltrates (*n*=18), central line associated thrombosis (*n*=6) or a combination of both (*n*=2), CVC exit site infection (1x) and probable aspergillosis (1x).

— *Unexplained fever*

In total 34 febrile episodes (30%) could not be related to MDI or CDI and were defined as unexplained fever. Sixteen of these episodes may have been associated with oral mucositis and a further two with oesophagitis.

RISK FACTORS FOR PERSISTENT FEVER

On the fourth day of antibacterial therapy, fever persisted in 25 patients (22%). The type of chemotherapeutical regimen was significantly different between the groups with and without persistent fever (*p*=0.01, table 3). Persistent fever presented most frequently following autologous HSCT; 17/50 (34%). Following allogeneic HSCT and non-HSCT chemotherapy persistent fever was seen in 18% and 7% of the patients, respectively.

Age, gender and underlying diagnosis were not related to persistent fever at t4. There was also no difference between those with or without persistent fever in terms of whether or not infection had been present at the onset of fever (p=0.47). Persistence of bacteraemia was equally distributed over the two groups with and without persisting fever (p=0.79).

Table 3 Influencing factors for persistent fever on t4 (n=113)

	Persistent fever n=25	No persistent fever n=88	p-value
Demographics			
– Age (years, mean and sd)	52 (±12)	51 (±14)	0.80[a]
– Male gender	13 (52%)	55 (63%)	0.36[b]
Diagnosis			0.26[b]
– AML, ALL, MDS	10 (40%)	48 (54%)	
– Other	15 (60%)	40 (46%)	
Therapeutic procedure			0.01[b]
– Non-HSCT chemotherapy	2 (8%)	28 (31%)	
– Autologous HSCT	17 (68%)	33 (38%)	
– Allogeneic HSCT	6 (24%)	27 (31%)	
Origin of fever			0.47[b]
Infectious (MDI and/or CDI)	16 (64%)	63 (72%)	
Unexplained fever	9 (36%)	25 (28%)	

AML Acute myeloid leukaemia
ALL Acute lymphoblastic leukaemia
MDS Myelodysplastic syndrome
HSCT Haematopoietic stem cell transplant
MDI Microbiologically defined infection
CDI Clinically defined infection

a Independent T-test
b Fisher's exact test

SIRS AND R-MEWS AND PERSISTENT FEVER (*n*=50)

A strong positive correlation was found between the number of SIRS criteria and the calculated value of R-MEWS at t1 (Spearman's ρ=0.81, p<0.01) and t4 (Spearman's ρ=0.75, p<0.01) indicating at least equal validity on the haematology ward. The number of SIRS criteria as well as the R-MEWS were similar at t1 for patients with and without persisting fever (p=0.77 and p=0.56 respectively) but were different at t4, even when body temperature was excluded. Significantly higher values were found for patients with persistent fever, indicating that clinical change occurred more often in those with persistent fever (table 4). Figure 1 shows the change in R-MEWS between t1 and t4 for each individual patient. Increase of R-MEWS occurs most frequently for those with persisting fever, decrease of R-MEWS was most seen in patients without fever at t4.

Table 4 Differences in clinical inflammatory scores between SIRS and R-MEWS for patients with and without persistent fever on t4 (*n*=50)

	Persistent fever *n*=17	No persistent fever *n*=33	*p*-value[a]
Cumulative R-MEWS on t1	3 [2-5.5]	3 [2-5]	0.56
Cumulative R-MEWS on t4	3 [2-5]	1 [0-2.5]	<0.01
Cumulative R-MEWS on t4 excl. fever	2 [1-3.5]	1 [0-2]	0.02
SIRS on t1	3 [3-3.5]	3 [3-3.5]	0.77
SIRS on t4	3 [2-4]	1 [1-2]	<0.01
SIRS on t4 excl. fever	2 [1-3]	1 [1-2]	0.01

Data are expressed as median with [IQR]

R-MEWS Radboudumc Modified Early Warning Score
SIRS Systemic inflammatory response syndrome

a Mann-Whitney-U test

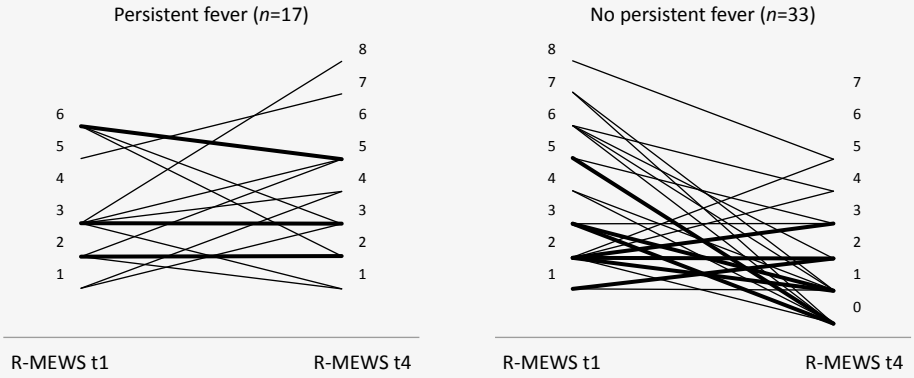

Figure 1 Change in Radboudumc Modified Early Warning Score (R-MEWS) between onset of fever (t1) and four days later (t4), compared between febrile (left) and afebrile (right) patients on day 4. The thickness of the lines represent the number of patients (range 1-4).

DISCUSSION

We showed a strong correlation between the number of SIRS criteria and the calculated value of R-MEWS, suggesting that R-MEWS is a valid alternative in daily practice to detect vital changes early on in the clinical status of febrile patients. R-MEWS can easily be incorporated into protocols for monitoring patients as it makes use of measurements already taken by nurses. R-MEWS is also useful as a dynamic instrument to trigger intensive supportive care and optimal resuscitation, including intensive care admission when required [15, 19].

It is worthy of note that approximately a quarter of patients treated with intensive chemotherapy have persistent fever despite early appropriate broad-spectrum antibacterial treatment at the onset of fever. In the current study this could not be explained by microbiologically or clinically defined infections nor by failing to institute antibacterial treatment in a timely manner. This phenomenon has been noted earlier and was assumed to be the natural course of fever even when the underlying infection was successfully treated with antibiotics [20]. This suggests another explanation for fever namely inflammation directly caused by chemotherapy. The complex pathobiology that leads to inflammation response due to direct toxicity of conditioning regimen has been described by Blijlevens *et al.* [21]. Van der Velden *et al.* also contended that mucotoxicity induced by a given conditioning regimen determines the pattern of inflammatory response, irrespective of the presence or absence of infection [22]. The same study also reported the mucotoxicity of melphalan which was given to the autologous HSCT recipients in the current study who suffered from persistent fever (34%) [22].

We cannot conclude with certainty that the type of conditioning regimen determines persistent fever, not at least because of the retrospective character of the study and the size of the population studied. However, the initial group comprised more than 100 first episodes of fever all of which developed during neutropenia following chemotherapy. That persistent fever affected almost 1 in 4 episodes despite adequate and timely treatment with broad spectrum antibacterials is a well known phenomenon [9]. Recent literature supports our contention that the type of conditioning therapy, and more specifically the mucotoxicity of the regimen, play a major role in inflammation which frequently manifests itself by persistent fever.

Our finding of higher R-MEWS at t4 and more patients with an increased R-MEWS at t4 compared to t1 for patients with persistent fever does suggest that this is the group that is most likely to develop critical illness. It might be interesting to investigate the relation between R-MEWS and clinical outcomes like ICU admission and hospital mortality, which

was in the current study not possible to retrospectively analyse because data were gathered only for eight days around the initial fever.

Of interest is the recent publication of Hands et al. showing that compliance in recording vital signs was better for sicker patients suggesting that nursing staff do manage patients with higher early warning scores differently from those with lower values [11]. This finding is supported in our population where R-MEWS on the fourth day of fever was completed significantly more often for those with persistent fever (68 versus 38%). Indeed this suggests that fever provides an extra stimulus to nurses to intensify measuring the vital signs. It is also recommended that vital signs should be monitored carefully when patients without fever are receiving antipyretics and corticosteroids as these suppress body temperature.

In conclusion, R-MEWS looks promising as a tool for determining clinically relevant changes in patients being treated with intensive chemotherapy for haematological malignancies. Future prospective multi-centre research should focus on further validation of this instrument in the context of neutropenic sepsis and its relation with adequate initiation of intensive supportive care. We were also able to study a population of neutropenic patients and identify inflammation due to the preceding therapeutic procedure, and not infection per se, as a likely determinant of persistent inflammation. These findings may contribute to a better understanding and management of neutropenic patients who develop critical illness following intensive treatment.

RECOMMENDATIONS FOR DAILY PRACTICE

1. Persisting fever after four days of adequate antibacterial treatment in neutropenic patients following intensive chemotherapy is associated with higher R-MEWS. R-MEWS might be a better predictor of clinical deterioration than solely the SIRS criteria, allowing to trigger appropriate intensive supportive care to be instituted in a timely manner.
2. A modified early warning score such as R-MEWS is feasible to be used in the clinic to monitor vital signs so as to detect any clinical deterioration in patients, whatever the cause.
3. R-MEWS merits formal investigation in a prospective longitudinal study to evaluate its usefulness in daily practice and its clinical utility in improving patient outcomes.

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5

Incidence of and risk factors for persistent gram-positive bacteraemia and catheter-related thrombosis in haematopoietic stem cell transplantation

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ABSTRACT

A cohort of 439 haematopoietic SCT recipients was analysed to determine the incidence of Gram-positive coccal bacteraemia and thromboembolic events associated with the use of central venous catheters (CVCs) and to determine risk factors for these complications. The incidences of persistent coagulase-negative staphylococcal (CoNS) bacteraemia, symptomatic thrombosis and thrombophlebitis were 25%, 9.6% and 6.6%, respectively. Duration of neutropenia (in days, odds ratio (OR) 1.02; p=0.04) and leftsided placement of the CVCs (OR 1.73; p=0.03) were independent risk factors for the occurrence of persistent CoNS bacteraemia, whereas the use of less mucotoxic conditioning regimens was associated with a lower risk (high-dose melphalan (HDM)/BEAM vs. other regimens, OR 0.24; p<0.001). Use of TBI, persistent CoNS bacteraemia and tip colonisation were all significantly associated with an increased risk of symptomatic thrombosis (OR 6.03, 3.36 and 2.80, respectively; p≤0.02). The risk factors found in this cohort of SCT recipients differed from those found in the general cancer population, showing an important role for persisting bacteraemia in the pathogenesis of CVC-associated thrombosis. Therefore, we constructed a new algorithm in order to improve catheter management and prevent these CVC-related complications.

INTRODUCTION

Central venous catheters (CVCs) are widely used for managing patients receiving intensive chemotherapy to prepare them for an autologous or allo-SCT [1]. The use of CVCs is not without complications, with some being related to the insertion procedure (for example, pneumothorax) and others (for example, infection and thrombosis) occurring later. The CVC infection mostly involves coagulase-negative staphylococci (CoNS) that originate from the resident commensal flora of skin and gut, and can occur through either an exogenous route (for instance, migration from the skin along the catheter tract or via catheter hub) or an endogenous route as a result of haematogenous seeding from a distant infection site or disrupted mucosal barriers of the oral cavity and gastrointestinal tract [2,3]. The pathogenesis of CVC-related thrombosis is complex and is thought to result from activation of coagulation pathways by the foreign material in the bloodstream with formation of a thrombin sheath covering the CVC, the occurrence of vascular endothelial damage and endothelial cell activation by disturbed haemodynamics [4]. Infection can also stimulate thrombus formation by aggravating coagulation, but the presence of a thrombus mass or thrombin sheath around the CVC also increases the risk for microbial colonisation and bacteraemia [5]. The CVC-related thrombosis can result in serious complications, including pulmonary embolism and, when infected, it increases the risk of endocarditis and septic embolisms considerably [6,7].

We employ a conservative approach towards the treatment of a single episode of bacteraemia due to CoNS and neither routinely employ antibiotics nor remove the CVC. This emanates from our observation that early-onset CoNS bacteraemia results from endogenous spread of the staphylococci from mucosal barrier injury to the oral cavity or gut and does not involve a primary infection of the device [8,9]. However, persistent CoNS bacteraemia increases the probability of an infection of the CVC and predisposes to device-related thrombosis of the subclavian vein. However, we wished to determine whether or not this hypothesis was justified and hence undertook a retrospective analysis to investigate the risk factors for persistent CoNS bacteraemia and thrombosis, define their relationship to each other and generate a CVC management algorithm based on our findings.

MATERIALS AND METHODS

STUDY POPULATION

We reviewed the records of all consecutive patients who had received a SCT from January 2006 to December 2011 at our tertiary care centre. We selected three groups of SCT recipients: group 1: those who had been given a conditioning regimen consisting of high-dose melphalan (HDM) or BEAM for an autologous SCT; group 2: those who had been given a myeloablative conditioning regimen consisting of CY together with either TBI or BU with or without idarubicin for an allo-SCT; and group 3: those who had been given a non-myeloablative conditioning regimen consisting mainly of CY together with fludarabine for an allo-SCT [10]. Patients who had received a graft from an unrelated donor had also received antithymocyte globulin.

SUPPORTIVE CARE

Patients did not receive haematopoietic growth factors or prophylactic anticoagulants. Antimicrobial prophylaxis consisted of 500mg ciprofloxacin and 500mg valaciclovir, both given twice daily. In case of fever during neutropenia, empirical therapy was started with 2000mg ceftazidime given three times daily intravenously. A single episode of CoNS bacteraemia was not a ground for modifying empirical therapy by adding a glycopeptide to the antimicrobial regimen.

CVC PROCEDURE, MANAGEMENT AND COMPLICATIONS

All patients had been managed using a nontunnelled, three or four lumen, uncuffed, 8.5 French, polyurethane catheter that was not coated with any antibiotics (Arrow International Inc., USA). CVCs had been inserted by trained personnel, namely, haematologists, physician assistants and nurse specialists. Catheter passports had also been filled out by a nurse during insertion to collect data regarding the CVC procedure. After CVC placement, the proper positioning and absence of pneumothorax had been confirmed by a chest X-ray. Maximal sterile barrier precautions were used during all insertions following Centers for Disease Control and Prevention (CDC) guidelines [11]. Local CVC management was achieved by using chlorhexidine 0.5%/alcohol 75% for disinfection [11, 12]. Antibiotic locks were not used at any time and glycopeptides were only given when clinically indicated.

Blood (10 mL) had been routinely drawn for aerobic culture each Monday and Thursday from each lumen of the CVC. At the onset of fever, 40mL of peripheral blood had been obtained for culture together with 10mL from each lumen of the catheter. A blood culture was considered positive if one or more bottles yielded a microorganism, except for CoNS, for which two separate positive blood cultures, drawn at the same time, yielding the same strain were required [13]. Persistent bacteraemia was defined as two or more consecutive episodes of bacteraemia, at least 24 h apart, involving the same bacterial species.

In case of CVC symptoms and signs of thrombosis, an ultrasonography of the upper extremity was performed. In case of a negative ultrasonography and high clinical suspicion of thrombosis, a venography was ordered. Symptomatic thrombosis was defined as a thrombus seen on imaging accompanied by signs and symptoms of upper extremity thrombosis. Septic thrombophlebitis was defined as symptomatic thrombosis accompanied by persistent CoNS [14].

STATISTICAL ANALYSIS

We employed descriptive statistics for patient, SCT procedure and CVC characteristics. Only data on the first CVC episode during SCT were included in the analysis. Data were expressed as frequencies, mean values with SD or median values with the range. Differences in median duration of neutropenia and CVC duration were evaluated using Mann-Whitney *U*-tests. Incidences of CoNS bacteraemia, persistent bacteraemia, symptomatic thrombosis and thrombophlebitis were calculated as the proportion of patients experiencing these complications as well as the rate per 1000 CVC-days.

The first episode of bacteraemia due to Gram-positive bacteria that occurred while the CVC was in place was recorded for each patient. Potential risk factors for the occurrence of persistent CoNS bacteraemia and thrombosis were evaluated by means of logistic regression. Potential risk factors were univariately tested with the Wald x^2 test. Those with a *P*-value of <0.20 were included in the multivariate analysis. The final multivariate model was selected through a backward selection procedure with $P<0.05$. Confounders that were considered clinically relevant were included in the selection procedure. Crude and adjusted odds ratios (ORs) with 95% confidence interval were presented. In addition, in each model, the ability to discriminate between patients with and without the complication at issue was quantified by the C-index. The association between two dichotomous variables was evaluated with the x^2 test. All statistical analyses were carried out in SAS 9.2 (Cary, NC, USA).

RESULTS

PATIENT CHARACTERISTICS

We initially reviewed 506 consecutive SCT recipients. A total of 67 patients were excluded from the analysis because of incomplete follow-up due to transfer to another hospital (*n*=36), death within the first week of SCT (*n*=7), multiple SCTs (*n*=20) and lack of surveillance blood cultures (*n*=4). The final cohort therefore consisted of 439 patients, of whom 245 (56%) had received an auto-SCT and the remaining 194 (44%) an allo-SCT. The characteristics of these patients and the SCT and CVC procedures are depicted in table 1. The CVCs of the 439 patients contributed to a total of 8273 catheter-days. Three-quarters of the CVCs had been placed on the right with almost all being positioned in the subclavian vein (95.9%). The median duration that CVCs were in place was 18 days (range 6–51). The median time to CVC removal was 17, 21 and 16 days for conditioning groups 1, 2 and 3, respectively.

Table 1 Patient, SCT procedure and central venous catheter characteristics

Characteristics (*n*=439[a])	Median (range)/*n* (%)
Age at SCT (years)	53 (16-66)
Male gender	265 (60%)
Diagnosis	
– AML/ALL/MDS	148 (34%)
– NHL	117 (27%)
– MM	137 (31%)
– CML/CLL	18 (4%)
– Other	19 (4%)

(cont. table 1)

Conditioning regimen	
– HDM (group 1)	140 (32%)
– BEAM (group 1)	73 (17%)
– CY+ATG+TBI/BU (group 2)	75 (17%)
– CY+FLu+ATG (group 3)	40 (9%)
– CY+TBI/BU (group 2)	15 (3%)
– Ida+CY+TBI/BU (group 2)	87 (20%)
– Other	9 (2%)
TBI	147 (33%)
Neutropenia duration (days)	13 (5-89)
– HDM/BEAM (group 1)	10 (5-31)
– Allogeneic myeloablative (group 2)	15 (5-89)
– Allogeneic nonmyeloablative (group 3)	18 (6-64)
Type of SCT	
– Autologous	245 (56%)
– Allogeneic, (M)MUD	103 (23%)
– Allogeneic, MRD	91 (21%)
Stem cell source (*n*=433)	
– Peripheral blood	382 (88%)
– BM	51 (12%)
Hospitalisation duration (days)	26 (13-218)
Duration CVC *in situ* (days)	18 (6-51)
Side of CVC placement (*n*=436)	
– Right side	328 (75%)
– Left side	108 (25%)

(cont. table 1)

CVC vessel (*n*=436)	
– Subclavian vein	418 (96%)
– Jugular vein	18 (4%)
Insertion attempts (*n*=274)	
– 1	166 (61%)
– >1	108 (39%)
Insertion time (*n*=265)	
– ≤2	174 (66%)
– 2-5	91 (34%)

ATG Antithymocyte globulin
CVC Central venous catheter
HDM High-dose melphalan
Ida Idarubicine
MDS Myelodysplastic syndrome
MM Multiple myeloma
MRD Matched related donor
(M)MUD (Mis)matched unrelated donor
NHL Non-hodgkin lymphoma

a Characteristics involve all 439 patients except when stated otherwise

GRAM-POSITIVE BACTERAEMIA

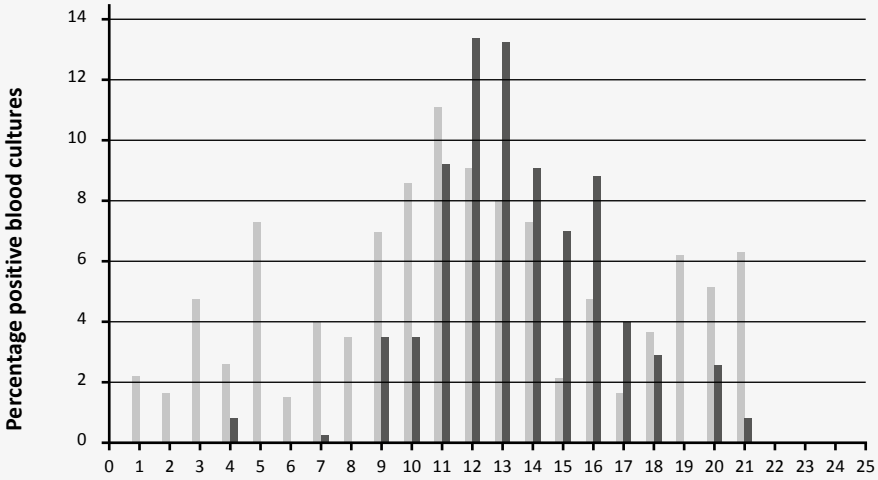
— *Incidence of Gram-positive bacteraemia*

CoNS bacteraemia was diagnosed in 186 (42.4%) patients during the period the CVC was in place, and persisted in 110 (25.1%) cases. Hence, 76 (40.9%) cases of CoNS bacteraemia resolved without additional antibiotic therapy. Bacteraemia due to oral viridans streptococci (OVS) occurred in 146 (33.3%) cases, and persisted in only six cases. There were only 17 (3.8%) cases of enterococcal bacteraemia. This corresponds to 22.5 CoNS, 13.3 persistent CoNS, 17.6 OVS and 2.0 enterococcal bacteraemias per 1000 catheter-days, with a median time to occurrence of bacteraemia of respectively 11.0, 11.0, 13.0 and 16 days after CVC insertion (figure 1). The peak incidence of CoNS and OVS bacteraemia occurred almost simultaneously, on days 10–14 and 11–14, respectively (figure 1). Of the 186 patients who did experience a CoNS bacteraemia, 33.9% (63) also experienced a bacteraemia with OVS, and in more than two thirds of them both microbes were cultured at the same day. Culture of the CVC tip after removal yielded positive results for CoNS in 33.3% (146/439) of cases.

Persistent CoNS bacteraemia was associated with a positive tip culture after CVC removal (x^2=82.18; p<0.0001).

— *Risk factors for persisting CoNS bacteraemia*

In univariate analysis, the risk factors that were associated with persisting CoNS bacteraemia (p<0.20) included age at transplantation, conditioning regimen, use of TBI, duration of neutropenia, stem cell source, side of catheter insertion and the vessel into which the device was inserted (table 2). In the multivariate analysis model, only conditioning regimens in groups 2 and 3 (OR=4.17), the leftsided placement of CVC insertion (OR=1.73) and a longer duration of neutropenia were significantly associated with an elevated risk of persistent CoNS bacteraemia (table 2). However, the type of conditioning was the strongest explanatory factor for persistent CoNS bacteraemia (group 1 (30/215, 14.0%) vs. groups 2 and 3 (80/224, 35.7%), p<0.001). The C-index of the multivariate model was 0.761, indicating good discriminatory performance of the incorporated factors for the occurrence of persistent CoNS bacteraemia.



Day	0	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
CNS	0	2	1	10	3	6	3	12	4	10	**22**	**24**	**15**	**17**	**20**	3	6	3	5	4	4	7	0	0	0	0
OVS	0	0	0	0	1	0	0	1	0	5	9	**20**	**22**	**28**	**25**	10	11	7	4	0	2	1	0	0	0	0

Figure 1 First positive blood cultures in time from placement of CVC and start of conditioning therapy. The upper panel indicates the proportion (positive blood culture/total number of blood cultures on that day) of the first positive blood cultures yielding CoNS (lighter bars) and OVS (darker bars). The lower panel indicates absolute number of the first positive blood cultures depicted for each days, with peak incidence values in bold (≥15 blood cultures positive). The peak incidence of CoNS and OVS bacteraemia occurred almost simultaneously, on days 10-14 and 11-14, respectively.

THROMBOTIC COMPLICATIONS

— *Incidence of symptomatic thrombosis and septic thrombophlebitis.*

Diagnostics had been performed in 48 (10.9%) of cases because of signs or symptoms indicative of an upper extremity thrombosis, and thrombosis was radiologically confirmed in 42 cases, giving a rate of 9.6% or 5.0 cases per 1000 catheter-days. Diagnosis had been established by ultrasonography alone in 19 cases, and a further 17 cases were diagnosed only after subsequent venography. The remaining six cases were diagnosed by either a venography or CT scan alone. The diagnosis of thrombosis was made in a median of 21 days (range 7–33) from CVC insertion. Septic thrombophlebitis occurred in 29 (6.6%) cases, which is 69.0% (29/42) of those with symptomatic thrombosis. Persistent CoNS bacteraemia had preceded the diagnosis of thrombosis in every case. Severe complications developed in 2 of these 42 cases: one case of symptomatic pulmonary embolism and one case of a superior vena cava syndrome. In two other patients, thrombophlebitis was confirmed by positron emission tomography/computed tomography in which septic pulmonary emboli were detected (figure 2) [15]. No deaths were attributed to the CVC-related complications.

As expected, the occurrence of persistent CoNS bacteraemia and/or thrombosis resulted in early removal of the CVC, and hence an overall shorter median time of the CVC remaining in situ (16 vs. 19 days, $p<0.0001$).

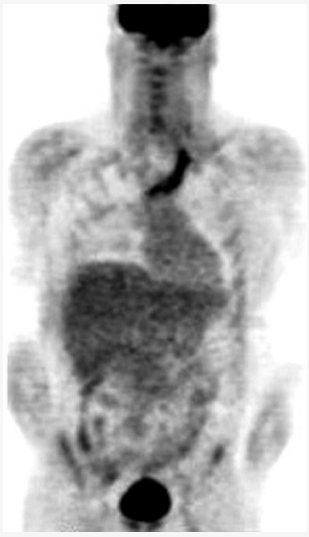


Figure 2 Septic thrombosis. Positron emission tomography (PET) scan of a patient with persisting fever and CoNS bacteraemia during neutropenia revealing a thrombophlebitis of the left brachiocephalic vein. This was missed on the initial ultrasonography that had been performed at approximately the same time as the PET scan, and only days later a second ultrasonography became positive (Courtesy of Dr Vos [15]).

— *Risk factors for symptomatic thrombosis*

In univariate analysis gender, conditioning type, use of TBI, duration of neutropenia, stem cell source, CVC side, occurrence of persistent bacteraemia and CVC tip culture were all associated ($p<0.20$) with the occurrence of symptomatic thrombosis (table 2). In multivariate analysis, only the use of TBI, occurrence of persistent CoNS bacteraemia and a positive CVC tip culture were significantly associated with increased risk. The C-index of the multivariate model was 0.868, indicating that discriminative ability for the occurrence of symptomatic thrombosis by these factors was high.

The occurrence of the persisting bacteraemia and symptomatic thrombosis were significantly correlated (x^2, $p<0.0001$). Patients who experienced a persistent CoNS bacteraemia developed a symptomatic thrombosis in 29 (26.4%) of 110 cases, opposed to only 13 (4.0%) of the 329 patients who did not (OR 8.70, 95% confidence interval 4.33–17.49, $p<0.01$). Hence, the negative predictive value of persistent CoNS bacteraemia for the occurrence of symptomatic thrombosis was high (that is, 96%), whereas the positive predictive value was low (that is, 26.5%).

Table 2 Univariate and multivariate analyses of risk factors for persistent coagulase-negative staphylococcal bacteraemia and CVC-related symptomatic thrombosis

Risk factors	Persisting CNS bacteraemia (*n*=186)				Symptomatic thrombosis (*n*=48)			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p*-value[a]	OR (95% CI)	*p*-value[a]	OR (95% CI)	*p*-value[a]	OR (95% CI)	*p*-value[a]
Age at transplantation (per year)	**0.99 (0.97-1.00)**	**0.12**	-	**NS**	**1.00 (0.97-1.03)**	**>0.20**	-	-
Gender (male vs. female)	1.02 (0.66-1.59)	>0.20	-	-	1.60 (0.84-3.02)	0.15	-	NS
Conditioning regimen (group 1 vs. 2/3*)	**0.29 (0.18-0.47)**	**<0.01**	**0.24 (0.14-0.42)**	**<0.01**	**0.12 (0.05-0.31)**	**<0.01**	**-**	**NS**
Total body irradiation (yes vs. no)	**2.86 (1.83-4.46)**	**<0.01**	-	**NS**	**6.83 (3.32-14.04)**	**<0.01**	**6.03 (2.75-13.26)**	**<0.01**
Neutropenia duration (per day)	**1.03 (1.01-1.06)**	**<0.01**	**1.02 (1.00-1.05)**	**0.04**	**1.03 (1.01-1.05)**	**0.02**	-	**NS**
Stem cell source (BM vs. PB)	**1.96 (1.06-3.62)**	**0.03**	-	**NS**	**1.97 (0.86-4.53)**	**0.11**	-	**NS**
CVC insertion side (left vs. right)	**1.72 (1.07-2.77)**	**0.03**	**1.73 (1.01-2.94)**	**0.03**	**2.53 (1.32-4.88)**	**<0.01**	-	**NS**
CVC vessel (jugularis vs. subclavia)	**1.95 (0.74-5.15)**	**0.18**	-	**NS**	**1.94 (0.54-7.01)**	**>0.20**	-	-
CVC insertion attempts (>1 vs. 1)	**1.31 (0.76-2.27)**	**>0.20**	**-**	**-**	**0.66 (0.29-1.52)**	**>0.20**	-	-
CVC insertion time (>5 vs. ≤5 minutes)	1.40 (0.79-2.46)	>0.20	-	-	0.58 (0.24-1.40)	>0.20	-	-
Persistent CNS bacteraemia (yes vs. no)	-	-	-	-	**8.70 (4.33-17.49)**	**<0.01**	**3.36 (1.50-7.54)**	**<0.01**
Tip culture CNS (positive vs. negative)	-	-	-	-	**6.76 (3.29-13.92)**	**<0.01**	**2.80 (1.19-6.55)**	**0.02**

CI Confidence interval
CVC Central venous catheter
CoNS Coagulase-negative staphylococcus
OR Odds ratio
NS P>0.05

* For the definition of groups, see the *Materials and Methods* section
a Only factors with *p*-value <0.20 are shown as only these were included in the multivariate analysis. Significant factors on multivariate analysis are indicated in bold.

All factors were corrected for the duration that the CVCs remained *in situ*.

DISCUSSION

We identified several risk factors for persistent CoNS bacteraemia and thrombosis. Persistent CoNS bacteraemia was significantly related to the duration of neutropenia, the conditioning regimen and a left-sided placement of the CVC. Persistence of bacteraemia requires a source of infection and inadequate eradication of the microorganism. This probably explains neutropenia being a risk factor, although residing macrophages and dendritic cells might sometimes be sufficient to eradicate these indolent opportunistic pathogens. This might also explain the fact that 40% of bacteraemias resolved without the use of additional antibiotic therapy. The CVC device itself is usually presumed to be the source of bacteraemia, whereas the mucosal barrier may well be the origin, as the conditioning regimen proved to be an independent and the strongest risk factor associated with persistent bacteraemia. The more myelotoxic regimens are also the most mucotoxic and these resulted in a fourfold increased risk. This suggests that, apart from neutropenia, persistent bacteraemia might well have been directly related to the mucotoxic effects of the conditioning regimen. Moreover, the staphylococci involved may well have originated from the gut as these are usually resistant to the quinolones used for prophylaxis and may overgrow on the gut surfaces left vacant by the microbiota that have been suppressed by the antibiotic. This suggestion is supported by the fact that most of the CoNS bacteraemias occurred 10–14 days after CVC insertion as did the occurrence of OVS bacteraemia, which is known to originate from oral and intestinal mucosal barriers at the peak of intestinal damage [10]. In addition, Costa et al. [8] have shown that most CoNS that were cultured from the blood of SCT recipients were more similar to those recovered from the mucosal surfaces than those from the skin. Although the mucosal barriers might well be the initial source of infection, the question remains of whether persistent bacteraemia results from continuing haematogenous seeding from the mucosa, a secondary infection of the CVC or, indeed, an ongoing primary CVC infection. Importantly, CVC insertion and care measures were implemented according to best practice, and hence colonisation and infection of the CVC via the insertion site by the skin flora was less likely [11].

The reason a left-sided placement increased the risk might be related to differences in anatomy and disturbed blood flow [1]. However, it might also be simply a consequence of our preference for a right-sided placement of the CVC over a left-sided placement, as the latter is only chosen when problems arose during the procedure or had occurred in the past (for example, earlier thrombosis). Using standardised CVC procedures in intensive care units has shown that the CVC site of insertion is unimportant, but the setting is not comparable to the haematology wards as few patients in the intensive care units suffer from mucositis and neutropenia induced by cytotoxic therapy [16].

The incidence of catheter-associated thrombosis was relatively high (9.5%), and is in the same range as found in prospective studies and retrospective studies of SCT recipients [17-20]. However, lower incidences have also been reported, although the use of prophylactic anticoagulants for CVC thrombosis might have influenced these results [21-23]. We found the use of TBI, occurrence of persistent CoNS bacteraemia and a positive catheter-tip culture -an indication of catheter colonisation- as the strongest risk factors for CVC-associated thrombosis. The use of TBI has seldom been noted as a risk factor for venous thrombosis, but has a pathophysiological basis as TBI is known to induce damage to the vascular endothelium, which is a known risk factor for thrombosis [24, 25]. CVC-related infection is a known risk factor for CVC associated thrombosis, but it has not been consistently reported in cohort analyses among patients with cancer, although it seems to play an important role in haematology patients and especially in those receiving a SCT [1]. The use of more myelotoxic and mucotoxic regimens to prepare for an SCT exposes patients to more tissue damage, including mucosal and endothelial damage, a higher incidence of bacteraemia, and thus a higher risk for thrombosis. Perturbation of endothelial integrity and function resulting from infection and the presence of intravascular foreign material and the procoagulant effect of infection contribute to enhanced coagulation and thrombus formation culminating in thrombophlebitis. As the definition of CVC-related infection is neither consistent nor easy to employ in clinical practice, thrombotic risk in SCT patients could be better established by monitoring for persistent positive blood cultures. This also obviates contentious discussions on the primary infection sources that are impossible to settle and only tend to confuse rather than clarify decision making.

We did not explore some risk factors for CVC-related thrombosis reported in a large meta-analysis, namely, catheter type, insertion site and catheter-tip position, as the CVCs we employed were of the same type, centrally inserted, and the tip position confirmed by imaging to ensure proper positioning [26]. Nor did we find support for left-sided insertion site and hereditary thrombophilia being risk factors for CVC-associated thrombosis as reported by Tesselaar et al [19]. Hereditary thrombophilia has not been assessed routinely in our patients, and the impact of the CVC insertion site was probably overshadowed in the multivariate analysis by the presence of persistent CoNS bacteraemia as these two variables were highly associated with one another.

In case of suspected deep venous thrombosis or persistent CoNS bacteraemia, the presence of thrombosis should be investigated by ultrasonography, although this diagnostic approach was not very effective in our cohort as we saw a false-negative rate of 47.2% [27]. Venography seemed more appropriate for establishing the diagnosis and may be more useful in haematology patients, although this approach has the disadvantage of detecting clinically irrelevant nonobstructive venous thrombi. In case of suspected thrombophlebitis,

positron emission tomography/computed tomography is a more attractive approach as it offers the possibility of detecting septic embolisms, although this requires more research [15]. Nevertheless, others have used ultrasonography successfully for the early detection of thrombophlebitis in selected groups of patients with CVC-related bacteraemia, thereby reducing complications and mortality [6].

As a retrospective analysis, this study has a number of limitations. First, there were missing data in some patients, mainly considering the CVC placement procedure, including number of insertion attempts and insertion time, and hence risk factors might have been missed. Second, the diagnosis of thrombosis depended upon clinical suspicion, as there was no active radiographic surveillance. Therefore, the incidence of thrombosis recorded during our study might actually be an underestimate. Nevertheless, these results reflect usual practice and the clinical significance of asymptomatic catheter-related thrombi remains unknown. The study is, however, very different in one respect, namely, by obtaining blood for culture twice a week from catheter insertion onwards we were able to detect CoNS bacteraemia before there were any signs of fever or infection and ten days before thrombosis was diagnosed.

The incidence of bacteraemia and symptomatic thrombosis we found was similar to that reported in studies on CVC complications of SCT recipients, even though we restricted antibiotic use and used no anticoagulants as prophylaxis [28, 29]. Moreover, we experienced no mortality related to the occurrence of thrombosis and thrombophlebitis. Nevertheless, thrombosis incidence was relatively high and morbidity related to CVC complications was still substantial, and hence there is clearly room for improvement. As persistent CoNS bacteraemia was a strong predictor for thrombosis, the early detection of persistent bacteraemia would likely point to an increased risk for thrombosis sufficiently early to institute appropriate interventions. Consequently, we have modified our clinical CVC care protocol to manage these complications (figure 3). The same restrictions towards the use of glycopeptides is maintained that seems appropriate if costs, toxicity and antibiotic resistance are to be minimised. The starting point is the strong association between persistent CoNS bacteraemia and subsequent complications. Hence, establishing persistent bacteraemia is crucial requiring further blood culture within two to three days of detecting. In case of persistent CoNS bacteraemia, the CVC should be removed unless there are cogent reasons to retain it. Should this be the case, then thrombosis should be excluded by venography, appropriate antibiotics should be started and a strict follow-up plan executed in order to monitor for CVC complications.

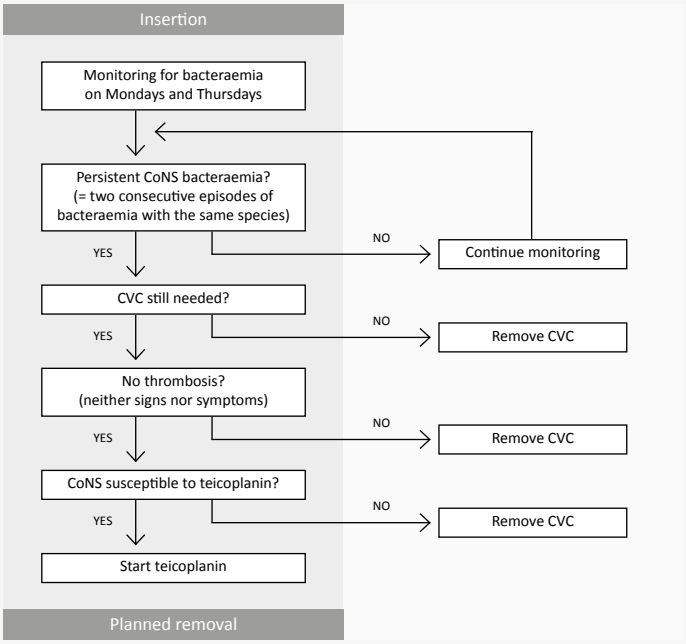


Figure 3 Algorithm for the management of CVC-related complications. This algorithm depicts our approach to managing CVCs used to manage SCT. Immediately after insertion, blood was obtained from culture every Monday and Thursday. When persistent bacteraemia due to CoNS is established, the question is asked of whether the catheter is still needed or not. If not, the catheter is removed. However, if the catheter is to be retained, the patients is examined for signs or symptoms of thrombosis and, if detected, treatment with teicoplanin is started, provided the CoNS isolate is susceptible. Otherwise the catheter is removed, blood cultures are obtained and appropriate antibiotic treatment is given until the infection is eradicated.

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PT 2

Management of the critically ill haematological patient

6

Trends in the outcomes of Dutch haematological patients receiving intensive care support

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ABSTRACT

BACKGROUND

Because of the assumed dismal prognosis there is still reluctance to admit haematological patients to the intensive care unit (ICU). This study was conducted to determine trends in outcome of allogeneic haematopoietic stem cell transplant (HSCT) recipients transferred to the intensive care unit in a Dutch tertiary care hospital.

METHODS

All patients who received allogeneic HSCT between 2004-2010 were included in the analyses. Baseline and outcome characteristics were compared and risk factors for ICU admission and survival were identified. Changes in outcome over time of three cohorts of HSCT recipients were investigated.

RESULTS

Of 319 consecutive HSCT recipients, 49 (15%) were transferred to the ICU for a median (IQR) of ten (6-45) days following their transplantation, of whom 43% were severely neutropenic and 90% had received systemic immunosuppressive therapy for graft-versus-host disease prophylaxis. Univariate logistic regression showed that transplantation from an unrelated donor and myeloablative conditioning were significant risk factors for ICU admission. Prolonged use of vasopressors, invasive mechanical ventilation and male gender were significant predictors for ICU mortality, while neutropenia and graft-versus-host disease were not. Over the years, APACHE II severity of illness scores remained unchanged (21.0±7.1, 20.1±5.6, 21.2±6.6), while 100-day post-transplant mortality of patients who had been transferred to the ICU decreased significantly from 78% (2004/2005) to 57% (2006/2007), and 35% (2008/2009).

CONCLUSIONS

While for allogeneic HSCT patients the severity of illness on admission to the ICU did not change, the 100-day post-transplant survival improved. These data indicate that reluctance to submit haematological patients to the ICU is not warranted.

INTRODUCTION

Patients with haematological malignancies are currently treated with intensive cytotoxic therapies often culminating in an allogeneic haematopoietic stem cell transplant (HSCT). A clear reduction in transplant-related mortality (TRM) was observed between 1967-2002, mainly due to prompt administration of antibiotics at the onset of fever, better prevention of infectious complications and improved clinical care [1-3]. Life-threatening complications now occur more frequently as a result of therapy rather than the haematological disease itself [4, 5]. These complications occur acutely, typically during the period of neutropenia when patients are profoundly immunocompromised [6], or during neutropenia recovery [7]. It is inevitable that some patients will develop medical problems requiring transfer to the intensive care unit (ICU), either for close monitoring or for intensive treatment. In the past, neutropenic patients who developed organ failure were considered to have such a dismal prognosis that physicians were reluctant to even consider admitting them to an ICU [8]. Since 2002, improved outcomes for these patients have been reported, and the importance of neutropenia as a predictor for ICU mortality was debated [9].

Respiratory insufficiency associated with sepsis is the most common indication for admission from the haematology ward to the ICU [5]. Approximately one in four HSCT recipients require endotracheal intubation and mechanical ventilation for acute respiratory failure [10]. Severe sepsis and septic shock are the most frequently observed reason for ICU admission [9].

The outcome of those patients who need critical care appears to have improved [11], although in the subgroup of HSCT recipients receiving mechanical ventilation the reported mortality rate still exceeds 80% [12] and acute graft-versus-host disease (aGvHD) is reported to be an independent predictor for death, specifically in combination with mechanical ventilation [10]. Early initiation of non-invasive ventilation is associated with significant reductions in the rates of endotracheal intubation and serious complications and an improved likelihood of survival until hospital discharge [13]. These results led to improved awareness of the benefits of early admission to an ICU, resulting in more allogeneic stem cell transplant recipients being transferred to the ICU. Nevertheless, also in the Netherlands, important differences between centres concerning ICU admission policies exist and more evidence is needed to show that ICU treatment of this specific transplant group is not futile.

In this study we investigated the changes in outcome over time of three cohorts of HSCT recipients and compared the outcome of those that needed intensive care treatment to those who did not.

DESIGN AND METHODS

DESIGN

The records of all consecutive patients admitted to the Department of Haematology of Radboud University Medical Center, a tertiary academic hospital, between 1 January 2004 and 1 January 2010, were retrospectively analysed. HSCT recipients were identified and only their first unplanned referral to the ICU (<100 days) was included in the study. An unplanned admission was defined as an admission because of acute deterioration and not for scheduled activities that needed intensive monitoring (e.g. broncho-alveolar lavage with non-invasive ventilation support). Demographic data as well as relevant haematological data including underlying disease, donor type, type of transplant and presence of GvHD were retrieved from electronic patient files. Risk scores for TRM developed by the European Group for Blood and Marrow Transplantation (EBMT) were calculated [14]. Clinical data during ICU admission and discharge, the reason for admission, the severity of illness during the first 24 hours, as well as three outcome measures namely, mortality, and the length of ICU admission and hospital stay were collected. The severity of illness on admission to the ICU was determined by indicators of organ failure and the APACHE II score [15]. The type and duration of mechanical ventilation, renal replacement therapy and vasopressor use were extracted from the medical records. The study has been carried out in the Netherlands in accordance with the applicable rules concerning the review of research ethics committees and informed consent.

TREATMENT PROTOCOL

The myeloablative (MA) conditioning regimen consisted mainly of high-dose cyclophosphamide with either idarubicin when a sibling donor was available or antithymocyte globulin (ATG) when the donor was unrelated, with or without total body irradiation. The non-myeloablative (NMA) conditioning regimen consisted mainly of cyclophosphamide and fludarabine, completed with ATG in case of an unrelated donor. ATG was added to the conditioning regimen to attain T lymphocyte depletion to prevent GvHD. During the study period the method of preparation and composition of the stem cell product did not change. Patients did not receive haematopoietic growth factors and anti-microbial prophylaxis consisted of 500 mg ciprofloxacin given twice daily and 500 mg valaciclovir given three times daily. Fluconazole was given at 200 mg a day only to those who were colonised with *Candida albicans*. Vital signs (temperature, heart rate, blood pressure, respiration rate, oxygen saturation) were monitored at least four times daily with an overnight control being included during severe neutropenia to avoid any delay in starting broad-spectrum antibacterial therapy at the onset of fever [16]. Empirical therapy was started once the axillary temperature equalled or exceeded 38.5°C.

ICU TRANSFER CRITERIA

No explicit ICU admission policy was adopted. The decision to admit a patient to one of the level 3 general ICUs of our hospital was made by the senior haematologist and the senior intensivist.

STATISTICAL ANALYSIS

Continuous variables were summarised using mean values and standard deviations (SD) or median values and interquartile range (IQR) if data were not normally distributed. To compare characteristics we applied the independent *t*-test for continuous variables and chi-squared or Fisher's exact tests in case of percentages. Univariate logistic regression analyses were used to identify factors associated with ICU admission and ICU mortality. The power of this study was inadequate to perform multivariate analyses.

Two-tailed *p*-values ‹0.05 were considered to indicate statistical significance. A hundred days post-HSCT survival was presented in a Kaplan-Meier curve comparing the three periods using the log-rank test. All statistical analyses were carried out with SPSS version 18.0.

RESULTS

ICU-group characteristics

Between 1 January 2004 and 1 January 2010, 319 patients received an allogeneic HSCT, of whom 49 patients were transferred to the ICU for a median (IQR) of ten (6-45) days following their transplantation. The most common underlying diagnoses were acute myeloid leukaemia (*n*=14, 29%), non-Hodgkin's lymphoma (*n*=10, 20%) and myelodysplastic syndrome (*n*=8, 16%). The depth of compromised immunity at the moment of ICU transfer was emphasised by the fact that 43% of the patients were severely neutropenic (neutrophil count of ≤0.5 x10^9/L) on ICU admission and 90% had received systemic immunosuppressive therapy for GvHD prophylaxis.

Infectious complications were the main reason for ICU admission (86%), with respiratory insufficiency reported as the main symptom (67%), followed by haemodynamic instability, sepsis and septic shock. Mortality rates at 100-days post-HSCT were significantly higher for the patients who required an ICU admission (53 versus 8% in HSCT patients who did not need intensive care, $p<0.01$). Length of stay in the hospital was significantly longer (median 45 days; range 36-70) for patients requiring an ICU admission compared with those without ICU admission (29 days; range 23-39); $p<0.01$.

RISK FACTORS FOR ICU ADMISSION

The characteristics of ICU patients were compared with those without intensive care treatment. Age and gender were distributed equally in both groups (table 1). Univariate analysis identified two haematological risk factors for ICU admission to be significant: an unrelated donor graft (OR=2.5, 95% CI 1.3-4.6) and MA conditioning (OR=2.3, 95% CI 1.1-4.7). The power of this study was inadequate to perform a multivariate analysis. The onset of aGvHD grade 2-4 within 100 days for those admitted to the ICU was 29% (14/49), similar to those not admitted to the ICU (30%).

Table 1 Demographic factors associated with ICU admission before 100 days post-HSCT (2004-2009, *n*=319)

	HSCT-recipients without ICU admission (*n*=270)	HSCT-recipients with ICU admission (*n*=49)	*p*-value	OR (95% CI)
Age (years)	48.2 (±11.0)	47.4 (±11.3)	0.64[a]	
Male gender	167 (62%)	29 (59%)	0.75[b]	
Unrelated donor	89 (33%)	27 (55%)	<0.01[b]	2.5 (1.3-4.6)
Myeloablative conditioning	162 (60%)	38 (78%)	0.02[b]	2.3 (1.1-4.7)
EBMT estimated risk (*n*=237/43)			0.54[c]	
– Low	1 (0%)	0 (0%)		
– Intermediate	63 (27%)	14 (33%)		
– High	173 (73%)	29 (67%)		

Data are expressed as mean (± standard deviation) or *n* with (%)

a Independent T-test
b Chi²-test
c Fisher's exact test

CHANGES IN ICU CHARACTERISTICS OVER THE YEARS

There were no changes in the number of days from HSCT to ICU admission (median 10, IQR 6-45 days after HSCT), length of ICU stay (median 4, IQR 1-12 days) or time post-ICU to hospital discharge (median 15, IQR 1-35 days) over time, nor did the APACHE II severity of illness on ICU admission and EBMT estimated risk of not surviving for five years change during the study period (table 2). The proportion of patients requiring endotracheal intubation tended to decrease, but this did not reach statistical significance. In contrast, the number of non-invasive ventilation days increased (*p*=0.02).

Table 2 Demographics, ICU characteristics and outcome of patients transferred to an ICU within 100 days post-HSCT in two-year periods (*n*=49)

	2004/2005 (*n*=9)	2006/2007 (*n*=23)	2008/2009 (*n*=17)
Age	46.3 (±11.5)	47.6 (±10.3)	47.8 (±13.2)
APACHE II on admission	21.0 (±7.1)	20.1 (±5.6)	21.2 (±6.6)
EBMT estimated risk	4.0 (±1.0)	3.6 (±1.4)	2.8 (±1.1)
Invasive ventilation (days)	0.4 [0.0-11.3]	1.5 [0.0-15.5]	1.3 [0.0-6.3]
Non-invasive ventilation (days)	0.0 [0.0-0.02]	0.3 [0.0-1.0]	0.2 [0.0-0.8]
Vasopressor use (days)	0.2 [0.0-3.9]	0.4 [0.0-3.0]	0.0 [0.0-1.4]
ICU mortality	4 (44%)	8 (35%)	4 (24%)
Hospital mortality	7 (78%)	12 (52%)	7 (41%)
100 day post HSCT mortality	7 (78%)	13 (57%)	6 (35%)

Data are expressed as mean (± standard deviation), median [IQR] or n with (%).

The number of days that vasopressor medication was required remained unchanged. ICU mortality was 44% (2004/2005) to 35% (2006/2007) and 24% (2008/2009) and hospital mortality 78% to 52% and 41%, but these trends did not reach statistical significance. Figure 1 illustrates the decrease in the 100-day post-HSCT mortality for patients who had been admitted to the ICU (p=0.02). A similar decrease was found for patients given MA conditioning (78% to 56% and 36%, respectively) and NMA conditioning (no patients in first period, 60% and 33% in period 2 and 3, respectively). While these improvements did not reach statistical significance, likely due to a type 2 error, they do illustrate that in both groups a comparable improvement in outcome is observed over time. The 100-day post-transplant mortality of the complete group of patients (n=319) remained constant over time between 15-19%.

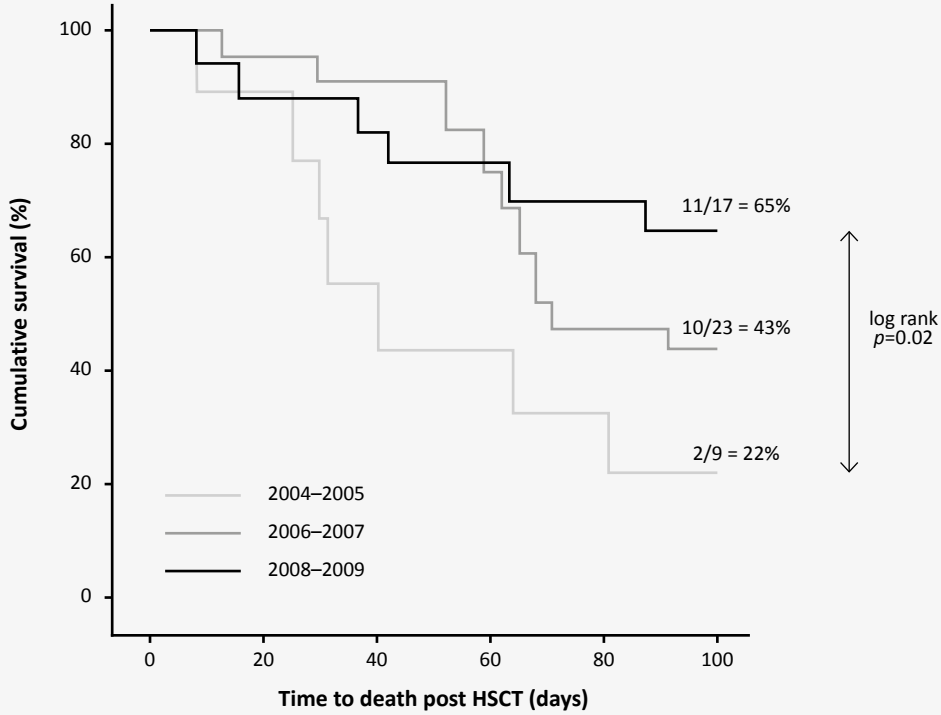

Figure 1 Kaplan-Meier survival curve until 100 days post-HSCT for patients with an ICU admission (*n*=49)

FACTORS ASSOCIATED WITH ICU SURVIVAL

Characteristics were compared between ICU survivors and non-survivors to determine the factors that were associated with survival of the patients who needed an ICU admission (table 3). Age and HSCT-related characteristics including donor type, bacteraemia, neutropenia and EBMT estimated risk score were similar in both groups. The duration that vasopressor medication was required ($p<0.01$), the number of days invasive ventilation was required ($p<0.01$) and male gender ($p=0.04$) were significant univariate predictors for ICU mortality. The APACHE II score ($p=0.07$) and receipt of MA conditioning ($p=0.08$) also tended to be related to ICU mortality. Neutropenia and both the presence of aGvHD grade 2-4 on ICU admission and the onset of aGvHD within 10 days post-HSCT were not shown to be risk factors for ICU survival.

Table 3 Demographic, haematological and ICU risk factors for ICU mortality (2004-2009, *n*=49)

	ICU survivors (*n*=33)	ICU non-survivors (*n*=16)	*p*-value	OR (95% CI)
Demographics				
– Age	47 (±12)	48 (±11)	0.77[a]	
– Male gender	16 (49%)	13 (81%)	0.04[d]	0.2 (0.1-0.9)
Haematological parameters				
– EBMT estimated risk (*n*=43)			1.00[d]	
- Intermediate	10 (35%)	4 (29%)		
- High	19 (66%)	10 (71%)		
– Myeloablative conditioning	23 (70%)	15 (94%)	0.08[d]	0.2 (0.0-1.3)
– Unrelated donor	17 (51%)	10 (62%)	0.47[b]	
– Bacteraemia on admission (*n*=42)	6/27 (22%)	6/15 (40%)	0.29[d]	
– Neutropenia on admission (*n*=40)	10/27 (37%)	7/13 (54%)	0.31[b]	
– GvHD on ICU admission	2 (6%)	2 (13%)	0.59[d]	
– GvHD <day 100	10 (30%)	4 (25%)	1.00[d]	
ICU parameters				
– APACHE II on admission	19.6 (±5.7)	22.9 (±6.5)	0.07[a]	1.1 (1.0-1.2)
– Invasive ventilation (days)	0.0 [0.0-5.1]	7.9 [1.6-23.7]	<0.01[c]	1.0 (1.0-1.1)
– Non-invasive ventilation (days)	0.2 [0.0-0.7]	0.1 [0.0-0.3]	0.68[c]	
– Vasopressor use (days)	0.0 [0.0-0.7]	2.4 [0.6-5.1]	<0.01[c]	1.5 (1.1-2.0)

Data are expressed as mean (± standard deviation), median [IQR] or proportions with (*n*).

a Independent T-test
b Chi²-test
c Mann-Whitney-U test
d Fisher's exact test

DISCUSSION

The present study shows that the proportion of HSCT patients admitted to the ICU during the last decade has risen. Receiving stem cells from an unrelated donor and MA conditioning were shown to be the major risk factors for ICU admission as one in four required ICU admission.

While their disease severity on ICU admission, as determined by APACHE II, remained similar, the 100-day transplant-related mortality decreased. Factors associated with ICU mortality were duration of vasopressor therapy, invasive mechanical ventilation and male gender. No correlation was found between the presence of neutropenia or GvHD and the risk for ICU admission or ICU mortality. ICU and post-ICU hospital mortality was low in our population compared with recent literature [17, 18]. Improved outcome for HSCT recipients might be explained by the fact that ICU treatment in general has improved, as is illustrated by higher ICU survival rates for the general adult ICU population [19] as well as in our own hospital. In addition, haematologists are more aware of the fact that admission to the ICU is feasible and effective, provided it is arranged at an early stage of deterioration.

Nevertheless, APACHE II scores during the study period did not decrease. While this cannot be deduced from our data, we have the impression that attitudes changed over time from 'no patient to be transferred to the ICU, unless….' to 'if needed, every patient should be transferred to the ICU, unless…'. Some authors propose that 'unlimited ICU treatment for a limited period', with full ICU support for e.g. four days and re-evaluation on day 5 could be an appropriate strategy of care for those patients with an unknown disease status or disease recurrence with available treatment options [20]. Our data show that 39% of the 100-day survivors needed six days or more on the ICU with a range for ICU survivors of 1-50 ICU days, implying that a decision about futility of treatment cannot be made within 4-6 days. Long-term physical, mental and social consequences of prolonged ICU admission and the effects of more extensive use of mechanical ventilation are now being studied in larger populations to determine the long-term effects of ICU treatment.

The finding that the duration of invasive mechanical ventilation and duration of vasopressor use predict ICU mortality is not surprising or new. It is well known that respiratory failure that requires mechanical ventilation and vasopressors indicates sepsis and shock and predicts mortality in almost all patient populations. Several studies have reported the use of mechanical ventilation in this profoundly immunocompromised population to be predictive for ICU mortality [21] and this is supported by the high mortality rates reported [22]. In our study population the use of non-invasive ventilation increased, relative to invasive ventilation over the years, and probably contributed to the better survival rates. However, prolonged use of non-invasive ventilation is still controversial [23].

The benefit of organ support in patients with late-onset complications related to aGvHD and high-dose corticosteroid treatment is contentious [24]. GvHD is regarded a poor prognostic factor for the critically ill HSCT recipient [10, 12]. It is remarkable that we found no indication that GvHD was related to ICU admission, nor ICU mortality. However, with the use of partially T-cell depleted grafts the overall incidence of GvHD was modest and the incidence of severe and refractory aGvHD was low. So, at least in this context, there should be no restrictions imposed on transferring these patients to an ICU when indicated.

As most ICU indications are associated with an infectious cause, haematology wards should optimise their procedures for early recognition and adequate treatment of infectious complications and their haemodynamic sequelae [25]. ICU survival seems importantly related to the extent of organ dysfunction [26], so employing monitoring systems such as vital signs based early warning scores to recognise acute clinical deterioration [11, 18] should be encouraged. Clearly, guidelines are needed to help haematologists decide when to transfer a patient to the ICU. As long as no explicit criteria for admission to the ICU are available, early consultation of intensive care physicians might improve accessibility to the ICU at an early stage of deterioration. The APACHE II might also help as it provides a clear indication of the severity of illness once the patient is admitted to the ICU even though it has not been validated for patients with haematological malignancies nor for HSCT recipients [27, 28].

Several limitations of our study need to be addressed. Obviously, caution is required as our study was retrospective in nature and the cohorts were relatively small in size. The absence of statistical significance of some endpoints, for example influence of MA/NMA conditioning on ICU mortality, is likely the result of limited power. Nevertheless, we were able to show an effect on clinically relevant outcome measures using a homogeneous cohort of haematological patients. The decrease in ICU and post-ICU hospital mortality did not reach statistical significance, possibly due to the limited power of the study. However, the impact of this decrease over time is relevant and shows better survival rates of HSCT patients requiring ICU treatment. In addition, the increased use of NMA regimens may be a confounder as the number of patients with NMA conditioning increased simultaneously with the observed decrease in mortality. Nevertheless, the reduction in mortality was similar for both patients given MA and NMA conditioning, indicating that the type of conditioning regimen is unlikely to explain the observed improvement in survival.

CONCLUSIONS

In line with general medical ICU patients, outcomes appear to have improved for allogeneic HSCT recipients who required intensive care treatment. Neutropenia and aGvHD were not associated with ICU survival. It appears plausible that an early transfer to the ICU could further improve short- and long-term survival. ICU admittance criteria and guidelines for early transfer to the ICU should be developed.

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7

Trends in admission prevalence, illness severity and survival of haematological patients treated in Dutch intensive care units

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ABSTRACT

PURPOSE

To explore trends over time in admission prevalence and (risk-adjusted) mortality of critically ill haematological patients and compare these trends to those of several subgroups of patients admitted to the medical intensive care unit (medical ICU patients).

METHODS

A total of 1,741 haematological and 60,954 non-haematological patients admitted to the medical ICU were analysed. Trends over time and differences between two subgroups of haematological medical ICU patients and four subgroups of non-haematological medical ICU patients were assessed, as well as the influence of leukocytopenia.

RESULTS

The proportion of haematological patients among all medical ICU patients increased over time [odds ratio (OR) 1.06; 95% confidence interval (CI) 1.03–1.10 per year; $p<0.001$]. Risk adjusted mortality was significantly higher for haematological patients admitted to the ICU with white blood cell (WBC) counts of ‹1.0 x 10^9/L (47%; 95% CI 41–54%) and ≥1.0 x 10^9/L (45%; 95% CI 42–49%), respectively, than for patients admitted with chronic heart failure (27%; 95% CI 26–28%) and with chronic liver cirrhosis (38%; 95% CI 35–42%), but was not significantly different from patients admitted with solid tumours (40%; 95% CI 36–45%). Over the years, the risk-adjusted hospital mortality rate significantly decreased in both the haematological and non-haematological group with an OR of 0.93 (95% CI 0.92–0.95) per year. After correction for case-mix using the APACHE II score (with WBC omitted), a WBC ‹1.0 x 10^9/L was not a predictor of mortality in haematological patients (OR 0.86; 95% CI 0.46–1.64; $p=0.65$). We found no case-volume effect on mortality for haematological ICU patients.

CONCLUSIONS:

An increasing number of haematological patients are being admitted to Dutch ICUs. While mortality is significantly higher in this group of medical ICU patients than in subgroups of non-haematological ones, the former show a similar decrease in raw and risk-adjusted mortality rate over time, while leukocytopenia is not a predictor of mortality. These results suggest that haematological ICU patients have benefitted from improved intensive care support during the last decade.

INTRODUCTION

Treatment for haematological malignancies is known to cause serious toxicity resulting in prolonged immune insufficiency and impaired mucocutaneous barriers [1]. Patients undergoing these intensive treatments are prone to infections and frequently require intensive care unit (ICU) monitoring and/or treatment. The most common indication for ICU admission is respiratory insufficiency [2]. Recent studies show that 15-28% of recipients of induction chemotherapy for acute myeloid leukaemia need to be admitted to the ICU during treatment [3,4]. For haematopoietic stem cell transplant recipients, ICU admission rates vary from 5 to 55% [5].

Extremely high mortality rates underlie the reticent attitude among both haematologists and intensivists to unplanned transfers of haematological patients to an ICU [6]. This controversial attitude towards ICU admission is comparable to that of clinicians with regards to patients with solid tumours, heart failure or liver cirrhosis. During the last decade perspectives on critically ill cancer patients have changed [7] and led, together with improved survival rates of patients admitted to general ICUs [8], to less reluctance on the behalf of haematologists and intensivists to admit patients with haematological malignancies to an ICU [9,10]. Where formerly neutropenic patients who developed organ failure were initially considered to have a dismal prognosis, nowadays the notion that neutropenia is predictive for ICU mortality is the subject of ongoing debate [11]. Recent studies have found that predominantly the need for mechanical ventilation, presence of invasive fungal infection, development of multi-organ failure and high severity of illness scores at admission are additional prognostic factors for mortality among cancer patients [2,12].

We investigated whether these new perspectives on ICU survival actually do influence the admission prevalence and outcome of haematological patients admitted to the ICU. Therefore, the aim of this study was to explore trends over time in admission prevalence and outcomes of critically ill haematological patients and to compare these data with those of non-haematological patients admitted to the medical ICU (medical ICU patients), specifically with patients with chronic heart failure, chronic liver cirrhosis and solid tumours.

DESIGN AND METHODS

PATIENT DATA

All consecutive patients admitted to ICUs participating in the Dutch National Intensive Care Evaluation (NICE) database between January 2004 and January 2012 were included in this study. To diminish bias by changes in case-mix, only ICUs that submitted patient data during the complete period were included. Admissions were considered to be due to a haematological disorder(s) when a haematological malignancy was recorded in the NICE or when ICU admission was requested by a haematologist. Patients for whom the recorded APACHE II (Acute Physiology and Chronic Health Evaluation II) score at admission made it impossible for the disorder to be related to a haematological disease were considered to be non-haematological patients. Patients admitted to the ICU for non-medical reasons (e.g. surgery, trauma) were excluded from entry into the study, as were patients admitted for diagnostic procedures generally performed in the ICU (e.g. bronchoalveolar lavage) and those with an ICU length of stay (LOS) of <24 h. Those patients who were readmitted to the ICU and patients with an unknown leukocyte count were also excluded.

The NICE registry contains information on patient admissions to >90% of all ICUs in the Netherlands. Data from the first 24 h of ICU admission are collected, including information on acute and chronic diagnoses, mechanical ventilation, minimum and maximum physiology and laboratory values, such as number of leukocytes, and need to calculate the APACHE II score [13]. In this study, the lowest white blood cell (WBC) count was used to define subgroups of haematological patients, with WBC $<1.0 \times 10^9$/L and WBC $\geq 1.0 \times 10^9$/L, because leukocytopenia is considered to negatively affect ICU outcome. No information was available on the ICU admission policies of the participating hospitals nor on specific haematological parameters, such as level of neutropenia, underlying haematological diagnosis, disease status and type and phase of haematological treatment, including whether or not haematopoietic stem cell transplant was performed.

We compared the haematological subgroup with other subgroups of severely ill patients for whom ICU admission is traditionally considered to be controversial, namely, those with solid tumours, chronic liver cirrhosis (defined as positive liver biopsy in combination with documented portal hypertension odds ratio OR earlier episodes of gastrointestinal bleeding caused by portal hypertension OR earlier episodes of liver failure, coma or encephalopathy) and chronic heart failure (New York Heart Association Class IV).

The NICE registry further records outcome data on LOS in the ICU and hospital, respectively, ICU readmission rate and ICU and in-hospital mortality. A number of measures have been implemented to improve data quality: the collected data are subject to several quality

checks, onsite data quality audits take place on a regular basis and data collectors participate in training sessions [14]. Site visits to ICUs are performed on a regular basis to investigate the number, types and causes of errors made in in-hospital mortality registration [15].

This study was carried out in the Netherlands in accordance with current regulations pertaining to review by research ethics committees and patient informed consent.

DATA ANALYSIS

We compared APACHE II scores, incidence of comorbidities (diabetes, chronic obstructive pulmonary disease (COPD), cardiovascular insufficiency, acute renal failure), the use of procedures/treatments in the ICU (mechanical ventilation, vasopressive medication) and LOS between two subgroups of haematological patients (WBC $<1.0 \times 10^9$/L and WBC $\geq 1.0 \times 10^9$/L) and four subgroups of non-haematological medical ICU patients (solid tumours, chronic liver cirrhosis, chronic heart failure and other medical ICU admissions). APACHE II scores were compared both with and without including the subscore for WBC. LOS is separately reported for survivors and non-survivors, and for both stay in the ICU and hospital, respectively.

Absolute and risk-adjusted hospital mortality rates were compared between haematological and non-haematological patients. The risk-adjusted mortality rate (RAMR) was calculated as the fraction of the number of deaths actually observed and the number of deaths predicted by the APACHE II model, multiplied by the average hospital mortality rate in the entire study cohort. It can be interpreted as the hospital mortality rate after correction for case-mix, using the APACHE II model. The RAMR has the same statistical properties as the standardised mortality ratio but allows for a better comparison of adjusted mortality rates between studies.

Three logistic regression analyses were carried out. To analyse the prevalence of haematological patients admitted to the ICU among medical ICU admissions over time, we used the mixed model logistic regression analysis for the entire cohort using haematological status (yes vs. no) as the response variable and calendar time as the covariate. To account for clustering in ICUs, we used a random coefficient model that allowed each ICU to have its own trend in prevalence over time. For comparison, trends over time were also analysed in the same way as for medical ICU patients with chronic liver cirrhosis, chronic heart failure and solid tumours.

To analyse whether trends in risk-adjusted hospital mortality over time differed between haematological and non-haematological patients, we used fixed-effects logistic regression analysis with hospital mortality as the response variable and the logit-transformed

APACHE II mortality risk score (to adjust for patient case-mix), calendar time and haematological ICU admission (yes vs. no) as covariates. We also included an interaction between calendar time and admission of haematological patients to the ICU. For comparison, trends in risk adjusted hospital mortality over time were similarly analysed for subgroups of patients with chronic liver cirrhosis, chronic heart failure and patients with a solid tumour, but without inclusion of 'haematological ICU admission' and its interaction with calendar time as covariates.

Finally, a similar fixed-effect logistic regression analysis was conducted within the group of haematological patients to assess the association between leukocytopenia at ICU admission and risk-adjusted hospital mortality. In this analysis, the logit-transformed APACHE II mortality risk, calendar time, leukocytopenia (modelled as WBC <1.0 x 10^9/L) and an interaction between calendar time and leukocytopenia were included in the model. Furthermore, to correct for volume–outcome effects, we added the number of haematological ICU admissions that took place in the same centre and same month as the ICU admission in question, as the continuous covariate to this model.

All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) version 20.01 (SPSS Inc., Chicago, IL) and R, version 2.14 [16].

RESULTS

PATIENTS

A total of 288,568 patients admitted to 36 ICUs participating in the Dutch NICE during the entire study period were included in our study, of which 2,935 admissions were identified as haematological patients. Following exclusion of those patients who did not fulfil our criteria (flowchart shown in figure 1), data of 1,741 patients with a haematological disease admitted for the first time to the ICU were included in the analyses: 1,673 of these patients (96%) were registered in the NICE as having a haematological malignancy, and 68 (4%) were admitted to the ICU admission upon request of the haematologist. Data on a group of 60,954 patients without a haematological malignancy admitted to the medical ICU were available for further analysis. The median [interquartile range (IQR)] WBC for haematological and non-haematological patients was 5.8 x 10^9/L [IQR 1.1–12.7] and 10.6 x 10^9/L [IQR 7.6–14.6], respectively.

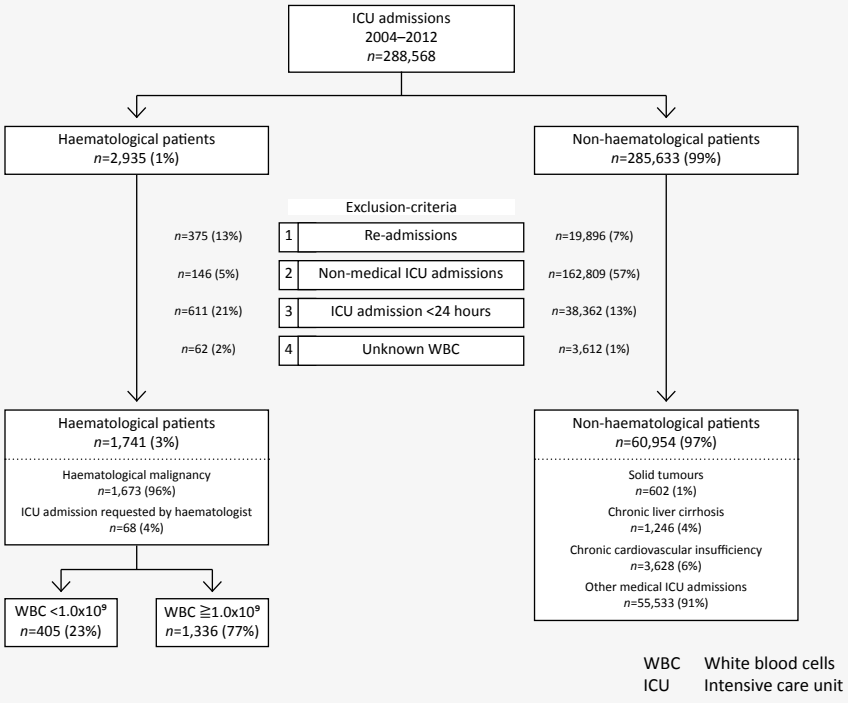

Figure 1 Flowchart illustrating the inclusion and exclusion criteria for entry into the study and for classification into haematological and non-haematological patient subgroups

Among all patients admitted to the medical ICU, 2.8% were due to haematological conditions, and this prevalence increased over time at 6% per year [odds ratio (OR) 1.06 annually; 95% confidence interval (CI) 1.03–1.10]. The number of patients with chronic liver cirrhosis admitted to the ICU (*n*=1,264; 2.0% of all medical admissions) also increased over time (OR 1.06; 95% CI 1.03–1.09), as did the number of admissions of patients with solid tumours (*n*=737, 1.1%; OR 1.16; 95% CI 1.10–1.22). The number of patients with chronic heart failure admitted to the ICU (*n*=3,672; 5.9%) decreased over time (OR 0.95, 95% CI 0.91–0.99).

Demographic and clinical characteristics of included patients, categorised according to subgroup (*n*=6), are shown in table 1. APACHE II scores at ICU admission (with and without omission of the WBC value) were 28.2 ±7.7 and 24.6 ±7.7 points, respectively, and generally higher for haematological patients with WBC ‹1.0 x 10^9/L than for the other subgroups of patients. For the haematological subgroup, APACHE II scores did not change over time, illustrating that on average the severity of illness at admission to the ICU did not change during the study period. Haematological patients, as well as patients with liver cirrhosis and heart failure, were more likely to suffer from acute renal failure, while a medical history of COPD and diabetes was more frequently present in the non-haematological patient groups (table 1).

ICU TREATMENT AND OUTCOME

Haematological patients and patients with liver cirrhosis were more likely to need vasopressor therapy than the other medical ICU patients, but less likely than patients with solid tumours and chronic heart failure. Mechanical ventilation was less frequently needed for patients with solid tumours (table 1).

Haematological patients had longer ICU and hospital LOS than non-haematological patients (both for survivors and non-survivors). For haematological patients, the longest LOS in the ICU and hospital was found for patients with leukocytopenia (WBC ‹1.0 x 10^9/L) (table 1). ICU readmission rates were higher in both haematological subgroups compared to non-haematological subgroups (table 1).

Absolute ICU (33.8%) and hospital (47.4%) mortality was higher for the whole group of haematological patients than for the whole group of non-haematological patients (ICU mortality 17.9%, hospital mortality 26.3%) and most specific for patients with leukocytopenia (WBC ‹1.0 x 10^9/L), with a mortality of 40.0 and 52.3%, respectively (table 2).

RAMR was higher for the whole group of haematological patients admitted to the ICU (RAMR 46%; 95% CI 42–49%) than for the whole group of non-haematological medical ICU patients (RAMR 18%; 95% CI 18–18%). Comparison of the subgroups revealed that risk-adjusted

mortality was higher for haematological medical ICU patients with WBC ‹1.0 x 10^9/L (47%; 95% CI 41–54%) and with WBC ≥1.0 x 10^9/L (45%; 95%CI 42–49%), respectively, than for non-haematological patients with chronic heart failure (RAMR 27%; 95% CI 26–28%) or with chronic liver cirrhosis (38%; 95%CI 35–42%), but it was not significantly different from that of patients with solid tumours (RAMR 40%; 95% CI 36–45%; table 2). The Kaplan-Meier plot for hospital survival of the six subgroups is shown in figure 2. Differences in absolute and risk-adjusted hospital mortality per subgroup for patients receiving mechanical ventilation or not in the first 24 h of ICU admission is reflected in figure 3.

For both haematological ICU patients and medical ICU patients, risk-adjusted mortality decreased over time, at 7% per calendar year (OR 0.93; 95% CI 0.92–0.95) (figure 4). This decrease over time was similar in both groups (p=0.79). Risk-adjusted mortality also decreased over time for patients with chronic heart failure (OR 0.93; 95% CI 0.88–0.98), patients with chronic liver cirrhosis (OR 0.90; 95% CI 0.82–0.98) and patients with solid tumours (OR 0.93; 95% CI 0.75–0.99). There was no significant difference in decrease over time for each subgroup compared to patients admitted to the ICU for haematological conditions. After correction for case-mix using the APACHE II score (with WBC omitted), leukocytopenia (WBC ‹1.0 x 10^9/L) was not a predictor of mortality (OR 0.86; 95% CI 0.46–1.64).

VOLUME-OUTCOME EFFECT HAEMATOLOGICAL ICU ADMISSIONS

A total of 36 centres admitted 1,741 haematological patients to their ICUs during the study period. When divided into four volume quartiles (each with nine hospitals), these volume quartiles have (raw) hospital mortality rates of 37.1% (median 18 admissions [IQR 15–21]), 44.7% (median 28 admissions [IQR 26–29]), 46.2% (median 35 admissions [IQR 34–39]) and 50.0% (median 90 admissions [IQR 64–141]), respectively. There was no effect of haematological patient-volume on risk-adjusted hospital mortality (OR 1.01; 95% CI 0.98–1.04; p=0.38).

Table 1 Characteristics of patients' subgroups

Characteristics	Haematological patient subgroups	
	Haematology WBC<1.0x10^9/L *n*=405	Haematology WBC≥1.0x10^9/L *n*=1,336
Demographics		
– Age, median (IQR)	58 (47-65)	64 (54-72)
– Male gender (%)	60.5	62.0
– WBC, median (IQR)[b]	0.2 (0.1-0.5)	7.1 (3.2-13.6)
– APACHE II severity of illness score (points)-with WBC (mean±SD)	28.2 ±7.7	25.7 ±8.1
– APACHE II severity of illness (points)-without WBC (mean±SD)	24.6 ±7.7	23.0 ±7.6
Chronic co-morbidity (%)		
– COPD[c]	2.2	5.5
– Renal insufficiency	4.0	8.9
– Cardiovascular insufficiency	1.7	2.8
– Diabetes	9.1	10.6
– Chronic dialysis	8.9	2.2
ICU treatment (%)[b]		
– Acute renal failure	20.7	19.0
– Vasopressors	56.0	55.8
– Mechanical ventilation	69.4	66.8
LOS ICU (days), median (IQR)		
– Survivors[d]	5.1 (2.1-10.7)	4.1 (2.0-9.5)
– Non-survivors	5.7 (2.4-11.2)	5.1 (2.4-11.0)
LOS in hospital (days), median (IQR)		
– Survivors[d]	36.5 (21.3-54.0)	22.0 (12.8-41.0)
– Non-survivors	23.3 (10.0-38.8)	15.0 (7.0-29.4)
Re-admission rate (%)	14.3	12.4

IQR Interquartile range
APACHE II Acute Physiology and Chronic Health Evaluation II
WBC White blood cells
SD Standard deviation
LOS Length of stay

a Overlapping subgroups (55 patients had >1 subgroup diagnosis)
b During the first 24h of ICU admission
c Chronic obstructive pulmonary disease (COPD) registered from 2007 onwards
d LOS was calculated for hospital survivors
e All medical ICU patients with cardiovascular insufficiency were included in the subgroup chronic heart failure.

Non-haematological patient subgroups			
Solid tumours *n*=602[a]	Chronic liver cirrhosis *n*=1,246[a]	Chronic heart failure *n*=3,628[a]	Medical ICU, other *n*=55,533
67 (58-74)	58 (50-65)	72 (63-78)	64 (51-75)
63.3	64.3	63.7	57.3
10.8 (7.3-15.4)	8.5 (5.6-13.1)	11.2 (8.3-14.9)	10.6 (7.6-14.6)
20.0 ±7.2	25.6 ±7.7	25.9 ±7.6	19.9 ±8.1
19.2 ±8.1	21.0 ±8.4	21.9 ±8.1	17.9 ±8.2
14.6	9.1	15.1	10.8
4.8	7.6	19.1	6.1
2.2	3.2	100.0	0.0[e]
11.6	15.2	18.9	11.8
0.3	0.7	3.5	1.7
11.0	26.0	21.0	12.0
66.6	52.5	65.8	46.8
44.4	62.4	65.0	60.2
3.0 (1.8-5.9)	2.9 (1.7-6.6)	3.3 (1.9-6.6)	3.2 (1.8-7.0)
3.1 (1.8-6.8)	4.3 (2.0-9.3)	3.9 (2.0-8.0)	4.2 (2.2-9.2)
16.0 (8.0-27.0)	15.0 (7.0-29.0)	16.0 (9.0-29.0)	15.0 (8.0-28.0)
7.0 (4.0-14.0)	10.0 (4.4-17.0)	8.0 (3.9-18.7)	8.0 (3.6-18.0)
5.8	7.9	9.3	7.0

Table 2 Raw and risk-adjusted mortality rates for patients' subgroups

Mortality rates	Haematological patient subgroups		Non-haematological patient subgroups			
	Haematology WBC<1.0x10^9/L *n*=405	Haematology WBC≥1.0x10^9/L *n*=1,336	Solid tumours *n*=602[a]	Chronic liver cirrhosis *n*=1,246[a]	Chronic heart failure *n*=3,628[a]	Medical ICU, other *n*=55,533
ICU mortality (%)	40.0	31.9	32.4	32.6	25.5	17.7
Hospital mortality (%)	52.3	45.9	44.9	46.7	37.6	24.9
RAMR[b] (%, 95% CI)	47.2 (41.0-54.0)	45.1 (41.6-48.8)	40.4 (36.2-45.1)	38.5 (35.4-41.7)	26.9 (25.5-28.4)	17.4 (17.2-17.8)

CI Confidence interval

a Overlapping subgroups (55 patients had >1 subgroup diagnosis)

b The risk-adjusted mortality rate (RAMR) was used to analyse the trend in time of hospital mortality between leukocyte strata. The RAMR was calculated as the fraction of deaths observed and deaths predicted by the APACHE II model, multiplied by the average hospital mortality rate in the entire dataset.

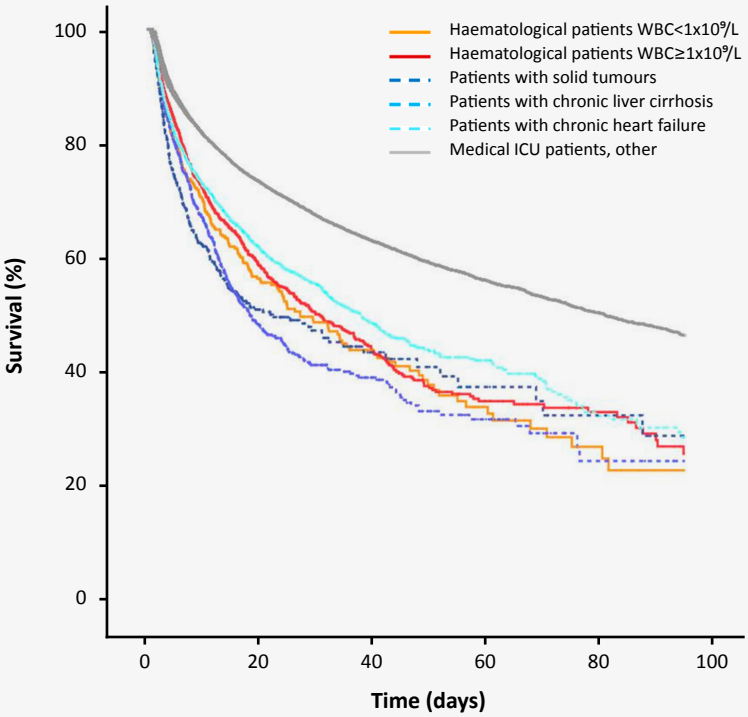

Figure 2 Kaplan-Meier plot for hospital survival for haematological and non-haematological medical patients admitted to the ICU

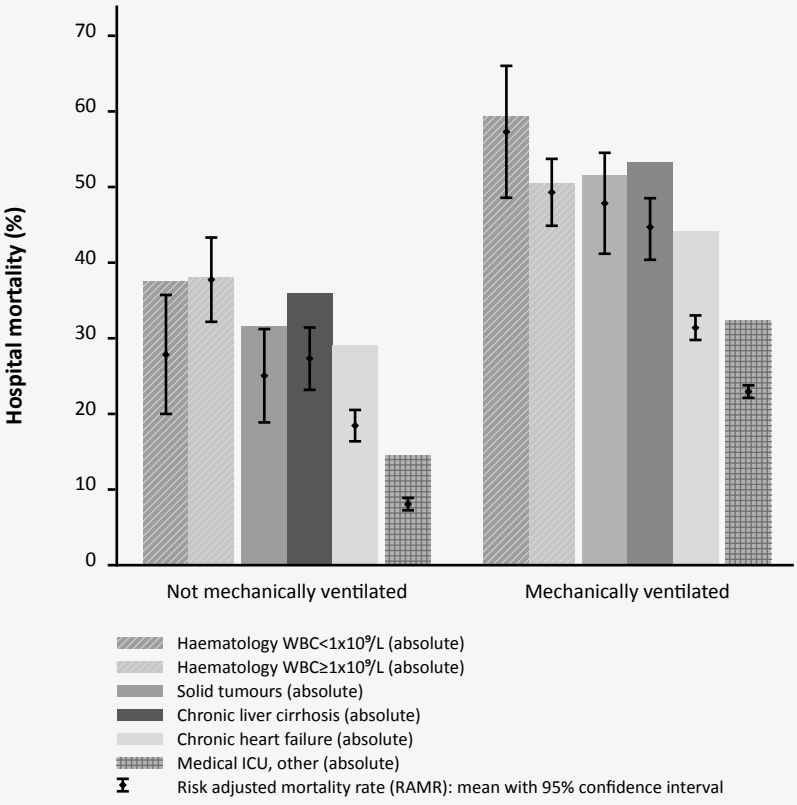

Figure 3 Absolute and risk-adjusted hospital mortality rates for subgroups of haematological and non-haematological medical patients admitted to the ICU without and with mechanical ventilation during the first 24h

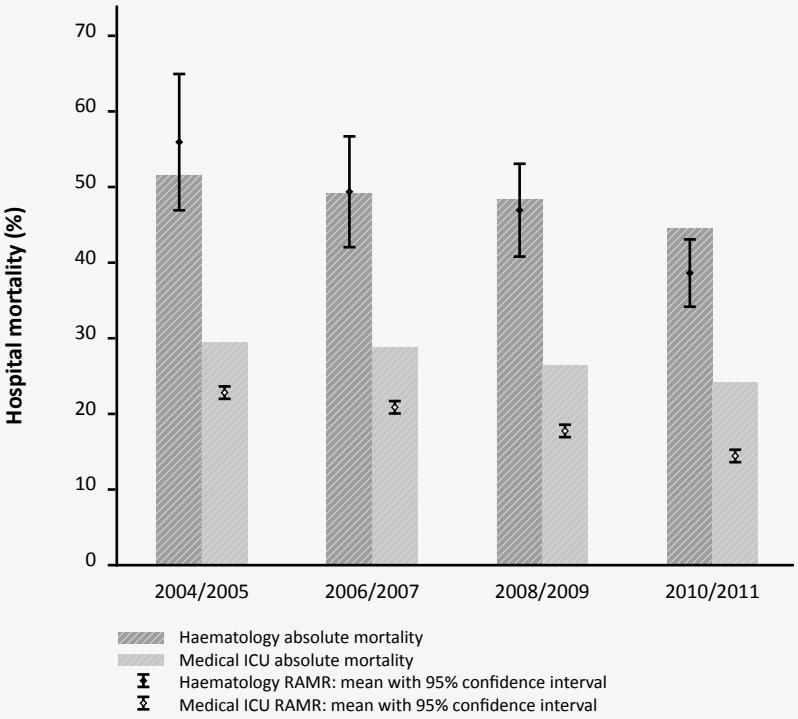

Figure 4 Absolute and risk-adjusted hospital mortality rates over time for the admission of haematological (*n*=1,741) and non-haematological (*n*=60,954) medical patients to the ICU

DISCUSSION

We report here on the changes over time in ICU admission prevalence and outcomes of more than 1,700 critically ill haematological patients and these changes in more than 60,000 non-haematological medical ICU patients, all admitted to 36 Dutch ICUs during the last decade. The main findings of our study are threefold. First, the proportion of haematological patients among all medical ICU admissions increased over time, suggestive of a change in ICU admission policy. Second, the prognosis of haematological ICU patients significantly improved to a similar extent as that of several subgroups of non-haematological medical ICU patients. Third, our data convincingly confirm that a WBC count of <1.0 x 10^9/L was not a predictor of in-hospital mortality in our ICU patients with haematological disorders. In addition to these findings, it is important to realise that the hospital mortality rate of haematological patients admitted to the ICU was approximately twofold higher than that of the non-haematological medical ICU patients, but similar to that of ICU patients with solid tumours. When mechanical ventilation was needed, mortality was higher for all of the subgroups investigated. The higher mortality of haematological patients was likely related to their underlying disease, its treatment and the need for more rigorous ICU therapy and was also reflected by the longer LOS in the ICU and hospital by our haematological patients. Our results on both ICU and hospital mortality rates are within the ranges of those for critically ill haematological patients in ICUs in France and Belgium [17], as well as for a cohort of critically ill haematological patients in the UK [18]. Taken together, these results not only indicate that the denial of ICU treatment to haematological patients is not warranted, but they also emphasise the need for appropriate criteria for referring this specific group of patients to an ICU and that intensive supportive care for haematological patients should be considered irrespective of the degree of leukocytopenia.

The improvement over time we observed is in accordance with the results of a recent publication in which 428 neutropenic patients with sepsis were studied [19]. While the comparable improvement in hospital survival between haematological and non-haematological patients might suggest that improved ICU care accounted for this improved prognosis, changes in haematological treatment regimens may also have contributed to this trend. Less organ damage, infection and severe acute graft versus host disease related to allogeneic hematopoietic stem cell transplantation has been reported [20], and non-myeloablative therapies are associated with improved ICU survival compared to myeloablative therapies [21]. The absence in the current study of a case-volume/outcome relationship is however surprising. Two previous studies describe that survival is higher in ICUs that admit larger numbers of critically ill haematological patients with acute respiratory failure and septic shock compared to ICUs that admit fewer haematological patients [22, 23]. We found an increase in crude mortality rates for hospitals with more admissions, but after adjusting for

casemix this association was no longer apparent, indicating that larger centres treat more severely ill patients, but do not have better or worse outcome results.

Until recently, published outcomes of haematological ICU patients were generally poor despite a growing number of studies demonstrating improvement [24, 25]. The perception that transfer to an ICU may be futile and that long-term outcomes for those who survive critical illness are rather poor has led to a reluctance among both haematologists and intensivists to admit patients to an ICU. In our view, this reluctance might delay ICU admission, resulting in a self-fulfilling prophecy of a detrimental outcome for haematological patients, as illustrated by the fact that the number of failing organs in patients upon ICU admission is directly related to ICU mortality among patients with haematological malignancies [26]. Moreover, in their recent publication Azoulay et al. report that among patients who were denied ICU admission because they were considered too sick to benefit from the ICU, approximately one of four survived until hospital discharge; in contrast, among patients who were considered too well to benefit from ICU admission, one of ten patients eventually died [17]. These results emphasise the need for a better specification of ICU admission criteria for haematological patients.

In addition, we feel that improved general ICU treatment options, such as those, for example, in sepsis and septic shock management [27] and in the field of mechanical (non) invasive ventilation [28], as well as more specific applicable haematological treatments, such as anti-fungal drugs and more aggressive diagnostic strategies, account for the better outcome in general medical ICU patients [8]. Such treatment options and diagnostic strategies have contributed to an awareness that ICU admission may not be futile for critically ill haematological patients. Importantly, haematological treatment and ICU admission have an irrefutable impact on the perceived quality of life, which is increasingly considered to be a major measure of outcome. However, the quality of life after a 1-year rehabilitation period has been found to be below the average of that of a generally healthy population [29], while it appears to be similar in haematological and non-haematological patients admitted to the ICU and in haematological patients who were not treated in the ICU [30].

We found that severity of illness on ICU admission, expressed by the APACHE II score, did not change during the study period. This observation suggests that the increase in admission of patients with haematological diseases was likely the result of a change in admission policy over time and that haematological patients were not admitted earlier (and were not less severely ill) to the ICU. Recently, a significant association was demonstrated in critically ill cancer patients between early intervention prior to ICU admission before the development of severe organ failure and a decreased hospital mortality rate. This finding is in accordance with our observed association between mechanical ventilation and increased mortality. It

also highlights the importance of early identification of any decline in vital organ function as the usual reason for ICU admission in critically ill cancer patients is the need to support failing organs [31]. The beneficial effects of earlier ICU admission and aggressive ICU treatment were also suggested by Hampshire et al., who found an increased hospital mortality for patients with an increasing length of hospital stay prior to ICU admission and those with severe sepsis [18]. Therefore, there may be room for improvement if guidelines for timely admission are established. An important role herein might be played by medical emergency outreach teams.

Several limitations to our study need to be addressed. Clinical registries, such as the NICE registry, provide unique opportunities to study very large cohorts over longer periods of time, as our study illustrates. Because of the large numbers, chance findings due to variations in case-mix are unlikely. However, the set of clinical variables that is recorded in the registry database must be determined beforehand; it will also often have limitations when specific subgroups, such as the haematological ICU population, are studied. A number of important confounding haematological variables, such as level of neutropenia, underlying haematological diagnosis, disease status and type and phase of haematological treatment, including whether or not haematopoietic stem cell transplant was performed, were not available for our analyses. Also, intensity and mucotoxicity of the applied chemotherapeutical treatment determines the pattern of inflammatory response, irrespective of the presence of infection [32], and these issues are unknown in our patients.

Nevertheless, we were able to compare haematological subgroups with several other groups of severely ill patients for whom ICU admission is traditionally considered to be controversial. We were able to demonstrate changes in clinically relevant outcomes of haematological patients transferred to an ICU, as well as a significant decrease in mortality over the years, and to compare this trend with those of other specific patient groups. In our view, it would be useful to evaluate ICU admission policies with the aim to facilitate decision making regarding patient admission to ICUs and thereby help avoid situations in which patients who may benefit from intensive treatment are deprived of life-saving therapies. We advise caution in generalising the results of our study, as well as those of published studies, due to possible variations in ICU admission policy and levels of ICU care provided, as well as differences in discharge criteria and settings and timing for the implementation of end-of-life decisions [33].

CONCLUSIONS AND FUTURE RECOMMENDATIONS

The results of this observational study show that the critically ill haematological patients in our study cohort had a higher mortality rate than specific subgroups of non-haematological medical ICU patients, but a similar one to patients with solid tumours. In our study,

differences between groups were most pronounced in those patients that required mechanical ventilation. We conclude that the hospital and ICU survival of haematological patients has improved over time in the Netherlands, similarly to that of non-haematological medical ICU patients and that leukocytopenia itself is not a predictor of mortality. Our results indicate that intensive supportive care for patients with haematological malignancies should be available without delay, irrespective of the degree of leukocytopenia. Further research is needed to define the best timing for transfer to the ICU in order to provide the patient with the best chance of survival and to determine the influence of specific haematological conditions, such as graft versus host disease and disease status.

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8

Long-term health related quality of life following intensive care during treatment for haematological malignancies

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ABSTRACT

OBJECTIVE

Long-term health related quality of life (HRQoL) was determined for patients admitted to the haematology ward who needed intensive care treatment (H-IC+) and compared with those who did not (H-IC-) as well as with that for patients admitted to the general ICU (nH-IC+).

METHODS

A cross-sectional study was carried out median 18 months after admission by employing the short form-36, checklist for individual strength, cognitive failure questionnaire and hospital anxiety and depression scale.

RESULTS

27 (79%) of the 34 H-IC+ patients approached, and 93 (85%) of the 109 H-IC- patients approached replied. Data were adjusted for relevant covariates and matched with those of 149 patients in the general ICU. Apart from the lower rolephysical functioning score for H-IC+ (p=0.04) no other differences were found between H-IC+ and H-IC-. Groups H-IC+ and nH-IC+ evaluated their HRQoL on SF-36 similarly, except for the lower aggregated physical component summary (PCS) for H-IC+ (p<0.0001). After adjusting for PCS, no significant differences in CIS, CFQ and HADS were observed between the groups.

CONCLUSIONS

Eighteen months after admission, patients treated for haematological malignancies reported similar HRQoL, whether or not they had received intensive care treatment, but reported a lower PCS than those of patients in the general ICU. Hence, there is no reason to assume that admission to the ICU has a negative impact on long-term HRQoL, so this should not affect the decision whether or not to transfer patients with haematological malignancies to the ICU.

INTRODUCTION

Survivors of critical illnesses are frequently left with a legacy of long-term physical, neuropsychiatric and quality of life impairments [1]. Patients who survive critical illness report significantly lower health related quality of life (HRQoL) after a year compared to their well being before intensive care unit (ICU) admission as well as that of the general population [2,3].

Treatment of patients with haematological malignancies has become increasingly intensive consisting of several cycles of high-dose chemotherapy, often followed by an allogeneic or autologous haematopoietic stem cell transplant (HSCT). As a consequence, these patients are at risk for critical illness. In the last decade the contribution of ICU's during treatment of haematological malignancies has significantly improved [4]. ICU physicians have been successful in improving survival beyond the acute stage of critical illness by emphasizing the importance of early recognition of clinical deterioration. Improved insight into the treatment of sepsis and the introduction of non-invasive and protective positive pressure ventilation strategies to overcome respiratory failure have also played a role [5-7].

Long-term HRQoL of patients being treated for haematological malignancies is relevant to assist physicians in their decision whether or not to admit the patient to the ICU. Recent reports are conflicting, as both persistent impaired HRQoL [3] and restorement of HRQoL 90 days following ICU discharge in 80% of survivors was determined [8]. No comparisons to haematological patients that did not need intensive care and non-haematological ICU patients were made.

With the current study we aim to determine long-term selfreported HRQoL, including fatigue, cognitive functioning, anxiety and depression of patients being treated for a haematological disease who were given intensive care and to compare these HRQoL scores with those of haematological patients who did not receive intensive care as well as those of a group of general medical ICU patients.

PATIENTS AND METHODS

ETHICS STATEMENT

The Committee on Research Involving Human Subjects (Arnhem-Nijmegen region CMO) approved the study protocol (study number 2010/306) and waived the need for informed consent since the objective of this study was to evaluate regular patient care. Patient privacy was guaranteed as all data were anonimised and evaluated in a blinded fashion.

PATIENTS WITH HAEMATOLOGICAL DISEASE

All consecutive patients who were admitted for five days or more to our tertiary care medical centre for treatment of a haematological malignancy during a one year period were eligible for the survey. Survivors were divided into two groups depending upon whether or not they had been admitted to the ICU. A HRQoL questionnaire was sent to them a median of 18 months after admission (range of 12-24 months). This same procedure was carried out twice on two consecutive years for those who were admitted to the ICU during treatment in order to enlarge the group (figure 1). Non-responders were sent a reminder six weeks later. Demographic and medical data were collected from the patient files.

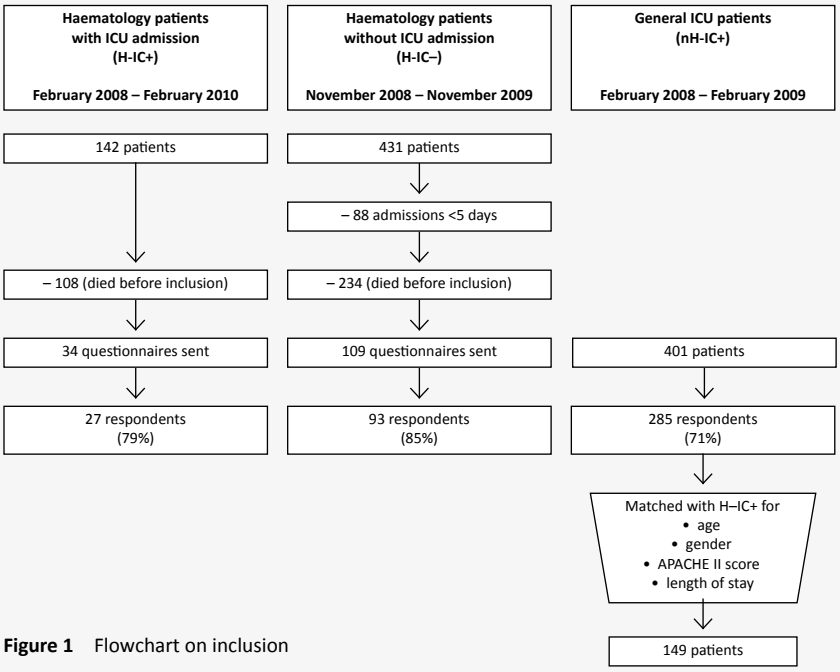

Figure 1 Flowchart on inclusion

GENERAL ICU PATIENTS

Data of general ICU patients without a haematological malignancy were retrieved from a group of 401 medical admission patients between February 2008 and February 2009. These patients were approached in a similar way as the haematological groups and non-responders were sent a reminder six weeks later. A total of 285 (71%) patients responded and 149 of these were meticulously matched with their haematological ICU counterparts for age, gender, APACHE II score and ICU length of stay. The methods of HRQoL measurement for this group was similar to that for the haematological groups [9].

ICU CHARACTERISTICS

There was no explicit ICU admission policy at the time and the decision to admit a patient to one of the level 3 general ICUs was made by the senior haematologists and intensivists. ICU characteristics and reason for ICU admission were extracted from patient files.

QUESTIONNAIRES

The following four different validated questionnaires were used to measure health related quality of life. The short form-36 (SF-36) contains eight multi-item dimensions covering various aspects of physical, social, emotional and mental health. Missing values were imputed according to the health survey manual [10] and aggregated summary scores were expressed in a physical component summary (PCS) and a mental component summary (MCS) ranging between 0–100, a higher score indicating a higher level of functioning [11]. The shortlist of the checklist individual strength-fatigue (CIS-fatigue), consisting of eight questions scoring on a 7-point Likert scale. The range of CIS-fatigue is 8–56, a higher score indicating more pronounced fatigue [12]. The validated Dutch translation of the cognitive failure questionnaire (CFQ) is self-reported [13] and consists of 25 questions on memory, distractibility, social blunders and names [14]. Each question was scored on a 5-point Likert scale. The total score on the CFQ ranges from 0–100, a higher score indicating more self-reported cognitive impairment. The hospital anxiety and depression scale (HADS) is a 14-item self-reporting measure of psychological distress and widely used for cancer patients [15]. The HADS has two subscales (anxiety and depression), each ranging from 0 to 21. Each item is rated on a scale from 0 ('not at all') to 3 ('very much') and higher scores indicate more anxiety and depression [16]. The non-haematological ICU patients did not receive the HADS questionnaire.

Thus, our self-reported HRQoL survey consisted of a total of 83 questions. The data obtained were recoded and subsequently scored according to their manuals. To guarantee patients' privacy, the survey was sent out anonymously and assigned a number. This allowed the primary and supervising investigator to match the returned survey with the patient's registry number held in a separate confidential database.

STATISTICAL ANALYSIS

All data were analyzed using SPSS version 20.0.0.1 (SPSS, Chicago, IL). The t-test was used for normally distributed variables, Mann-Whitney U test for variables that were not normally distributed and the Chi-square test for binary variables. Correlations between physical component summary and mental component summary were determined using Pearson's correlation coefficient.

Significant differences between the variables were considered as covariates. Since data were not normally distributed, a logtransformation was performed in order to perform a multivariate analysis of covariance. Since this was an exploratory study, and to increase sensitivity for putative differences between the groups, there was no correction for multiple testing. Statistical significance was defined as a p-value ‹0.05.

RESULTS

CHARACTERISTICS OF PATIENTS WITH HAEMATOLOGICAL DISEASE

In total 573 patients were eligible, of which 143 patients could be approached for the study (figure 1). Mortality during this long-term follow-up was significantly higher for H-IC+ (108/142, 76%), compared to group H-IC- (234/431, 45%) (p<0.0001).

In H-IC+ 34 questionnaires were sent out and 27 questionnaires (79%) were completed, median 15 months [Inter Quartile Range (IQR) 12-20] following admission. The mean APACHE II score was 18.5±9.2 (table 1). In total 109 questionnaires were sent to haematological patients that did not need ICU treatment and 93 questionnaires (85%) were completed, median 16 months [IQR 13-20] following admission. In both groups the proportion of patients admitted for an allogeneic or autologous haematopoietic stem cell transplant, chemotherapy or complications were comparable. No significant differences in demographic characteristics were found between the groups, except for the proportion of acute leukaemia/MDS which was higher in H-IC+ (p=0.008, table1). Hospital length of stay was significantly longer for H-IC+ (median 33 days [interquartile range 25-42]), compared to H-IC- (21 days [11-27], p<0.001) or nH-IC+ (18 days [10–37], p<0.001).

CHARACTERISTICS OF GENERAL ICU PATIENTS

In total 149 general ICU patients were matched with the haematological patients that needed ICU treatment. Twenty-six (17%) patients had a proven infection of which eighteen patients had a sepsis. The mean APACHE II score was 19±5.4 (table 1).

Table 1 Demographic characteristics of responding patients with and without ICU admission

	Haematology patients with ICU admission (*n*=27)	Haematology patients without ICU admission (*n*=93)	General ICU patients (*n*=149)
Age	52.8 (±14.2)	53.5 (±13.3)	56.9 (±16.7)
Gender (M)	17 (63%)	54 (58%)	72 (48%)
APACHE II score	18.5 (±9.2)	n.a.	19.0 (±5.4)
LOS-hospital (days)	33 [25-42][a]	21 [11-27]	18 [10-37][b]
LOS-ICU (days)	5 [2-10]	n.a.	4 [2-10]
Diagnosis (*n*, %)			
– Acute leukaemia and MDS (AML, ALL and MDS)	13 (48)[a]	20 (22)	
– Malignant lymphoma (NHL, M.Hodgkin and M.Waldenström)	7 (26)	28 (30)	
– Multiple myeloma	4 (15)	28 (30)	
– Chronic leukaemia (CML and CLL)	1 (4)	13 (14)	
– Other	2 (7)	4 (4)	
Hospital admission reason (*n*, %)			
– Allogeneic HSCT (SIB, VUD and SIB-RIC)	6 (22)	15 (16)	
– Autologous HSCT	4 (15)	29 (31)	
– Non-HSCT chemotherapy	7 (26)	16 (17)	
– Complications (after non-HSCT chemotherapy, after HSCT or without preceding treatment)	10 (37)	33(36)	

Data are expressed as mean with (±) standard deviation or median with IQR unless other reported.

AML Acute myeloid leukaemia
ALL Acute lymphoblastic leukaemia
MDS Myelodysplastic syndrome
NHL Non-Hodgkin lymphoma
SIB Sibling donor
VUD Volunteer unrelated donor
SIB-RIC Sibling donor, reduced intensity conditioning

a Statistically significantly different (P<0.05) compared with haematology patients without ICU admission
b Statistically significantly different (P<0.05) compared with haematology patients with ICU admission

HEALTH RELATED QUALITY OF LIFE QUESTIONNAIRES

Haematological diagnosis and length of hospital stay served as covariates for the SF-36 analysis and were complemented by the Physical Component Summary as covariate for the analyses of CIS-fatigue, CFQ and HADS differences between the groups.

— *Short Form-36*

H-IC+ respondents reported a similar HRQoL to H-IC- in almost all domains of the SF-36, with the exception of a difference in the Role Physical dimension namely, H-IC+ reported more problems with work or other daily activities as a result of physical health (p=0.04) (table 2). Compared to nH-IC+, H-IC+ reported a lower score on the resulting aggregated PCS (p<0.001), while the aggregated MCS was not different between the groups. The results for the other domains of the SF-36 were similar (figure 2). No correlations were found between the PCS and MCS as Pearson correlation coefficients were r=0.22 for H-IC+ (p=0.30), r=0.14 for H-IC- (p=0.90) and r=0.10 for nH-IC+ (p=0.28). Both H-IC+ and H-IC- survivors evaluated their HRQoL on several domains of the SF-36 worse compared with the age-adjusted general Dutch population of which the reference values are reflected in table 2.

Table 2 Results of Short Form-36 measurements median 16 months after ICU discharge, adjusted for covariates

SF-36†	Haematology patients with ICU admission (n=27)	Haematology patients without ICU admission (n=93)	General ICU patients (n=149)	General population subgroup age 41-60[11] (reference values)
Physical functioning	52.9 ±27.6	64.6 ±27.6	52.2 ±32.0	84.0 ±19.6
Role-physical	35.2 ±35.5[a]	40.3 ±42.8	38.0 ±41.1	74.5 ±36.8
Bodily pain	71.8 ±25.1	74.1 ±24.5	68.7 ±28.5	71.8 ±24.1
General health	45.6 ±21.5	46.3 ±23.4	48.8 ±22.0	69.7 ±20.6
Social functioning	72.7 ±26.4	66.1 ±26.3	67.0 ±25.8	83.5 ±22.1
Vitality	56.0 ±16.7	54.7 ±20.5	54.3 ±19.6	68.6 ±20.2
Role-emotional	65.4 ±40.8	76.0 ±37.9	61.0 ±43.2	81.6 ±33.2
Mental health	75.4 ±19.0	74.0 ±17.7	68.8 ±19.2	75.6 ±18.5
Physical component summary	36.7 ±8.5	39.1 ±11.6	48.0 ±9.7[b]	n.a.
Mental component summary	49.6 ±11.2	48.4 ±10.7	47.9 ±9.8	n.a.

Data are expressed as mean with (±) standard deviation.

† Adjusted for diagnose acute leukaemia and MDS and LOS-in hospital using log transformed data (not shown)
a Statistically significantly different (P<0.05) compared with haematology patients without ICU admission
b Statistically significantly different (P<0.05) compared with haematology patients with ICU admission

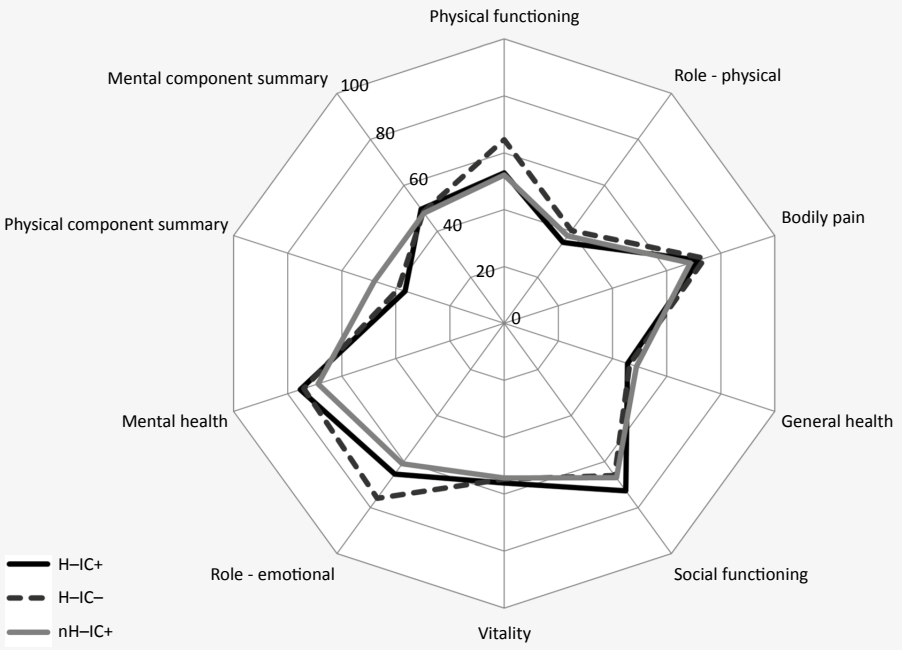

Figure 2 Spider graph of the Short Form-36 measurements median 16 months after ICU discharge, adjusted for covariates

— *Checklist individual strength-fatigue*

No significant differences between H-IC+ and H-IC- or H-IC+ and nH-IC+ were found for self evaluated fatigue score after adjusting for covariates (table 3).

— *Cognitive Failure Questionnaire*

Cognitive failure was similar after adjusting for covariates on all measured cognitive dimensions between H-IC+ and H-IC-. The overall cognitive functioning tended to be better for H-IC+ than for nH-IC+ (p=0.06) (table 3).

— *Hospital anxiety and depression scale*

Adjusted results showed no differences in anxiety or depression between H-IC+ and H-IC- a median 16 months after admission (table 3). For nH-IC+ were no data available.

Table 3 Results of Checklist Individual Strength, Cognitive Failure Questionnaire and Hospital Anxiety and Depression Scale.
Measurements median 16 months after ICU discharge, adjusted for covariates

	Haematology patients with ICU admission (*n*=27)	Haematology patients without ICU admission (*n*=93)	General ICU patients (*n*=149)
CIS†Ж			
CIS - total	31.4 ±12.8	28.8 ±13.4	33.3 ±13.9
CFQ†Ж			
Memory	7.3 ±4.1	7.1 ±4.6	8.2 ±5.4
Distractibility	10.2 ±5.9	10.8 ±5.6	11.7 ±6.9
Social blunders	6.0 ±4.1	6.5 ±3.8	7.9 ±5.4
Names	3.6 ±2.0	3.1 ±2.0	3.2 ±2.1
CFQ - total	27.5 ±16.0	26.7 ±13.8	28.8 ±16.0
HADS†Ж			
Anxiety	5.4 ±5.2	4.9 ±4.2	n.a.
Depression	4.3 ±4.1	4.6 ±3.7	n.a.
HADS - total	9.4 ±8.9	9.5 ±7.2	n.a.

Data are expressed as mean with (±) standard deviation.

† Adjusted for diagnose acute leukaemia and MDS and LOS-in hospital using log transformed data (not shown)
Ж Adjusted for PCS

DISCUSSION

The main finding of the present study is that a median of 18 months after admission to an ICU, patients who had been treated for a haematological disease and were admitted to an ICU experienced only a lower quality in the physical aspects of their life compared with those admitted to the ICU without a haematological disease. Patients treated for a haematological malignancy who had not been admitted to the ICU reported only better role-physical functioning. In addition, the long-term health related mental quality of life as well as fatigue, cognition, anxiety and depression was similar between the groups. As we did not correct for multiple testing, the small differences between groups appear not to be of clinical relevance.

It is likely that complications following haematological treatment and HSCT both influence physical functioning and the ability to perform social activities [17]. The fact that the only differences in HRQoL concerned physical aspects may have been due to complications during haematological treatment that necessitated the ICU admission [18].

The recent publication by Oeyen et al [3], in which long-term quality of life was prospectively assessed in haematological patients one year after ICU discharge, reports poor QoL outcomes at one year, particularly for the haematological subgroup. However, physical complications of haematological treatment are likely to be related to the severity of the underlying disease, its treatment and need for more rigorous ICU therapy and seem to require longer rehabilitation periods than one year and also exceeds the median 18 months reported in our current study. This is what may distinguish patients with haematological malignancies from general ICU patients and seems confirmed in a recent study [19] where the PCS at five years post-HSCT was similar to those of nH-IC+ in our study at 18 months. These studies represent the limited amount of evidence available on long-term HRQoL. ICU survival and subsequent hospital survival have improved the past decade to such extent that long-term HRQoL becomes more important in the decision to admit or not admit a critically ill patient to the ICU. Our finding that long-term HRQoL is comparable in haematological patients with and without an ICU admission is of relevance. This emphasizes the need for more long-term HRQoL studies that may correct the assumption that patients should not be admitted to the ICU assuming that the long-term outcome will be poor.

The absence of any correlation between the physical and mental component summary scores in all subgroups is remarkable, but has been described earlier [20]. Curbow et al found that recipients of stem cell transplant reported more positive changes in relationship and existential/psychological domains and more negative changes in the physical health domain [21]. The same has been observed for survivors of meningococcal septic shock, who,

despite suffering from severe skin scarring or extensive amputation, did not show more behavioural problems as predictor for poorer HRQoL, nor more cognitive dysfunction [22]. In fact, cancer survivorship is a well-recognized phenomenon in which patients confronted with a life threatening illness are faced with the necessity to accommodate to the disease leading to acceptance of and adjustment to the illness [23]. These patients might experience a similar condition higher than they would have if they had not experienced a serious illness [24].

The strength of the current study is the explorative character and clinical relevance of the results, comparing H-IC+ with both H-IC- and nH-IC+ patients. However, there are also relevant limitations that need to be addressed. Despite the high response rate on the questionnaires, the possibility of non-response bias [25] cannot ruled out. Also the study was undertaken in such a specific population that only a relatively small number of patients could be analyzed. As a consequence, it was not feasible to analyze data for the subgroup of allogeneic HSCT recipients who may be more likely to experience treatment-related physical complications such as graft-versus-host-disease (GvHD), that are known to influence HRQoL [26]. The type of conditioning regimen, female gender, younger age, inadequate social support and pre-transplant psychological distress have also been reported to be predictors for a poorer HRQoL following HSCT [27]. Disease status and performance status preceding intensive treatment for haematological diseases can usually be assumed to be good to be qualified, but further baseline characteristics such as social status and pre-existing distress could not be considered as the study was retrospective. Moreover, we only measured HRQoL once where serial measures would have been more informative on changes over time. Nevertheless, patients with haematological malignancies form a unique subpopulation of ICU patients and our cohort represents one of the largest with long-term HRQoL evaluations currently available. This is increasingly becoming considered to represent a relevant measure of outcome.

CONCLUSIONS

In conclusion, there is no support for the assumption that patients undergoing treatment for a haematological malignancy who are admitted to the ICU have a worse long-term HRQoL than those who are not. Therefore the risk of a poorer long term quality of life should no longer be used as an argument not to admit these patients to the ICU.

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9

General discussion and future perspectives

SUMMARY

High-dose chemotherapy alone or combined with radiotherapy, followed by haematopoietic stem cell transplantation (HSCT) is, in many cases, still the only way to cure haematological malignancies. Such treatment is known to cause serious toxicity including bone marrow aplasia, mucosal barrier injury and inflammation as well as infection that might escalate to life-threatening septic shock. Treatment consists of adequate and timely antimicrobial and supportive care that requires early detection, selection and action.

To address the question '*Can we further improve our standards of care in the management of fever in neutropenic haematological patients?*", the first part of this thesis focussed on the initial management of the febrile neutropenic haematological patient. **Chapter 2** sought answer to the question how to detect fever immediately at its onset when patients are hospitalised for intensive chemotherapy, since fever is still regarded the most important way of identifying an inflammatory process during neutropenia [1] and clinical practice guidelines focus on prompt institution of empirical broad-spectrum antibacterial therapy [2, 3]. We described the results of an audit performed in allogeneic HSCT recipients in which the body temperature was determined by the standard method via the axilla compared to that using a device that measures temperature continuously via the groin since this is most likely to be isolated from outside air. We found that patients experienced only slight problems with the device over time and that the values of both methods correlated well. Moreover, empirical antibacterial therapy could be started 2.5 hours sooner as a result of the earlier detection of fever using this device. **Chapter 3** focussed on the initiation of empirical antibacterial treatment at the onset of fever during neutropenia. An audit was performed on the haematology ward to determine whether there was any delay in starting antibiotic treatment and to define the main reasons for this delay. Based on that evaluation, standing orders for initiating antibacterial treatment and a new approach to taking blood cultures were developed, implemented and evaluated with respect to short- and long-term implications. In the initial audit, the mean time interval between the onset of fever and the administration of antibacterial therapy was 75 minutes (standard deviation (SD) ±46.1). This could be shortened significantly to 32 minutes (SD±17.6) by implementing the modified protocol. **Chapter 4** explored the value of two instruments developed to detect changes in vital signs that occur during systemic inflammation. We found that the Modified Early Warning Score, R-MEWS adopted by the Radboud University Medical Center, was practical and appeared promising as a tool to determine clinical deterioration following the systemic inflammation that occurs after treatment with intensive chemotherapy. As inflammation can be caused by bacterial infection, a cohort of 439 HSCT recipients was analysed in **Chapter 5** to determine the incidence of Gram-positive bacteraemia and thrombo-embolic events associated with the use of central venous catheters (CVC). The incidences of persistent

coagulase-negative staphylococcal (CoNS) bacteraemia, symptomatic thrombosis and thrombophlebitis were 25%, 9.6% and 6.6%, respectively. The duration of neutropenia (odds ratio (OR) 1.02) and left-sided placement of the CVCs (OR 1.73) were independent risk factors significantly associated with the occurrence of persistent CoNS bacteraemia, whereas the use of less mucotoxic conditioning regimens was associated with a lower risk (HDM/BEAM versus other regimens, OR 0.24). Use of Total Body Irradiation, persistent CoNS bacteraemia and tip colonisation were all significantly associated with an increased risk of symptomatic thrombosis (OR 6.0, 3.4 and 2.8, respectively). The risk factors found in this cohort of HSCT recipients differed from those found in the general cancer population, suggesting an important role for persisting bacteraemia in the pathogenesis of CVC-associated thrombosis in haematological patients.

Patients with cancer were generally not considered to benefit from ICU treatment but recent publications report a marked improvement of ICU survival of patients with solid tumours as well as those undergoing intensive haematological treatment including haematopoietic stem cell transplantation. Currently, ICU admission policies are being developed for this population. To address the question '*What are the trends in ICU admissions of critically ill haematological patients and what is their outcome?*', the second part of the thesis focussed on the outcome over time of critically ill haematological patients who required ICU admission. **Chapter 6** explored trends in outcome of allogeneic HSCT recipients transferred to the intensive care unit in a Dutch tertiary care hospital. All patients who had received an allogeneic HSCT between 2004 and 2010 were included in the analyses. Baseline and outcome characteristics were compared and risk factors for ICU admission and survival were identified. Changes in outcome over time of three cohorts of HSCT recipients were investigated. This showed that transplantation from an unrelated donor and myeloablative conditioning treatment were significant risk factors for ICU admission. Prolonged use of vasopressors, invasive mechanical ventilation and male gender were significant predictors for ICU mortality, while the presence of neutropenia and graft-versus-host disease were not. Over the years, APACHE II severity of illness scores at ICU admission remained unchanged (21.0±7.1, 20.1±5.6, 21.2±6.6), while the 100 day post-transplant mortality of patients who were transferred to the ICU significantly decreased from 78% (2004/2005) to 57% (2006/2007) and 35% (2008/2009). **Chapter 7** explored trends over time in admission prevalence and outcome of 1,741 critically ill haematological patients admitted to ICUs in the Netherlands and entered into the National Intensive Care Evaluation database and compared these trends to those of several subgroups of patients suffering from other severe diseases, that were also admitted to the ICU. Trends over time and differences between two subgroups of haematological medical ICU patients and four subgroups of non-haematological medical ICU patients were assessed, as well as the influence of leucopenia. Over the years, the risk-adjusted hospital mortality rate significantly decreased in

both the haematological and non-haematological group with an OR of 0.93 (95%CI 0.92–0.95) per year. After correction for case-mix using the APACHE II score at ICU admission, a leucocyte count <1.0x10^9/L was not a predictor of mortality for haematological patients (OR 0.86; 95%CI 0.46–1.64). We found no case-volume effect of ICU admissions on mortality for haematological ICU patients. While mortality is significantly higher in the haematological group of medical ICU patients than in subgroups of non-haematological patients, the former showed a similar decrease in raw and risk-adjusted mortality rate over time, while leucopenia was not a predictor of mortality. In **Chapter 8,** the long-term health related quality of life (HRQoL) was determined in a single centre tertiary hospital, for patients admitted to the haematology ward who needed intensive care treatment and compared to those who did not as well as with that for non-haematological patients admitted to the general ICU. Data were adjusted for relevant covariates and matched with those of 149 patients admitted in a general ICU. Eighteen months after admission, patients treated for haematological malignancies who needed intensive care reported similar HRQoL compared to haematological patients that did not. Nevertheless, a lower Physical Component Summary was reported compared to non-haematological patients of the general ICU. Hence, there is no reason to assume that admission to the ICU has a negative impact on long-term HRQoL of patients with a haematological malignancy, so this assumption should not affect the decision to withhold transferring patients with haematological malignancies to the ICU when necessary.

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

Failure to recognise and appropriately respond to signs of inflammation/infection in patients treated for haematological malignancies who are clinically deteriorating is clearly a clinically relevant issue. A 3-step approach was proposed to address this.

STEP 1 — TO DETECT (PREDICTORS OF) CLINICAL DETERIORATION AT THEIR ONSET

The overall care and outcome of patients with cancer, especially haematological malignancies, have improved significantly over the years [4], not in the least because of better diagnosis and management of systemic inflammation due to cytotoxic treatment whether or not accompanied by opportunistic infections. Further improvement depends on tracking and tracing signs of clinical deterioration due to sepsis as early as possible.

Recent literature provides better information about which patients are most likely to suffer from haematological and mucosal toxicity [5]. Therefore intensified monitoring of vital signs is required because of expected clinical deterioration where early recognition is of vital interest. This requires an individual monitoring plan in which the frequency of vital signs measurements can be increased up to continuous measurements for high risk patients. When temperature measurements are unreliable, for example during steroid treatment, it is important to monitor changes in other vital signs as well.

During neutropenia, respiratory insufficiency is the main indication for ICU admission. So, respiratory rate, oxygen saturation, but also other early signs of sepsis including hypotension and tachycardia should be monitored during the whole period of risk. In the near future this may be expanded to other parameters such as blood viscosity [6] or biomarkers [7]. Innovative technology may help such as wireless devices and other e-tools that monitor vital signs continuously without hindering patient mobility.

The onset of fever is more or less predictable for certain cohorts and tends to present outside office hours. It was shown that initiation of empirical antibacterial treatment by nurses is safe and effective as it averts serious delays in the start of sepsis resuscitation bundles. Moreover, the continuous presence of nurses, who are familiar with patients' baseline characteristics, may further improve the adequate guideline-based initial treatment of early sepsis, especially if the following suggestions are taken into account.

FUTURE PERSPECTIVES

1. Define risk periods individually, per treatment, based on: underlying disease, type of treatment and comorbidity. During the risk periods intensified monitoring of vital signs is warranted in order to initiate the sepsis resuscitation bundle at the first sign of sepsis.

2. Develop and validate minimal invasive means to continuously monitor inflammation and organ dysfunction, such as body temperature, respiratory and haemodynamic changes.
3. Nurses should have delegated authority to initiate treatment of inflammation/infection when changes in any of the vital signs is detected, to avoid any delay. Appropriate protocols and guidelines need to be developed and evaluated and knowledge and skills should be guaranteed by adequate education.

STEP 2 — TO SELECT THOSE AT RISK FOR CRITICAL ILLNESS AS EARLY AS POSSIBLE

The management of critically ill cancer patients requires specialized skills of professionals and close collaboration between the intensivist and haematologist. The improvement in the outcome of critically ill cancer patients is, to a certain extent, the direct result of better multidisciplinary collaboration between intensive care and haematology wards. ICU clinicians are more experienced in setting aims of critical care based on the presence of organ failure and the potential to reverse this. In case of clinical deterioration, the medical emergency team (MET) should be aware of how vulnerable the patient with a malignant disease is and not wait too long to decide that intensive care treatment is warranted. A clear institutional protocol will improve the outcomes for these patients.

ICU admission criteria for patients with or without haematological malignancies are essentially the same but it might be important to take into account the risk of rapid clinical deterioration associated with severe neutropenia. There is a need for a specific instrument to predict clinical changes in the haematological neutropenic population. Neither R-MEWS nor APACHE seem sufficient for this purpose. The change in R-MEWS over time (Δ R-MEWS) might prove a better instrument but further clinical studies are required.

FUTURE PERSPECTIVES

1. Adequate selection of those at risk for critical illness is needed to define tailor-made monitoring plans, leading to an improved track-and-triggering system defined specifically for the population and to grade clinical changes aiming to detect and treat respiratory and haemodynamic changes before becoming irreversible.
2. As such, close collaboration between intensivists and haematologists is needed to increase the expertise required for all aspects of the general management of patients with haematological malignancies and to provide optimal care to this population.
3. More studies are needed to provide more insight into the relevance of type and status of malignancy, the timing and reason for admission to the ICU, and to determine the impact of the nature and number of organ failure for the prediction of the outcome of patients admitted to the ICU.

4. Interventional studies are also needed to demonstrate the potential benefit of a given approach, e.g. use of specific admission and discharge criteria.

STEP 3 — ACTION; ADEQUATE EN TIMELY

The APACHE II severity-of-illness scores taken on admission of patients with haematological malignancies who were transferred to the ICU were quite high, being approximately 21 in our single-centre study [8] and 24 in the national ICU evaluation database [9]. A higher APACHE score is also associated with a poorer prognosis, but does not necessarily translate this into a quantitative and individual chance of survival [10]. Referral at an earlier stage of clinical deterioration may prove more effective by providing a better chance of survival and a reduction in the number of unplanned ICU days [11]. The Slippery Slope diagram (figure 1) shows how to intervene in the process of patient deterioration with two key interventions, namely Clinical Review and Rapid Response [12].

In situations when a patient can stay in the haematology unit, the medical and nursing staff should be aware of the critical condition of this specific patient. Meticulous evaluation two or three times daily with appreciation of the different organ systems and vital signs should be performed.

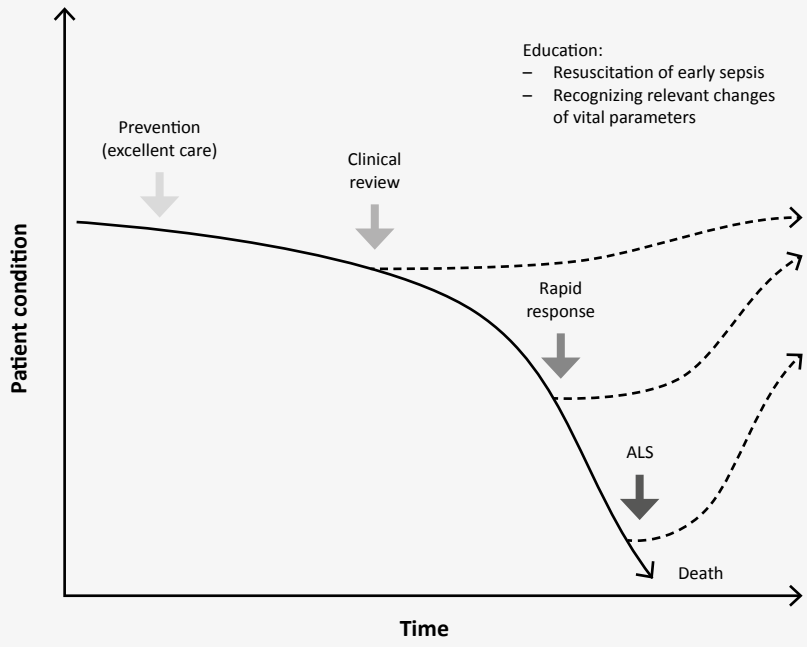

Figure 1 Graphical view of the natural course of clinical deterioration (adapted from dr. Charles Hawkhurst Pain at the 2014 Managing the Deteriorating Patient Conference)

FUTURE PERSPECTIVES

1. Multidisciplinary training for the initial treatment of respiratory insufficiency, as the major indication for ICU referral, should be mandatory for medical and nursing staff on haematology wards where high-risk patients (like those with acute myeloid leukaemia or HSCT recipients) are treated. All staff members should be familiar with applying the basic principles of airway management including oxygen administration and the first steps of basic life support.
2. Earlier ICU referral resulting in lower severity-of-illness on ICU admission should be encouraged at the onset of organ failure and preferably before treatment with invasive ventilation or vasopressor medication is inevitable. For some malignancies, where deterioration due to disease or initial treatment (caused by e.g. tumour lysis syndrome or diffuse intravascular coagulation) can be expected, there might be indication to start treatment under strict monitoring already on an ICU.
3. In case a patient is transferred to an ICU, continuity of care and cure should be guaranteed favourably by using the same (electronic) patient file, evidence based checklists e.g. on antibacterial treatment or transfusion and mutual multidisciplinary consultation at least once daily.
4. More studies should focus on the impact of structural multidisciplinary rehabilitation programs immediately following ICU admission, critical illness and ICU care on the long-term survival of patients with cancer, including performance status, quality of life and ability to receive further treatment for the underlying malignancy.

MAIN MESSAGE

We fully endorse that ICU admission should not be withheld from critically ill patients with haematological malignancies. Therefore, it is crucial that the critical illness which requires monitoring or organ support, is detected at its onset and treated adequately at the earliest stage with the intention of limiting further damage to organ systems so as to provide the best possible chance of survival and recovery within a limited rehabilitation period.

In order to achieve this, evidence-based guidelines should be developed to provide uniformity concerning the **detection** of the onset of critical illness when patients are still on the haematology ward, the **selection** of patients, as well the **timing of consulting** an intensivist or medical emergency team as the **timing of ICU admission** and **action** taken to provide adequate treatment of severe sepsis and septic shock and any necessary intensive supportive care.

To strive for optimal illness-related survival rates while maintaining an acceptable quality of life, we need to learn more about optimal detection and treatment of inflammation and sepsis, how to better select patients who are actually offered ICU treatment and the time-frames within which adequate action should take place to provide the best healthcare in the best equipped location for these purposes. Future studies should aim to provide guidance

to clinicians to allow timely decisions to be made about whether ICU care is required, e.g. to develop a prognostic tool in which the phase of treatment and haematological disease status are incorporated, to minimise unnecessary procedures.

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PT 3

APPENDIX

Nederlandse samenvatting

Dankwoord

Afkortingenlijst

Publicatielijst

Curriculum vitae

Appendix

Nederlandse samenvatting

SAMENVATTING

Hoge dosis chemotherapie gevolgd door een hematopoëtische stamceltransplantatie (HSCT) is voor veel patiënten nog steeds de enige kans om van een hematologische maligniteit te genezen. Een dergelijke behandeling gaat vaak gepaard met ernstige toxiciteit waaronder beenmergaplasie en beschadiging van de slijmvliesbarrières. Daarnaast treedt inflammatie op en hebben patiënten een verhoogde kans op infectie. Deze infectie kan zich ontwikkelen tot een septische shock, een levensbedreigende situatie. De behandeling bestaat uit antimicrobiële behandeling gecombineerd met supportieve zorg en vereist onmiddellijke detectie van de eerste signalen van sepsis, bij een vroege en juiste selectie van patiënten die daar voordeel van zullen hebben.

Het eerste deel van dit proefschrift richt zich op de behandeling van de neutropene hematologische patiënt met koorts. Om de vraag *'Kunnen we de zorg voor febriele neutropene patienten die worden behandeld voor een hematologische maligniteit nog verder verbeteren?'* te beantwoorden, zochten we in **hoofdstuk 2** naar een methode om koorts meteen bij het ontstaan ervan te kunnen detecteren. Koorts wordt in de neutropene fase namelijk nog steeds beschouwd als de belangrijkste aanwijzing voor een systemisch inflammatoir proces [1]. Klinische richtlijnen benadrukken het onmiddellijk starten met empirische breed-spectrum antibacteriële therapie bij neutropene patiënten met koorts [2, 3]. Wij beschreven een pilot waarbij op twee manieren de lichaamstemperatuur werd gemeten bij 33 patiënten die een allogene HSCT ondergingen. De lichaamstemperatuur werd zowel gemeten met de standaard axillaire methode vijf keer per dag alsmede met een sensor in de lies die continue de temperatuur weergaf en alarmeerde bij de vooraf ingestelde grenswaarde. Patiënten gaven aan slechts in geringe mate hinder te ondervinden van de continue metingen. We vonden een goede correlatie tussen de waarden van deze twee methoden. Bovendien vond dankzij de continue temperatuurmetingen een snellere detectie van koorts plaats en kon de empirische antibacteriële therapie 2,5 uur eerder worden gestart. **Hoofdstuk 3** was gericht op het proces van starten met empirische antibacteriële behandeling nadat bij een patient koorts was gedetecteerd. We onderzochten op verpleegafdeling hematologie middels een eerste audit of er sprake was van vertraging bij het starten van een behandeling met antibiotica, om daarna de mogelijke oorzaken te onderzoeken. Op basis van de resultaten van deze evaluatie werd een gedelegeerde opdracht voor het starten van antibacteriële behandeling door verpleegkundigen ontwikkeld alsmede een nieuwe werkwijze voor het afnemen van bloedkweken. Beide interventies werden vervolgens geïmplementeerd en zowel na zes maanden als vier jaar opnieuw geëvalueerd. In de initiële audit was de gemiddelde tijd tussen het optreden van koorts en de eerste toediening van levensreddende antibacteriële therapie 75 minuten. Deze tijd werd aanzienlijk verkort tot 32 minuten door de correcte uitvoering van het gewijzigde protocol. **Hoofdstuk 4** onderzocht de bruikbaarheid van een

Modified Early Warning Score (MEWS), een instrument dat wordt gebruikt om klinisch relevante verandering te herkennen gebaseerd op verandering van de vitale functies. In deze studie vergeleken we de waarde van de R-MEWS (de MEWS zoals deze in het Radboudumc wordt toegepast) met het aantal Systemic Inflammatory Response Syndrome (SIRS) criteria dat optrad tijdens de neutropene koortsepisode van 113 patiënten, gedurende de behandeling van een hematologische ziekte. We vonden dat de waarde van de R-MEWS goed correleert met het aantal SIRS-criteria en veelbelovend is als indicator om patiënten met een verhoogd risico op ontwikkeling van sepsis te selecteren.

Omdat een inflammatoire respons zowel kan worden veroorzaakt door slijmvliesbeschadiging ten gevolge van de cytotoxische therapie als door een bacteriële infectie werd een cohort van 439 HSCT-patiënten geanalyseerd in **hoofdstuk 5**. Centraal veneuze katheters (CVK's) worden vaak gebruikt als veneuze toegang bij patiënten die worden behandeld met een hoge dosis chemotherapie om de gevolgen van de slijmvliesbeschadiging (mucositis) te kunnen behandelen. Het gebruik van een CVK is echter een risicofactor voor infectie met onder meer coagulase-negatieve Stafylococcen (CoNS) en Staphylococcus aureus en kan zelfs leiden tot trombose. Het doel van de studie was om de incidentie van Gram-positieve bacteriëmie en trombo-embolische gebeurtenissen, gerelateerd aan het gebruik van centraal veneuze katheters, te bepalen. De incidentie van persisterende (in 2 of meer opeenvolgende kweken aanwezige) CoNS bacteriëmie, symptomatische trombose en tromboflebitis was respectievelijk 25%, 9,6% en 6,6%. De duur van neutropenie (odds ratio (OR) 1,02 per dag) en linkszijdige plaatsing van de centraal veneuze katheter (OR 1,73) werden als onafhankelijke risicofactoren significant geassocieerd met het optreden van persisterende CoNS bacteriëmie. Het gebruik van minder mucotoxische conditioneringsschema's werd juist geassocieerd met een lager risico (HDM / BEAM versus andere regimes, OR 0,24). Het gebruik van totale lichaamsbestraling, persisterende CoNS bacteriëmie en kathetertip kolonisatie waren allemaal significant geassocieerd met een verhoogd risico op symptomatische trombose (OR 6,0, 3,4 en 2,8 respectievelijk). De risicofactoren in dit cohort van HSCT-patiënten suggereren een belangrijke rol voor persisterende bacteriëmie in de pathogenese van CVK-geassocieerde trombose bij hematologische patiënten.

Van patiënten die behandeld worden voor kanker werd lange tijd gedacht dat ze geen voordeel zouden hebben van een behandeling op een intensive care (IC). Recente publicaties melden echter een verbetering van de IC-overleving van zowel patiënten met solide tumoren als patiënten die een intensieve hematologische behandeling zoals hematopoietische stamceltransplantatie hebben ondergaan. Om de vraag te kunnen beantwoorden *'Welke trends zijn er met betrekking tot de behandeling van ernstig zieke patiënten met hematologische maligniteiten op een intensive care afdeling?'* richt het tweede deel van het proefschrift zich op de veranderende uitkomsten van IC-opname. **Hoofdstuk 6**

onderzocht trends in de uitkomst van allogene HSCT-patiënten die werden opgenomen op de intensive care van een tertiair centrum, te weten het Radboudumc. Alle patiënten die een allogene HSCT hadden ondergaan tussen 2004 en 2010 zijn opgenomen in de analyses. Baseline kenmerken en uitkomsten van de IC-behandeling werden vergeleken en risicofactoren voor een IC-opname en overleving werden geïdentificeerd. Hieruit bleek dat zowel een HSCT met stamcellen van een niet-verwante donor als myeloablatieve conditionering belangrijke risicofactoren voor IC-opname waren. Langdurig gebruik van vasopressoren en invasieve beademing op de IC alsmede het mannelijk geslacht bleken significante voorspellers voor overlijden op de IC, terwijl de aanwezigheid van neutropenie en graft-versus-host ziekte bij opname op de IC dat niet was. In de loop der jaren bleef de ziekte-ernst bij opname op een IC volgens APACHE II (Acute Physiology And Chronic Health Evaluation) vergelijkbaar, waarbij de transplantatie gerelateerde mortaliteit van HSCT-patiënten daalde van 78% (2004/2005) naar 57% (2006/2007) en 35% (2008/2009). Mogelijk is er verdere winst te behalen door het aanpassen van IC-opnamecriteria. **Hoofdstuk 7** onderzocht trends in de tijd in de prevalentie en mortaliteit van 1741 hematologische patiënten die werden opgenomen op een IC in Nederland tussen 2004 en 2012. Gegevens die in de Nationale Intensive Care Evaluatie (NICE) databank waren ingevoerd werden geanalyseerd en vergeleken met vier subgroepen van patiënten die ook waren opgenomen op een IC, te weten patiënten met solide tumoren, chronische levercirrose, chronisch hartfalen en overige medische IC-patiënten. Veranderingen in de tijd en verschillen tussen de twee hematologische subgroepen en vier subgroepen van niet-hematologische patiënten werden beoordeeld, evenals de invloed van leukopenie. In de loop der jaren daalde het voor risico gecorrigeerde ziekenhuis sterftecijfer aanzienlijk voor zowel de hematologische als niet-hematologische groep met een OR van 0,93 per jaar. Na correctie voor de relevante klinische kenmerken van de populatie met behulp van de APACHE II score bleek dat een leukocyten aantal van kleiner dan $1{,}0 \times 10^9$ / L geen voorspeller was van mortaliteit voor hematologische patiënten (OR 0,86). We vonden bovendien geen volume-effect op de mortaliteit voor de hematologische IC-patiënten. We concludeerden dat de mortaliteit significant hoger was in de groep van hematologische patiënten dan in de subgroepen van niet-hematologische patiënten, waarbij beide groepen een vergelijkbare afname in zowel het ruwe als het risico gecorrigeerde sterftecijfer lieten zien en leukopenie geen voorspeller bleek van mortaliteit. In **hoofdstuk 8** werd gekeken naar de aan gezondheid gerelateerde kwaliteit van leven (QoL), 18 maanden na een opname op de IC tijdens behandeling van een hematologische ziekte. Dit werd vergeleken met de QoL van hematologische patiënten die geen IC-opname nodig hadden, en ook met die van niet-hematologische patiënten die werden opgenomen op de IC. De gegevens werden gecorrigeerd voor relevante co-variaten en gematched op leeftijd, geslacht, APACHE II score en opnameduur met die van 149 patiënten die waren opgenomen op een algemene IC. Achttien maanden na de opname gaven patiënten die behandeld werden

voor hematologische maligniteiten en IC-zorg nodig hadden gehad, een vergelijkbare QoL aan in vergelijking met hematologische patiënten die geen IC-opname nodig hadden. Er werd wel een lagere Physical Component Score (verzamelscore van de fysieke items van de vragenlijst) gerapporteerd in vergelijking met niet-hematologische patiënten. We vonden dat er geen reden is om aan te nemen dat opname op de IC een negatief effect heeft op de ervaren Qol van patiënten met hematologische maligniteiten, 18 maanden na de IC-opname. We concluderen dat deze aanname niet van invloed zou moeten zijn op de beslissing om patiënten met hematologische maligniteiten over te plaatsen naar een IC wanneer dat nodig is.

ALGEMENE DISCUSSIE EN TOEKOMSTPERSPECTIEVEN

Het niet of te laat herkennen van tekenen van ontsteking / infectie of niet adequaat reageren bij patiënten die klinisch verslechteren tijdens de behandeling van een hematologische maligniteit is een klinisch relevant probleem. Een 3-staps-benadering wordt voorgesteld om dit te verbeteren:

STAP 1 – ONMIDDELLIJKE DETECTIE VAN (VOORSPELLERS VAN) KLINISCHE VERSLECHTERING

De zorg voor en de uitkomsten van patiënten met kanker, met name hematologische maligniteiten, is aanzienlijk verbeterd de afgelopen jaren [4], niet in het minst door de verbeterde diagnostiek en behandeling van systemische inflammatie die optreedt als een direct gevolg van de cytotoxische behandeling. Verdere verbetering is mogelijk door het zo vroeg mogelijk traceren en behandelen van klinische verslechtering voordat deze resulteert in multi-orgaan falen.

Recente literatuur laat zien welke patiëntengroepen het grootste risico lopen op hematologische en mucosale toxiciteit [5] die leidt tot koorts en klinische verslechtering. Intensievere controle van de vitale functies is nodig omdat bij klinische verslechtering vroegtijdige herkenning van vitaal belang is. Dit vereist een individueel plan voor monitoring van de vitale functies, waarbij de frequentie van metingen kan worden opgebouwd tot continue metingen bij patiënten in de risicoperiode. Hierbij moet er rekening mee worden gehouden dat temperatuurmetingen onbetrouwbaar kunnen zijn, bijvoorbeeld tijdens een behandeling met corticosteroïden, waardoor het belangrijk is om ook veranderingen in andere vitale functies nauwgezet te volgen.

Tijdens een periode van neutropenie is respiratoire insufficiëntie de belangrijkste risicofactor voor een IC-opname. Ademhaling en zuurstofsaturatie, maar ook andere vroege tekenen van sepsis waaronder hypotensie en tachycardie moeten in de gaten worden gehouden tijdens de gehele risicoperiode. Het gebruik van innovatieve technologie zoals draadloze apparatuur en andere e-tools die vitale functies voortdurend controleren zonder van invloed te zijn op de bewegingsvrijheid van patiënten kan hierbij van waarde zijn.

De periode waarin koorts optreedt is redelijk voorspelbaar en gebeurt veelal buiten kantooruren waardoor niet altijd direct een arts beschikbaar is. Er werd in hoofdstuk 3 aangetoond dat het starten met empirische antibacteriële behandeling door verpleegkundigen veilig en effectief is en vertraging in het opstarten van de sepsisresuscitatiebundels kan voorkomen. Bovendien pleit de 24-uurs aanwezigheid van verpleegkundigen, die vertrouwd zijn met de uitgangskenmerken van de patiënt, voor een grotere rol in het initiëren van de behandeling van sepsis. Hiertoe worden de volgende suggesties gedaan.

AANBEVELINGEN

1. De te verwachten risicoperiode definiëren voor elke patient op basis van onderliggende ziekte, type behandeling en comorbiditeit. Tijdens deze risicoperiode is intensieve bewaking van vitale functies noodzakelijk om de sepsisresuscitatiebundel te kunnen starten bij de eerste tekenen van sepsis.
2. Het ontwikkelen en valideren van minimaal invasieve apparatuur om de eerste signalen van ontsteking en het ontstaan van orgaanfalen zoals verandering van lichaamstemperatuur, ademhaling en hemodynamische veranderingen continu inzichtelijk te hebben met een minimale beperking van de bewegingsvrijheid van de patient.
3. Verpleegkundigen moeten de gedelegeerde bevoegdheid hebben om de initiële behandeling van ontsteking / infectie op te starten, zodra er een verandering in een van de vitale functies wordt gedetecteerd, om vertraging te voorkomen. Passende protocollen en richtlijnen moeten daartoe worden ontwikkeld en geëvalueerd. Kennis en vaardigheden van verpleegkundigen moeten door adequaat onderwijs worden gegarandeerd.

STAP 2 - ZO VROEG MOGELIJK SELECTEREN WELKE PATIËNTEN RISICO LOPEN

De zorg voor ernstig zieke kankerpatiënten vereist specialistische vaardigheden van professionals en een nauwe samenwerking tussen de intensivist en hematoloog. De verbetering in de uitkomsten van intensive care opnames bij patiënten met kanker is tot op zekere hoogte het directe gevolg van betere multidisciplinaire samenwerking tussen intensive care en hematologie afdelingen. IC-artsen hebben deskundigheid en ervaring in de zorg voor patiënten met orgaanfalen en de mogelijkheden om deze te behandelen. In het geval van beginnende klinische verslechtering, moet het Medical Emergency Team (MET) zich bewust zijn van de kwetsbaarheid van patiënten met een kwaadaardige ziekte en voortvarend zijn met de beslissing of intensive care behandeling gerechtvaardigd is. Duidelijke richtlijnen op het gebied van de timing van MET-consultatie en IC-opnamecriteria op landelijk en instellingsniveau zullen de uitkomsten voor deze patiënten mogelijk verder verbeteren.

De criteria om op een IC te worden opgenomen zijn voor patiënten met of zonder hematologische maligniteit in essentie gelijk. Het kan echter van belang zijn om te anticiperen op een versnelde klinische achteruitgang die wordt geassocieerd met ernstige neutropenie. Er is behoefte aan een specifiek instrument dat klinische verandering in de hematologische neutropene populatie beter kan objectiveren. R-MEWS is niet toereikend voor dit doel en de APACHE score is niet bedoeld als risico-inschatter per patient. Een snelle verandering van R-MEWS in de tijd (Δ R-MEWS) zou wellicht een betere indicator kunnen zijn, maar verdere klinische studies zijn nodig om dit te bevestigen.

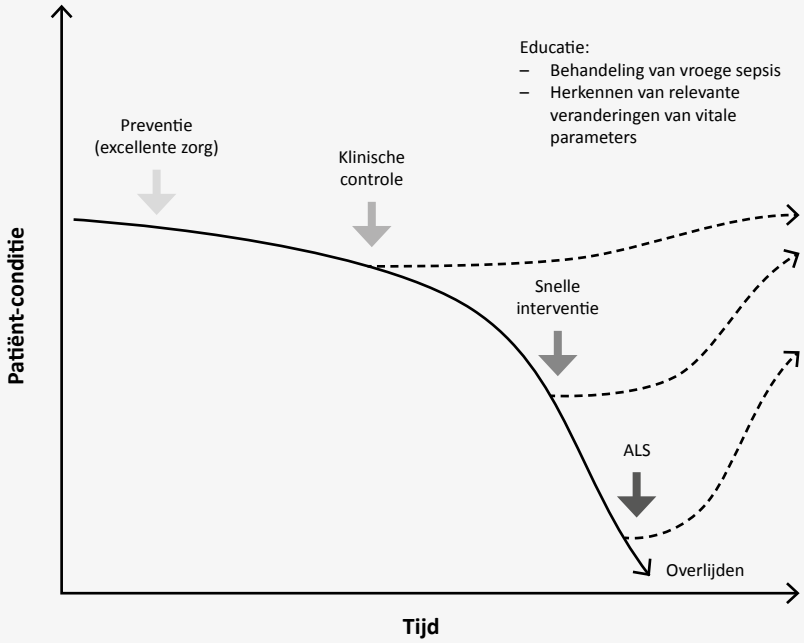
AANBEVELINGEN

1. Een adequate selectie is nodig van hematologische patiënten die het risico lopen op verdere klinische achteruitgang en moet leiden tot op de individu afgestemde bewaking van vitale functies. Er is behoefte aan een beter track-and-trigger systeem om de patiënten die zouden profiteren van intensievere ondersteunende zorg op het goede moment te selecteren. Dit instrument zou zich met name moeten richten op het graderen van respiratoire en hemodynamische veranderingen, zodat deze adequaat behandeld kunnen worden voordat ze onomkeerbaar worden.
2. Nauwe samenwerking tussen intensivisten en hematologen is nodig om voor alle aspecten van de behandeling van patiënten met hematologische maligniteiten de deskundigheid te verhogen en optimale zorg voor deze populatie te kunnen aanbieden.
3. Meer onderzoek is nodig om beter inzicht te verkrijgen in de rol van de onderliggende ziekte en mate van respons op de behandeling, het moment en de reden van de IC-opname en de impact van de mate van orgaanfalen op de uitkomst van patiënten die worden opgenomen op een intensive care.
4. Interventiestudies zijn nodig om het effect van specifieke opname en ontslagcriteria te kunnen beoordelen.

STAP 3 - ADEQUATE EN TIJDIGE ACTIE

De APACHE II ernst-van-ziekte scores, bij opname op een IC, voor patiënten met hematologische maligniteit waren vrij hoog: rond de 21 in ons single-center onderzoek [6] en rond de 24 in de nationale IC-evaluatie database [7]. Een hogere APACHE II score wordt geassocieerd met een slechtere prognose, maar vertaalt zich niet noodzakelijk in een kwantitatieve en individuele kans om te overleven [8]. Verwijzing in een vroeger stadium van klinische achteruitgang zou effectief kunnen zijn en een grotere overlevingskans bieden met een vermindering van het aantal ongeplande IC-dagen [9]. Het zogenaamde 'Slippery slope'-diagram (figuur 1) geeft een indruk hoe en wanneer er ingegrepen kan worden in het proces van klinische achteruitgang. Een sleutelrol is hierbij weggelegd voor 'klinische controle' en 'snelle interventie' [10].

In de situatie dat een patiënt na beoordeling door een intensivist of het MET op de hematologieafdeling kan blijven moet het medisch en verpleegkundig personeel zich continu bewust zijn van de kritische toestand van deze specifieke patiënt. Nauwgezette multidisciplinaire evaluatie van de verschillende orgaansystemen en vitale functies moet structureel minimaal twee of drie keer per dag worden uitgevoerd.



Figuur 1 Grafische weergave van het natuurlijke beloop van klinische verslechtering (gedeeltelijk overgenomen van dr. Charles Hawkhurst Pain tijdens de 'Managing the deteriorating patient conference' in 2014)

AANBEVELINGEN

1. Multidisciplinaire training van de initiële behandeling van respiratoire insufficiëntie, de belangrijkste indicatie voor IC-opname tijdens neutropenie, zou verplicht moeten zijn voor medisch en verpleegkundig personeel op de afdelingen hematologie waar hoog-risico patiënten behandeld worden. Alle medewerkers moeten vertrouwd zijn met de basisprincipes van luchtwegmanagement, inclusief het toedienen van zuurstof en de eerste stappen van basic life support.
2. IC-verwijzing met een lagere ernst van ziekte moet worden aangemoedigd. Bij voorkeur zo spoedig mogelijk na het ontstaan van orgaanfalen en zeker vóórdat een behandeling met invasieve beademing of bloeddrukverhogende medicatie onvermijdelijk is. Wanneer klinische verslechtering verwacht kan worden als gevolg van de onderliggende ziekte dan wel de initiële behandeling (zoals tumorlyse syndroom of diffuse intravasale stolling) kan dat een indicatie zijn om de behandeling al op een IC te beginnen.
3. Continuïteit van zorg en behandeling moet gegarandeerd blijven bij overplaatsing naar een IC. Dit kan worden gewaarborgd door gebruik van hetzelfde (bij voorkeur

elektronische) patiëntendossier, evidence based checklists aangaande antibacteriële behandeling of transfusie en een wederzijds multidisciplinair overleg ten minste eenmaal per dag.

4. Meer onderzoek moet zich richten op het effect van multidisciplinaire revalidatieprogramma's en op de lange termijn kwaliteit van leven van patiënten met kanker na een IC-opname. Hierbij moeten de performance status en de mogelijkheid om verdere behandeling van de onderliggende ziekte te kunnen ondergaan worden meegenomen.

TAKE HOME MESSAGE

We dragen de opvatting uit dat een IC-opname per definitie niet mag worden onthouden aan ernstig zieke patiënten met een hematologische maligniteit. Hierbij is het cruciaal dat de levensbedreigende aandoening die intensieve monitoring of orgaanvervangende behandeling vereist in een zo vroeg mogelijk stadium wordt gedetecteerd en behandeld met de bedoeling om verdere schade aan de orgaansystemen te beperken teneinde de best mogelijke overlevingskansen te verkrijgen met een beperkte herstelperiode. De uiteindelijke lange termijn prognose wordt bepaald door een geslaagde behandeling van de hematologische maligniteit.

Om dit te bereiken moeten evidence based richtlijnen worden ontwikkeld om uniformiteit te verkrijgen in de detectie van levensbedreigende complicaties wanneer patiënten nog op de hematologie afdeling verblijven, de selectie van patiënten bij wie het consulteren van een intensivist of interventieteam noodzakelijk is en de acties die moeten worden uitgevoerd om adequate behandeling van ernstige sepsis en septische shock met optimale ondersteunende zorg mogelijk te maken.

Toekomstige studies moeten gericht zijn op de tijdige beslissing of IC-behandeling van meerwaarde is, om onnodige opname en behandeling op een IC te minimaliseren. Dit door bijvoorbeeld het ontwikkelen van een prognostisch instrument waarin naast de mate van orgaanfalen ook de fase van de behandeling en de hematologische ziektestatus zijn opgenomen.

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Appendix

Dankwoord

DANKWOORD

Ooit ben ik aan dit promotietraject begonnen met de gedachte dat we de zorg voor mensen met een hematologische ziekte zouden kunnen verbeteren. Het ging me daarbij vooral om de mensen die, tijdens de toch al loodzware en onzekere route naar genezing, geconfronteerd werden met een levensbedreigende situatie als direct gevolg van de behandeling. Om dit tot een goed einde te kunnen brengen heb ik mogen samenwerken met zeer gedreven personen van verschillende afdelingen in en buiten het Radboudumc zonder wie dit boekje er nooit was gekomen. Nu het eenmaal zo ver is wil ik op deze plek iedereen die op welke manier dan ook behulpzaam of anderszins betrokken is geweest heel hartelijk bedanken. Zonder iemand tekort te willen doen wil ik de volgende mensen in het bijzonder bedanken:

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PROMOTOREN

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CO-PROMOTOREN

Dr. J. Peter Donnelly — Beste Peter, wat heb je mij veel geleerd de afgelopen jaren over het doen van onderzoek en over de beginselen van de microbiologie. Onze vele afspraken de afgelopen jaren waren nooit voorspelbaar en dus ook nooit saai, maar bovenal hartelijk en gemeend. Altijd een anekdote paraat om het punt dat je duidelijk wilde maken te illustreren. Ik heb me zeer gesteund gevoeld de afgelopen jaren.

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Beste prof. dr. Kullberg, prof. dr. Van Achterberg, prof. dr. Van der Graaf en prof. dr. Gerritsen, dank dat jullie bereid waren om plaats te nemen in de manuscriptcommissie en dank voor de kritische beschouwing en goedkeuring van het manuscript.

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Naast de promotoren en co-promotoren wil ik ook alle anderen die een rol hebben gespeeld bij het tot stand komen van de artikelen hartelijk danken voor hun bijdrage (in alfabetische volgorde): Mark van den Boogaard, Marielle van der Burgt, Andrea Evers, Bernard Fikkers, Ton de Haan, Hans van der Hoeven, Nicolette de Keizer, Britta Laros, Niels Peek, Nelly Peer, Floor Ploos van Amstel, Carin Potting, Anke Richters, Patrick Sturm, Ilona Verburg, Paul Verweij. Veel dank!

MEDEWERKERS AFDELING HEMATOLOGIE

Als stagiaire kwam ik in 1993 op A51 binnenwandelen. Ik wist nog maar heel weinig van het ziekenhuis en de patiënten op kamer 15 schoten spontaan in een lachstuip toen ik de thermometer ging zoeken en de koelkast opentrok. Dat het toch nog goed kwam is voor een groot deel te danken aan Eva, die me door de stage heen heeft gesleept. De jaren die volgden waren fascinerend, vaak intensief qua patiëntenzorg, maar bovenal ook gezellig en in een professionele, patiëntgerichte atmosfeer en met aandacht voor elkaar. Ik denk met veel plezier terug aan de wisselende diensten, de nachten waarin het kon spoken maar waar soms ook nog een spelletje Risk gespeeld kon worden. Er is op dat gebied veel veranderd de afgelopen jaren vrees ik…

Als verpleegkundig specialist besloot ik in 2014 om mijn professionele geluk elders te zoeken. Dat neemt niet weg dat een warme herinnering blijft bestaan aan een bijzondere afdeling, een mooi dynamisch specialisme en de bijzondere mooie mensen die zich tot dit specialisme aangetrokken voelen: je weet pas wat je mist als het er niet meer is. Allemaal heel erg bedankt, met een speciale vermelding voor het *'hert'* van de afdeling (you know who you are!). Vandaag is ook de dag dat ik echt afscheid kan nemen van de afdeling, ik hoop jullie allemaal te zien!

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Beste allemaal, de afgelopen jaren is er in steeds sterkere mate ruimtegebrek geweest: in mijn agenda, in mijn hoofd, in mijn sociale leven. Des te aangenamer waren de momenten dat ik wél wist te ontsnappen aan SPSS, Word, Excel, reference manager en concept-artikelen, laatste concepten, allerlaatste concepten, revisies en drukproeven. Of het nu ging om een wedstrijd in De Goffert (Jan, Paul, Antal), een optreden in het onvolprezen Doornroosje (Anton, Remco) of de buitenschoolse activiteiten van FC Biercelona. Het was een genoegen, een fijne afleiding van wat (te) lang (te) veel van mijn aandacht in beslag heeft genomen.

Bijzonder verfrissend zijn de buitenlandse uitstapjes met Toine, Peter en Patrick. Vanuit de gedachte dat we mooie voetbalwedstrijden wilden zien (wat soms ook lukte, zo herinner ik me nog een Real Madrid – Barcelona in 1997) zijn we nu bijna cultuurhistorisch bezig en schromen we zelfs niet om een museum binnen te gaan. Ik hoop nog veel van de wereld met jullie te zien en er achter te komen wie destijds de linksback van Oranje had moeten zijn… Geweldig dat jullie er ook vandaag bij zijn.

Beter een goede buur… Bachstreet Boys (and girls), wat hebben we het eigenlijk gezellig samen: spontane borrels in het park, een winter-BBQ bij -15°C en naar Oranje op het WK kijken, telkens in een andere tuin met bij de landen passende gerechten. Dank daarvoor en voor alle andere gezelligheid.

Lieve Aad en Riet, Simone, Eveline, Alexander. Jullie hebben het hele traject van nabij meegemaakt met alle ups en downs. Dank voor de support en interesse, en de Brabantse gezelligheid. Ook voor de praktische hulp als we het eens niet geregeld kregen met de planning of oppas.

Mam, pap (volgens de kids ben je een sterretje in de ruimte) en Alexandra: jullie stonden letterlijk aan de wieg van wie en wat ik nu ben. Daar doet dit proefschrift niets aan af. Normaal doen is al gek genoeg heb ik vaak gehoord en dat is ook zo. Bedankt daarvoor.

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Lieve Ingrid, je zou gaan beginnen met de master geriatrische fysiotherapie als voor mij het afronden van het proefschrift in zicht was. Op de dag van de verdediging ben je alweer halverwege het derde jaar… zo gaan die dingen bij ons nu eenmaal. De afgelopen jaren waren druk en we hebben zeker gemerkt dat niets vanzelf gaat. Toch zijn we er in geslaagd om alle hoofden boven water te houden en dat is grotendeels jouw verdienste geweest. Dank voor alle support en het warme nest dat het bij ons thuis altijd is en hopelijk nog heel lang zal blijven.

Appendix

Afkortingenlijst

AFKORTINGENLIJST

(H)SCT	(Haematopoietic) stem cell transplantation
(M)MUD	(Mis)matched unrelated donor
AA	Aplastic anaemia
ALL	Acute lymphoblastic leukaemia
AML	Acute myeloid leukaemia
APACHE II	Acute physiology and chronic health evaluation II
ATG	Anti-thymocyte globulin
BEAM	BCNU, etoposide, cytarabine, melphalan
CDI	Clinically defined infection
CML	Chronic myeloid leukaemia
CoNS	Coagulase-negative staphylococcus
COPD	Chronic obstructive pulmonary disease
CST	Continuous measurement of the skin temperature
CVC	Central venous catheter
Cyclo	Cyclophosphamide
EAT	Episodic axillary temperature measurement
GvHD	Graft-versus-host disease
HDM	High dose melphalan
HEPA	High-efficiency particulate air
HL	Hodgkin Lymphoma
HRQoL	Health related quality of life
ICU	Intensive care unit
Ida	Idarubicin
LOS	Length of stay

MA	Myeloablative
MDI	Microbiologically defined infection
MDS	Myelodysplastic syndrome
MEWS	Modified early warning score
MM	Multiple myeloma
NHL	Non-Hodgkin lymphoma
NICE	National intensive care evaluation
NMA	Non-myeloablative
OVS	Oral viridans streptococci
PET	Positron emission tomography
RAMR	Risk adjusted mortality rate
SIB	Sibling
SIRS	Systemic inflammatory response syndrome
SSC	Surviving sepsis campaign
TBI	Total body irradiation
TLI	Total lymphoid irradiation
TRM	Transplant related mortality
VUD	Voluntary unrelated donor
WBC	White blood cell count

Appendix

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Appendix

Curriculum vitae

CURRICULUM VITAE

Maarten van Vliet werd op 31 juli 1971 geboren in Nijmegen. Na het behalen van het atheneumdiploma aan het toenmalige Elshof college in Nijmegen (1990) studeerde hij verpleegkunde aan de Hogeschool van Nijmegen, alwaar hij in 1994 zijn diploma behaalde. Hierna heeft hij twee jaar gewerkt op de intensieve behandelunit van Maria Roepaan in Ottersum, voor mensen met zowel een verstandelijke beperking als ernstige gedragsproblematiek. Daarnaast werkte hij op invalbasis op de afdeling hematologie van het Radboudumc waar hij in 1996 een vaste aanstelling kreeg als verpleegkundige. Aldaar begon Maarten in 2001 aan de masteropleiding advanced nursing practice (MANP) welke hij in 2003 met goed resultaat afrondde. Hiermee werd hij geregistreerd als verpleegkundig specialist intensieve zorg bij somatische aandoeningen.

In deze functie werd de vitaal bedreigde hematologische patiënt zijn belangrijkste aandachtsgebied met als doelstelling het verhogen van de patiëntveiligheid en kwaliteit van zorg. Hij heeft een rol gespeeld bij de implementatie van het medical emergency team (MET) en continue monitoring van vitale functies op de verpleegafdeling. Daarnaast heeft hij verpleegkundig consulentschap opgezet met als doel continuïteit van zorg te bieden aan patiënten die op de intensive care werden opgenomen.

Naast patiëntenzorg en onderzoek was Maarten tot en met 2015 als docent actief op de Radboud Zorgacademie binnen zowel de complementmodule hematologie verpleegkunde (CHV) als de opleiding tot intensive care verpleegkundige (VICV).

Binnen het Radboudumc is Maarten lid van de coördinatiegroep verpleegkundig specialisten. Daarnaast is hij sinds 2008 met tussenpozen lid van de landelijke congresredactie van de 'VenVN oncologiedagen' en was hij één van de initiatiefnemers van het landelijk netwerk verpleegkundig specialisten hematologie. Dit netwerk ging later op in de special interest group hematologie van VenVN oncologie, waarna hij nog vier jaar in het dagelijks bestuur heeft gezeten. Vanaf 2013 is Maarten lid van de werkgroep die een landelijke richtlijn over de plaatsing en behandeling van de hemato-oncologische patiënt op de intensive care afdeling ontwikkelt. Sinds 2014 maakt hij deel uit van de werkgroep deskundigheidsbevordering van het netwerk verpleegkundig specialisten oncologie.

Vanaf augustus 2014 is Maarten werkzaam op afdeling medische oncologie van het Radboudumc met als aandachtsveld de urologische oncologie.

Maarten woont samen met Ingrid en samen hebben zij twee kinderen: Dennis en Anna.