REVIEW

The management of critically ill patients with haematological malignancies

N. Kusadasi[1,2]*, M.C.A. Müller[3], D.J. van Westerloo[4], A.E.C. Broers[5], M.G.E.C. Hilkens[6], N.M.A. Blijlevens[7] on behalf of the HEMA-ICU study group

[1]Department of Intensive Care Medicine, Erasmus Medical Center, Rotterdam, the Netherlands, [2]Department of Intensive Care Medicine, Utrecht University Medical Center, the Netherlands, [3]Department of Intensive Care Medicine, Academic Medical Center, Amsterdam, the Netherlands, [4]Department of Intensive Care Medicine, Leiden University Medical Center, Leiden, the Netherlands, [5]Department of Haematology, Erasmus Medical Center Rotterdam, the Netherlands, [6]Department of Intensive Care Medicine, Radboud University Medical Center, Nijmegen, the Netherlands, [7]Department of Haematology, Radboud University Medical Center, the Netherlands, *corresponding author: n.kusadasi@umcutrecht.nl

ABSTRACT

The management of critically ill patients with haematological malignancy (HM) still shows inter- and intra-regional differences. Our objective in this updated review was to address the evidence supporting the potential treatment options, based on multidisciplinary processes, of critically ill patients with HM. A stepwise approach to the critical care pathway of this patient population from the triage to ICU admission to ICU discharge was chosen to emphasise certain key findings. Our main focus relied on significant issues of decision-making in daily clinical routine. The plethora of studies shifted the pragmatic treatment policy into an evidence-based approach. The transfer of a patient with HM from the haematology ward to the ICU and vice versa should be based on a well-defined clinical care process in which the haematologists and intensivists are in close collaboration and direct communication. A protocolised clinical approach to treat a critically ill patient with HM seems helpful to optimise patient-oriented care and patient safety.

KEYWORDS

Critically ill, haematological malignancies, outcome, prognostic factors, systemic review

INTRODUCTION

In the last decades, there has been increasing evidence regarding the improved survival of patients with haematological malignancies (HM) admitted to the intensive care unit (ICU). The management of the critically ill patient with HM has shifted from no admission to a short ICU admission period. Clinicians often follow a pragmatic policy, as described by several groups.[1-4] Patients undergoing first-line immunotherapy and chemotherapy regimens and those with low-grade malignancies and partial/complete remissions receive full treatment. Patients for whom there is uncertainty about the benefit of ICU support, in terms of survival, are admitted and receive full ICU treatment. In this last group, reassessment after 3 to 5 days is often desirable, and if there is no improvement or a deterioration, the treatment can then be adjusted. For patients who are not undergoing treatment modalities for urgent HM, a highly restricted to no ICU admission policy is followed.

However, there are still considerable inter- and intra-regional differences in the ICU admission policy for the patient with HM.[5,6] These discrepancies in admission policy formed the basis for the development of a Dutch guideline discussing the pathways of care for critically ill patients with HM. This guideline has been approved by the Dutch Society of Intensive Care and will shortly be approved by the Dutch Society of Haematology. A concise and precise summary of the guideline has recently been published.[7] Because new evidence was published recently we decided to review this for a more general public of

internists. The level of evidence of these studies was similar to that used in the guideline and showed mainly an evidence level of B for methodological quality according to CBO / EBRO guidelines (www.cbo.nl). We refer the reader to the guideline for a detailed description of the level of evidence-based recommendations. The existing knowledge supports the substantial contribution of a multidisciplinary approach in the treatment of critically ill patients with HM. Haematologists and intensivists play a central role in this. Notably, most studies have a heterogeneous patient population and a descriptive study design, either retrospective or prospective.

In this review we performed a stepwise approach to the critical care pathway of this patient population. The triage from consultation to ICU admission to ICU discharge was chosen to emphasise certain key findings. Our main focus relied on significant issues of decision-making in daily clinical routine during ICU admission. The factors influencing this triad will be addressed based on evidence and summarised in consecutive order in the subheadings below. In doing so, we aim to optimise the collaboration between the haematologists and intensivists. This in turn might improve the evidence-based decision-making in daily clinical routine of critically ill patient with HM.

ICU ADMISSION AND OUTCOME OF PATIENTS WITH HAEMATOLOGICAL MALIGNANCIES

The prognosis of patients with HM has improved in recent decades through chemotherapy dose adjustments, the prevention of nosocomial infections and the introduction of new antiviral and antifungal drugs. The survival of vitally threatened patients has improved with early sepsis recognition and intervention and lung protective mechanical ventilation. There is increasing evidence about improved survival of patients with acute or chronic and myeloid or lymphoid derived HM admitted to the ICU.[8-11] There are several studies regarding the outcome of patients with acute myeloid leukaemia admitted to the ICU. Just recently, ICU and hospital survival of patients with diffuse large B-cell lymphoma was described as 75.7% and 70.3%, respectively.[12] Different clinical emergencies related to HM necessitate adjusted ICU support, such as successful first-induction chemotherapy in the ICU after pre-treatment with oral hydroxyurea for patients with HM-related leukostasis.[13,14] The mortality has been shown to be lower for patients pre-treated with hydroxyurea (34% vs. 19%, p = 0.047).[14]

The post-ICU long-term prognosis seemed to be primarily influenced by the successful continuation of haematological treatment regimes. Patients with allogeneic stem cell transplantation (SCT) receiving reduced intensity conditioning seemed to have better 1- and 5-year post-ICU survival than patients undergoing myeloablative conditioning, as shown by Townsend and colleagues.[15] In that article, however, ICU admissions within 5 years after SCT were included indicating different ICU admission reasons at different time points after SCT. Also the long-term health-related quality of life (HRQoL) of patients with HM seemed to be similar to that of patients who were not admitted to the ICU.[16] These data indicate that the assumption that ICU admission has a negative impact on HRQoL is unfounded and that the decision to admit a patient to the ICU should not depend on this assumption. If the HM is refractory with a poor prognosis, transfer to an ICU is highly undesirable. The same applies when the patient or family has expressed the wish not to undergo life-sustaining treatments.[1,17-19] For an objective approach to a clinical problem, some have divided patients with HM into subgroups. These subgroups, as proposed by Bird et al.,[3] can help to decide whether admitting a patient with HM to the ICU could positively influence survival. In this study poor predictors were defined as relapsed or failed treatment, disease unresponsive to therapy, and/or successive failure of > 2 organ systems.

In conclusion, available evidence shows that the survival of HM patients has significantly improved in recent years. Additionally, the quality of life after ICU admission seemed comparable with patients without HM. There is ample evidence in favour of a broad ICU admission policy for patients with HM.

TIMING OF ICU ADMISSION AND OUTCOME OF PATIENTS WITH HAEMATOLOGICAL MALIGNACIES

The increased delay between the onset of the first symptoms to ICU admission of a patient with HM has been shown to be an independent predictor of mortality.[20] Several researchers have described the importance of so-called early warning scores and the early involvement of ICU outreach teams and medical emergency teams in the early ICU admission of patients with HM.[21-24] The duration of less than 24 hours from the onset of the first symptoms to ICU admission was associated with improved survival.[25] Lengliné et al. emphasised the importance of early ICU admission (defined as admission at presentation of acute symptoms and before induction chemotherapy).[13] These authors show that late ICU admission (defined as admission from the haematology ward) resulted in an increase in the use of mechanical ventilation (60% vs. 33%) and use of vasopressors (60% vs. 16%), longer ICU

stay (9 [6-25] vs. 5 [2-9] days) and decreased ICU survival (65% vs. 79%) compared with early ICU admission. In a prospective study of patients with cancer (84% of the patients had HM), Mokart et al. showed that a delay of more than 2 days from the start of respiratory symptoms to ICU admission was associated with higher 28-day ICU mortality.[26] These authors state that early ICU admission for patients with malignancy and acute respiratory failure could lead to better survival.

Altogether, the majority of the publications emphasise the importance of early ICU admission in critically ill patients with HM. However, the term 'early' is not clearly defined, making it difficult to properly define the justified timing of admission in daily routine. A very limited number of studies used as definition either the arrival at the hospital or 1 to 4 days from the onset of symptoms to the ICU admission. It can be concluded that delayed ICU admission is associated with increased mortality. Based on expert opinion, admission should be as early as possible, ideally before development of multiple organ failure.

RESPIRATORY SUPPORT AND OUTCOME OF PATIENTS WITH HAEMATOLOGICAL MALIGNANCIES

Many studies indicate that early mechanical ventilation can favourably impact the prognosis. In a recent retrospective study, the feasibility of high-flow nasal cannula oxygen (HFNO) therapy for acute respiratory failure in patients with HM was evaluated.[27] Of the 45 patients, 33% successfully recovered, and 67% required invasive mechanical ventilation due to failure of this treatment. In addition, in immunocompromised patients (approximately 60% HM) with hypoxaemic acute respiratory failure, support with HFNO improved neither mechanical ventilatory assistance nor patient comfort nor survival rates compared with oxygen delivered via a Venturi mask.[28,29] In contrast, recent studies indicate that immunocompromised patients with hypoxaemic acute respiratory failure treated with non-invasive ventilation (NIV) might be associated with an increased risk of intubation and mortality compared with those treated with HFNO.[30,31]

Others emphasise the importance of NIV at an early stage, indicating that it results in a significant decrease in mortality.[32,33] Although non-invasive modalities can be seen as an interesting alternative for invasive mechanical ventilation in patients with acute respiratory failure, others stress the high percentage of NIV failure in these patients. An Italian retrospective study compared NIV with invasive mechanical ventilation.[32] In this study, 21% of the patients received NIV at ICU admission and 46% of these patients later required invasive mechanical ventilation. Also a Spanish prospective multicentre study of 450 patients with HM shows that 60% of patients initially treated with NIV later required invasive mechanical ventilation.[34] Mortality in this latter group was 80%. The odds ratio of death was 5.74 for NIV failure and 3.13 for invasive mechanical ventilation at ICU admission. In a randomised study, Wermke et al. showed no advantage of NIV on the study endpoints of ICU admission frequency, need for endotracheal intubation and survival.[35] These authors and others described the severity of illness and the presence of adult respiratory distress syndrome as risk factors for this NIV failure.[32,35-38] They also emphasised that this subgroup of patients is precisely the one for which early endotracheal intubation should be considered. In conclusion, a few studies indicate that early non-invasive support (NIV and/or HFNO) may favourably influence the prognosis in some subpopulation of patients. Others emphasise the importance of early endotracheal intubation in patients with a high probability of NIV failure.

PROGNOSTIC FACTORS OF CRITICALLY ILL PATIENTS WITH HM

A broad range of haematological and ICU prognostic factors have been evaluated during the ICU admission of patients with HM.[39] The evaluated ICU severity of illness scores were the Acute and Chronic Health Evaluation (APACHE) II/III/IV, Simplified Acute Physiology Score (SAPS) and Sequential Organ Failure Assessment (SOFA) scores. High APACHE IV and SOFA scores have been shown to be related to ICU mortality.[40-42] Others emphasised ICU support-related factors as being significant for mortality rates. In this perspective, the use of mechanical ventilation, vasopressors and haemodialysis were associated with 60.5%, 57.5% and 36.8% mortality, respectively.[25]

There is also plethora of evidence focussing on the impact of haematological factors on ICU mortality. Here we want to briefly focus on neutropenia, Eastern Cooperative Oncology Group score (ECOG, also known as the WHO performance score or Zubrod score) and allogeneic SCT patients in consecutive order. In a retrospective study the combination of a positive blood culture and neutropenia seemed to be associated with increased 28-day mortality suggesting that this could be of additional value when assessing mortality risk in this patient group.[43] In contrast, in a recent meta-analysis, there was no significant impact of neutropenia on mortality (risk difference of mortality, 9%; 95% CI -15 to +33) in critically ill cancer patients[44] nor was neutropenia of importance in the Dutch NICE cohort.[11] In addition, an ECOG score > 2 at ICU discharge

(hazard ratio 11.15 (4.63 to 26.87)), haematological disease recurrence (hazard ratio 9.74 (3.80 to 24.93)) and discontinuation of the planned haematological treatment (hazard ratio 4.35 (1.29 to 14.71)) have been shown to be independent predictors of late mortality after ICU admission.[45]

In a recent single-centre retrospective study, the incidence of allogeneic SCT-related complications requiring an ICU admission was described as 22%, with an ICU and 1-year mortality rate of 44% and 84%, respectively.[46] In this study, a degradation of the SOFA score at day 3 of ICU stay, need for mechanical ventilation and occurrence of active graft versus host disease were the main predictive factors of mortality. Among these parameters, the need for mechanical ventilation seemed to be a striking determinant, as it dramatically increased the risk of mortality. Others evaluated the prognostic value of the Haematopoietic Cell Transplantation-Specific Comorbidity Index (HCT-CI) in ICU patients with allogeneic SCT. This index is designed to predict the outcome after allogeneic SCT, and it has proven to provide valid and reliable scoring of pretransplant comorbidities that predicts non-relapse mortality and survival.[47] Since then it has been used for clinical studies and patient counselling before HCT. In this perspective, Bayraktar and colleagues showed that HCT-CI values > 2 were associated with high hospital mortality, and HCT-CI values > 4 were associated with decreased overall survival compared with values from 0 to 1.[48] In this study, ICU admission during a conditioning regimen for allogeneic SCT and the use of reduced-intensity conditioning regimens were associated with low hospital mortality. In an overview article, Jackson et al. reported that short-term survival was related to ICU admission diagnosis, while long-term survival was influenced by underlying haematological disease.[49]

Again others combined haematological- and ICU-related factors to predict the prognosis of patients with HM admitted to ICU. In a recent retrospective study, Pohlen and colleagues created an ICU survival score based on independent prognostic factors for decreased survival after ICU discharge.[50] These factors were defined as relapse or refractory disease, previous allogeneic SCT, time between hospital admission and ICU admission, time spent in ICU, impaired diuresis, Glasgow Coma Scale < 8 and haematocrit ≥ 25% at ICU admission. The risk stratification into three risk groups, based on this score, has been shown to discriminate distinct survival rates after ICU discharge. These authors emphasise that a substantial portion of critically ill patients with acute myeloid leukaemia will benefit from intensive care. However, they express their doubts about the usefulness of this score in decision-making on whether to pursue or withdraw ICU treatment for an acute myeloid leukaemia patient because of the retrospective design of the study.

All available data indicate the need for reassessment to evaluate the expected prognosis shortly after ICU admission and limit a prolonged – and above all, an unjustified – ICU stay. In this perspective, the time course of organ dysfunction over the first 6 ICU days differed significantly between survivors and non-survivors in cancer patients (70% having HM).[51] After 3 days of ICU support non-survivors showed increasing organ failure scores, while survivors showed decreasing scores. These were more accurate for predicting survival on day 6 than at admission or on day 3. Therefore, a period of 3 to 5 days seemed a reasonable amount of time to allow for reassessment. At the time of reassessment, clinicians can take into account the ICU severity of illness scores (APACHE IV and SOFA scores), the haematological disease status and the ECOG score as mentioned above. In addition to these factors, HCT-CI use can be valuable in patients with allogeneic SCT.

Although the predictive value of individual prognostic factors for ICU mortality differs depending on the specific patient, disease and treatment characteristics, the result of their combination and change over time can guide the clinician in decision-making at the time of reassessment, as ultimately each treatment adjustment is a case-by-case decision at patient's bedside.

THE MULTIDISCIPLINARY TREATMENT APPROACH

Recently, Schellongowski cited evidence in support of a multidisciplinary approach in the treatment of critically ill haematological and oncological patients.[52,53] Saillard et al. summarised the decision-making process of critically ill allogeneic SCT patients admitted to ICU.[54] These authors emphasise that a rational policy of ICU admission triage is hard to manage, as each decision on ICU admission is a case-by-case decision at the patient's bedside. They suggest the close collaboration between haematologists and intensivists being crucial in this context. From this point of view, a multidisciplinary panel of experts, brought together by the French Intensive Care Society, summarised their recommendations about the management of this specific patient population.[55] In short, they advocate additional studies since most of the provided recommendations were obtained from low levels of evidence. We want to focus on the additional role of a pharmacist in the multidisciplinary approach of the treatment of critically ill patients with HM. In this perspective, Soares et al. showed that the presence of clinical pharmacists in

the ICU (odds ratio [OR] 0.67; 95% CI 0.49 to 0.90), number of protocols (OR 0.92; 95% CI 0.87 to 0.98), and daily meetings between oncologists and intensivists for care planning (OR 0.69; 95% CI 0.52 to 0.91) were associated with lower mortality.[56] They also showed that the implementation of protocols (OR 1.52; 95% CI 1.11 to 2.07) and meetings between oncologists and intensivists (OR, 4.70; 95% CI, 1.15 to 19.22) were independently associated with more efficient resource use. In addition, Coutsouvelis et al. described that medication information transfer by a pharmacist at ICU admission ensured that the medication was prescribed correctly and at the right times.[57] This may improve both continuity of care and patient safety. A recent multivariate analysis showed that a low voriconazole level was associated with young age, having an HM, the prophylactic use of voriconazole and the use of proton-pump inhibitors.[58] In this same study, a low voriconazole level was an independent predictor of therapy failure. In addition, Blackburn and colleagues showed recently that an increased volume of distribution of aminoglycosides (amikacin and tobramycin) was identified in critically ill patients with HM, and that current dosing yielded a suboptimal concentration (peak) in the majority of patients.[59] Taken together, these studies indicate the importance of drug monitoring and the crucial role of the pharmacist in the critical care pathway. Almost all of the published articles emphasise that the complexity of patients with HM and the risk of deficits in communication and information transfer necessitate a multidisciplinary approach.

VOLUME-OUTCOME RELATIONSHIP IN CRITICALLY ILL PATIENTS WITH HM

In a retrospective study of 1753 haematological patients with acute respiratory failure, LeCuyer et al. described that the mortality in ICUs with a high volume (> 30 patients with HM admitted to the ICU each year) was lower than that of ICUs with a low volume (< 12 patients with HM admitted to the ICU each year).[60] However, this finding was only clear after adjusting for prognostic factors for ICU mortality and the use of propensity scores. This volume effect was not observed in a recently published Dutch National Intensive Care Evaluation (NICE) database analysis.[11] Albeit, an increasing number of articles emphasise the importance of centralisation for severe sepsis treatment. These studies show an inverse relationship between the number of severe sepsis admissions and hospital mortality.[61-63] Gaieski et al. showed that the hospital mortality of severe sepsis patients with one organ failure in low-volume ICUs (defined as < 50 cases admitted to the ICU each year) was 18.9%, while the hospital mortality in high-volume ICUs (defined as > 500 cases admitted to the ICU each year) was 10.4%.[61] Similar differences were also found in cases of severe sepsis with multiple organ failure. Although these data cannot directly be extrapolated for ICU patients with HM, they do suggest the importance of treatment in centres with haemato-oncological expertise.

POST-ICU PROGNOSIS OF PATIENTS WITH HM

There are limited data about the post-ICU period for patients with HM. The available literature mainly focuses on the long-term prognosis and quality of life, as described in a previous section of this review. We emphasise the importance of the consultant intensive care nurse (CIN) and medical intervention team (MET) during the early post-ICU period. Endacott et al. found that the CIN can play an important role in preventing complications after ICU discharge.[64] Green and Edmonds found that ICU readmissions decreased from 2.3% to 0.5% within 5 years after the implementation of a CIN.[65] In another study, the presence of a CIN resulted in the early detection of clinical deterioration and the prevention of complications such as ICU readmission.[66] Additionally, the implementation of a MET seemed to improve hospital survival and reduced the number of ICU readmissions.[67] The implementation of a CIN and/or a MET may play an important role in improving the quality of care for patients with HM after ICU discharge. The designation of a responsible group of nurses in both departments can optimise continuity of care and the exchange of expertise and low-threshold consultation. Although there are no data on this matter, it is also important to discuss the ICU readmission policy and any treatment restrictions upon discharge. It appears that haematological ICU patients need more time to physically rehabilitate than non-haematological ICU patients, often longer than 1.5 years.[68] This could be explained in part by the combination of underlying disease, haematological treatment and the impact of an ICU admission on physical well-being. In turn, these physical limitations seem to affect patients' experienced quality of life in the long-term.[16,69] Because of this, several authors indicate the importance of beginning physical rehabilitation as early as possible, ideally during the ICU admission.[70,71]

CONCLUSION

The prognosis of critically ill patients with HM has improved in the last decade. The plethora of studies shifted the pragmatic treatment policy into a more evidence-based approach. The transfer of a patient with HM from the

haematological ward to the ICU and vice versa should be based on a well-defined clinical care pathway in which the haematologists and intensivists are in close collaboration and direct communication.

ACKNOWLEDGEMENTS

We want to thank all members of the HEMA-ICU study working group for their support.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Afessa B, Azoulay E. Critical care of the hematopoietic stem cell transplant recipient. Crit Care Clin. 2010;26:133-50.
2. Azoulay E, Moreau D, Alberti C, et al. Predictors of short-term mortality in critically ill patients with solid malignancies. Intensive Care Med. 2000;26:1817-23.
3. Bird GT, Farquhar-Smith P, Wigmore T, Potter M, Gruber PC. Outcomes and prognostic factors in patients with haematological malignancy admitted to a specialist cancer intensive care unit: a 5 yr study. Br J Anaesth. 2012;108:452-9.
4. Cohen J, Drage S. How I manage haematology patients with septic shock. Br J Haematol. 2011;152:380-91.
5. Van Vliet M. Intensive supportive care during treatment for haemtological malignancies, from detection and selection to action. Nijmegen: Radboud University Nijmegen, 2015.
6. Garrouste-Orgeas M, Montuclard L, Timsit JF, et al. Predictors of intensive care unit refusal in French intensive care units: a multiple-center study. Crit Care Med. 2005;33:750-5.
7. Schuitemaker LM, Muller MCA, Kusadasi N, et al. Guideline summary: Intensive care admission, treatment and discharge of critically ill haemato-oncological patients. Neth J Crit Care. 2017;25:80-3.
8. Ferra C, Marcos P, Misis M, et al. Outcome and prognostic factors in patients with hematologic malignancies admitted to the intensive care unit: a single-center experience. Int J Hematol. 2007;85:195-202.
9. Lengline E, Chevret S, Moreau AS, et al. Changes in intensive care for allogeneic hematopoietic stem cell transplant recipients. Bone Marrow Transplant. 2015;50:840-5.
10. Lim Z, Pagliuca A, Simpson S, et al. Outcomes of patients with haematological malignancies admitted to intensive care unit. A comparative review of allogeneic haematopoietic stem cell transplantation data. Br J Haematol. 2007;136:448-50.
11. Van Vliet M, Verburg IW, van den Boogaard M, et al. Trends in admission prevalence, illness severity and survival of haematological patients treated in Dutch intensive care units. Intensive Care Med. 2014;40:1275-84.
12. Wohlfarth P, Carlstrom A, Staudinger T, et al. Incidence of intensive care unit admission, outcome and post intensive care survival in patients with diffuse large B-cell lymphoma. Leuk Lymphoma. 2016;57:1831-8.
13. Lengline E, Raffoux E, Lemiale V, et al. Intensive care unit management of patients with newly diagnosed acute myeloid leukemia with no organ failure. Leuk Lymphoma. 2012;53:1352-9.
14. Mamez AC, Raffoux E, Chevret S, et al. Pre-treatment with oral hydroxyurea prior to intensive chemotherapy improves early survival of patients with high hyperleukocytosis in acute myeloid leukemia. Leuk Lymphoma. 2016;57:2281-8.
15. Townsend WM, Holroyd A, Pearce R, et al. Improved intensive care unit survival for critically ill allogeneic haematopoietic stem cell transplant recipients following reduced intensity conditioning. Br J Haematol. 2013;161:578-86.
16. Van Vliet M, van den Boogaard M, Donnelly JP, Evers AW, Blijlevens NM, Pickkers P. Long-term health related quality of life following intensive care during treatment for haematological malignancies. PLoS One. 2014;9:e87779.
17. Cruz VM, Camalionte L, Caruso P. Factors associated with futile end-of-life intensive care in a cancer hospital. Am J Hosp Palliat Care. 2015;32:329-34.
18. Geerse DA, Span LF, Pinto-Sietsma SJ, van Mook WN. Prognosis of patients with haematological malignancies admitted to the intensive care unit: Sequential Organ Failure Assessment (SOFA) trend is a powerful predictor of mortality. Eur J Intern Med. 2011;22:57-61.
19. Vandijck DM, Depuydt PO, Offner FC, et al. Impact of organ dysfunction on mortality in ICU patients with hematologic malignancies. Intensive Care Med. 2010;36:1744-50.
20. De Montmollin E, Tandjaoui-Lambiotte Y, Legrand M, et al. Outcomes in critically ill cancer patients with septic shock of pulmonary origin. Shock. 2013;39:250-4.
21. Austin CA, Hanzaker C, Stafford R, et al. Utilization of rapid response resources and outcomes in a comprehensive cancer center. Crit Care Med. 2014;42:905-9.
22. Bokhari SW, Munir T, Memon S, Byrne JL, Russell NH, Beed M. Impact of critical care reconfiguration and track-and-trigger outreach team intervention on outcomes of haematology patients requiring intensive care admission. Ann Hematol. 2010;89:505-12.
23. Song JU, Suh GY, Park HY, et al. Early intervention on the outcomes in critically ill cancer patients admitted to intensive care units. Intensive Care Med. 2012;38:1505-13.
24. Young RS, Gobel BH, Schumacher M, Lee J, Weaver C, Weitzman S. Use of the modified early warning score and serum lactate to prevent cardiopulmonary arrest in hematology-oncology patients: a quality improvement study. Am J Med Qual. 2014;29:530-7.
25. Azoulay E, Mokart D, Pene F, et al. Outcomes of critically ill patients with hematologic malignancies: prospective multicenter data from France and Belgium--a groupe de recherche respiratoire en reanimation onco-hematologique study. J Clin Oncol. 2013;31:2810-8.
26. Mokart D, Lambert J, Schnell D, et al. Delayed intensive care unit admission is associated with increased mortality in patients with cancer with acute respiratory failure. Leuk Lymphoma. 2013;54:1724-9.
27. Lee HY, Rhee CK, Lee JW. Feasibility of high-flow nasal cannula oxygen therapy for acute respiratory failure in patients with hematologic malignancies: A retrospective single-center study. J Crit Care. 2015;30:773-7.
28. Lemiale V, Mokart D, Mayaux J, et al. The effects of a 2-h trial of high-flow oxygen by nasal cannula versus Venturi mask in immunocompromised patients with hypoxemic acute respiratory failure: a multicenter randomized trial. Crit Care. 2015;19:380.
29. Lemiale V, Resche-Rigon M, Mokart D, et al. High-Flow Nasal Cannula Oxygenation in Immunocompromised Patients With Acute Hypoxemic Respiratory Failure: A Groupe de Recherche Respiratoire en Reanimation Onco-Hematologique Study. Crit Care Med. 2017;45:e274-e80.
30. Coudroy R, Jamet A, Petua P, Robert R, Frat JP, Thille AW. High-flow nasal cannula oxygen therapy versus noninvasive ventilation in immunocompromised patients with acute respiratory failure: an observational cohort study. Ann Intensive Care. 2016;6:45.
31. Frat JP, Ragot S, Girault C, et al. Effect of non-invasive oxygenation strategies in immunocompromised patients with severe acute respiratory failure: a post-hoc analysis of a randomised trial. Lancet Respir Med. 2016;4:646-52.
32. Gristina GR, Antonelli M, Conti G, et al. Noninvasive versus invasive ventilation for acute respiratory failure in patients with hematologic malignancies: a 5-year multicenter observational survey. Crit Care Med. 2011;39:2232-9.
33. Squadrone V, Massaia M, Bruno B, et al. Early CPAP prevents evolution of acute lung injury in patients with hematologic malignancy. Intensive Care Med. 2010;36:1666-74.
34. Molina R, Bernal T, Borges M, et al. Ventilatory support in critically ill hematology patients with respiratory failure. Crit Care. 2012;16:R133.
35. Wermke M, Schiemanck S, Hoffken G, Ehninger G, Bornhauser M, Illmer T. Respiratory failure in patients undergoing allogeneic

hematopoietic SCT--a randomized trial on early non-invasive ventilation based on standard care hematology wards. Bone Marrow Transplant. 2012;47:574-80.

36. Depuydt PO, Benoit DD, Vandewoude KH, Decruyenaere JM, Colardyn FA. Outcome in noninvasively and invasively ventilated hematologic patients with acute respiratory failure. Chest. 2004;126:1299-306.
37. Groeger JS, White P, Jr., Nierman DM, et al. Outcome for cancer patients requiring mechanical ventilation. J Clin Oncol. 1999;17:991-7.
38. Price KJ, Cardenas-Turanzas M, Lin H, Roden L, Nigam R, Nates JL. Prognostic indicators of mortality of mechanically ventilated patients with acute leukemia in a comprehensive cancer center. Minerva Anestesiol. 2013;79:147-55.
39. Den Boer S, de Keizer NF, de Jonge E. Performance of prognostic models in critically ill cancer patients – a review. Crit Care. 2005;9:R458-63.
40. Bos MM, de Keizer NF, Meynaar IA, Bakhshi-Raiez F, de Jonge E. Outcomes of cancer patients after unplanned admission to general intensive care units. Acta Oncol. 2012;51:897-905.
41. Cornet AD, Issa AI, van de Loosdrecht AA, Ossenkoppele GJ, Strack van Schijndel RJ, Groeneveld AB. Sequential organ failure predicts mortality of patients with a haematological malignancy needing intensive care. Eur J Haematol. 2005;74:511-6.
42. Vandijck DM, Benoit DD, Depuydt PO, et al. Impact of recent intravenous chemotherapy on outcome in severe sepsis and septic shock patients with hematological malignancies. Intensive Care Med. 2008;34:847-55.
43. Van Beers EJ, Muller MC, Vlaar AP, Spanjaard L, van den Bergh WM, Group H-IS. Haematological malignancy in the intensive care unit: microbiology results and mortality. Eur J Haematol. 2016;97:271-7.
44. Bouteloup M, Perinel S, Bourmaud A, et al. Outcomes in adult critically ill cancer patients with and without neutropenia: a systematic review and meta-analysis of the Groupe de Recherche en Reanimation Respiratoire du patient d'Onco-Hematologie (GRRR-OH). Oncotarget. 2017;8:1860-70.
45. Bernal T, Pardavila EV, Bonastre J, et al. Survival of hematological patients after discharge from the intensive care unit: a prospective observational study. Crit Care. 2013;17:R302.
46. Platon L, Amigues L, Ceballos P, et al. A reappraisal of ICU and long-term outcome of allogeneic hematopoietic stem cell transplantation patients and reassessment of prognosis factors: results of a 5-year cohort study (2009-2013). Bone Marrow Transplant. 2016;51:256-61.
47. Sorror ML, Maris MB, Storb R, et al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. Blood. 2005;106:2912-9.
48. Bayraktar UD, Shpall EJ, Liu P, et al. Hematopoietic cell transplantation-specific comorbidity index predicts inpatient mortality and survival in patients who received allogeneic transplantation admitted to the intensive care unit. J Clin Oncol. 2013;31:4207-14.
49. Jackson K, Mollee P, Morris K, et al. Outcomes and prognostic factors for patients with acute myeloid leukemia admitted to the intensive care unit. Leuk Lymphoma. 2014;55:97-104.
50. Pohlen M, Thoennissen NH, Braess J, et al. Patients with Acute Myeloid Leukemia Admitted to Intensive Care Units: Outcome Analysis and Risk Prediction. PLoS One. 2016;11:e0160871.
51. Lecuyer L, Chevret S, Thiery G, Darmon M, Schlemmer B, Azoulay E. The ICU trial: a new admission policy for cancer patients requiring mechanical ventilation. Crit Care Med. 2007;35:808-14.
52. Schellongowski P, Kiehl M, Kochanek M, Staudinger T, Beutel G, Intensive Care in Hematologic-Oncologic P. Intensive care for cancer patients: An interdisciplinary challenge for cancer specialists and intensive care physicians. Memo. 2016;9:39-44.
53. Schellongowski P, Sperr WR, Wohlfarth P, et al. Critically ill patients with cancer: chances and limitations of intensive care medicine-a narrative review. ESMO Open. 2016;1:e000018.
54. Saillard C, Blaise D, Mokart D. Critically ill allogeneic hematopoietic stem cell transplantation patients in the intensive care unit: reappraisal of actual prognosis. Bone Marrow Transplant. 2016;51:1050-61.
55. Schnell D, Azoulay E, Benoit D, et al. Management of neutropenic patients in the intensive care unit (NEWBORNS EXCLUDED) recommendations from an expert panel from the French Intensive Care Society (SRLF) with the French Group for Pediatric Intensive Care Emergencies (GFRUP), the French Society of Anesthesia and Intensive Care (SFAR), the French Society of Hematology (SFH), the French Society for Hospital Hygiene (SF2H), and the French Infectious Diseases Society (SPILF). Ann Intensive Care. 2016;6:90.
56. Soares M, Bozza FA, Azevedo LC, et al. Effects of Organizational Characteristics on Outcomes and Resource Use in Patients With Cancer Admitted to Intensive Care Units. J Clin Oncol. 2016;34:3315-24.
57. Coutsouvelis J, Corallo CE, Dooley MJ, Foo J, Whitfield A. Implementation of a pharmacist-initiated pharmaceutical handover for oncology and haematology patients being transferred to critical care units. Support Care Cancer. 2010;18:811-6.
58. Hoenigl M, Duettmann W, Raggam RB, et al. Potential factors for inadequate voriconazole plasma concentrations in intensive care unit patients and patients with hematological malignancies. Antimicrob Agents Chemother. 2013;57:3262-7.
59. Blackburn LM, Tverdek FP, Hernandez M, Bruno JJ. First-dose pharmacokinetics of aminoglycosides in critically ill haematological malignancy patients. Int J Antimicrob Agents. 2015;45:46-53.
60. Lecuyer L, Chevret S, Guidet B, et al. Case volume and mortality in haematological patients with acute respiratory failure. Eur Respir J. 2008;32:748-54.
61. Gaieski DF, Edwards JM, Kallan MJ, Mikkelsen ME, Goyal M, Carr BG. The relationship between hospital volume and mortality in severe sepsis. Am J Respir Crit Care Med. 2014;190:665-74.
62. Shahul S, Hacker MR, Novack V, et al. The effect of hospital volume on mortality in patients admitted with severe sepsis. PLoS One. 2014;9:e108754.
63. Walkey AJ, Wiener RS. Hospital case volume and outcomes among patients hospitalized with severe sepsis. Am J Respir Crit Care Med. 2014;189:548-55.
64. Endacott R, Chaboyer W, Edington J, Thalib L. Impact of an ICU Liaison Nurse Service on major adverse events in patients recently discharged from ICU. Resuscitation. 2010;81:198-201.
65. Green A, Edmonds L. Bridging the gap between the intensive care unit and general wards-the ICU Liaison Nurse. Intensive Crit Care Nurs. 2004;20:133-43.
66. McIntyre T, Taylor C, Eastwood GM, Jones D, Baldwin I, Bellomo R. A survey of ward nurses attitudes to the Intensive Care Nurse Consultant service in a teaching hospital. Aust Crit Care. 2012;25:100-9.
67. Ball C, Kirkby M, Williams S. Effect of the critical care outreach team on patient survival to discharge from hospital and readmission to critical care: non-randomised population based study. BMJ. 2003;327:1014.
68. Le RQ, Bevans M, Savani BN, et al. Favorable outcomes in patients surviving 5 or more years after allogeneic hematopoietic stem cell transplantation for hematologic malignancies. Biol Blood Marrow Transplant. 2010;16:1162-70.
69. Kentish-Barnes N, Lemiale V, Chaize M, Pochard F, Azoulay E. Assessing burden in families of critical care patients. Crit Care Med. 2009;37(10 Suppl):S448-56.
70. Connolly B, Douiri A, Steier J, Moxham J, Denehy L, Hart N. A UK survey of rehabilitation following critical illness: implementation of NICE Clinical Guidance 83 (CG83) following hospital discharge. BMJ Open. 2014;4:e004963.
71. Gosselink R, Bott J, Johnson M, et al. Physiotherapy for adult patients with critical illness: recommendations of the European Respiratory Society and European Society of Intensive Care Medicine Task Force on Physiotherapy for Critically Ill Patients. Intensive Care Med. 2008;34:1188-99.