GUIDELINES ON THE MANAGEMENT AND ADMISSION TO INTENSIVE CARE OF CRITICALLY ILL ADULT PATIENTS WITH HAEMATOLOGICAL MALIGNANCY IN THE UK

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Keywords: sepsis, chemotherapy, critical illness, haematological malignancy
SUMMARY OF KEY RECOMMENDATIONS

• Hospitalized patients with haematological malignancy are at risk of developing critical illness. An aggregate track and trigger system, such as the National Early Warning Score (NEWS) should be in place to monitor patients. (1C)

• Severe sepsis and respiratory failure are common reasons for admission to critical care and patient assessment should focus on these. Recommendations of the Surviving Sepsis campaign should be followed if sepsis is suspected, including immediate/early removal of indwelling catheters, particularly if no alternative focus of infection is identified. (1C)

• Intensive Care Unit (ICU) referral should involve direct discussion between an ICU consultant and a haematology consultant. (1D)

• Patients with haematological malignancy who are clearly in the process of dying with irreversible illness or competent adults who decline treatment should not be referred to critical care. (1D)

• Critical care survival is largely determined by the acute critical illness rather the underlying haematological malignancy. Patients appropriate for further life-extending treatment or with good performance status should be considered for an unrestricted critical care ‘ICU Trial’. (1C)

• Use of non-invasive ventilation (NIV) in the ward setting should not normally be undertaken in patients with haematological malignancy. (1C)

• Patients with a related presentation who have undergone allogeneic haemopoietic stem cell transplantation (HSCT) should be transferred, where feasible, to an ICU attached to a level 3 British Committee for Standards in Haematology (BCSH) unit. (1D)

• Inter-hospital and intra-hospital transfer should follow the procedures recommended in the Intensive Care Society (ICS) 2011 Guidelines for the Transport of the Critically Ill Adult (1C)
This guideline is intended to be of use to haematologists and intensivists practising in the UK, and outlines some of the major considerations in the management of the critically ill patient with haematological malignancy.

Methodology
The guideline group was selected to be representative of UK experts in the management of haematological malignancies and in critical care, and included representation from both the British Society of Haematology (BSH) and the Intensive Care Society (ICS). Recommendations are based on a review of published English language literature up to December 2014. A PubMed search was conducted using the Medical Subject Heading (MeSH) terms Haematological Malignancy, Outcome, Intensive Care or Critical Care. Identified abstracts were checked by two investigators for relevant content (Appendix S1). The writing group produced a draft guideline, which was reviewed by the BSH ‘Sounding Board’ of approximately 50 UK Haematologists and by the ICS Joint Standards Committee. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature was used to evaluate levels of evidence and to assess the strength of recommendations.


INTRODUCTION AND BACKGROUND

Critical illness in patients with haematological malignancy (HM) is often due to complications of treatment. The 2008 National Audit of deaths following Systemic Anti-Cancer Therapy [National Confidential Enquiry into Patient Outcome and Death (NCEPOD), 2008] highlighted the need for rapid, integrated management of severe chemotherapy complications, based on formally agreed care pathways. According to the British Committee for Standards in Haematology (BCSH) ‘Guidelines on Facilities for the Treatment of Haematological Malignancies: Levels of Care’ [Matthey et al, 2010], there should be on-site access to an intensive care unit (ICU) where patients are receiving curative inpatient treatment for acute leukaemia, or anti-cancer treatment of equivalent or greater intensity (level IIIB or III), equating to level II or higher according to National Institute for Health and Clinical Excellence (NICE) Guidance [NICE, 2003]. Where there is no on-site access to ICU
beds (e.g. BCSH level IIA units or lower), there should be established arrangements for the transfer of patients who need critical care [NCEPOD, 2008].

Historically, some clinicians have adopted a nihilistic approach to admitting patients with HM to ICU. Reluctance to admit such patients to critical care is based on early literature reporting high mortality [Denardo et al, 1989; Paz et al, 1993] and much of the persisting pessimism surrounding ICU admission for haematology patients results from this: In 1999, the American College of Critical Care Medicine stated that ‘patients with haematological or metastasized solid malignancies are poor candidates for ICU admission with a mortality rate of up to 90%. Immediate treatment limitations/refusal of ICU admission is advocated’ [Task Force of the American College of Critical Care Medicine, Society of Critical Care Medicine 1999].

Over the last decade, as new data have emerged, it has become clear that this statement requires re-examination: A large 2009 study across 178 ICUs in England, Wales and Northern Ireland showed, ICU mortality of 43.1% and in-hospital mortality of 59.2% among patients with a HM; substantially less than previous studies had suggested [Hampshire et al, 2009].

This guideline aims to provide an up-to-date, evidence-based review of the literature on outcome for ICU admission in patients with HM, and gives pragmatic guidance for haematologists and intensivists.

**ADULT PATIENTS WITH HAEMATOLOGICAL MALIGNANCY; ICU OUTCOME DATA**

Outcome for patients with HM admitted to ICU has historically been poor. In the 1990s, case series on outcome following mechanical ventilation after bone marrow transplantation reported ICU survival of, typically, less than 20%, and, in some series, less than 5%. Such reports, together with published critical care guidelines may have contributed to the critical care community taking an unduly pessimistic view of the potential benefits of advanced life support techniques for all patients with HM.

The majority of publications identified from a search of PubMed using the MeSH terms haematological malignancy, outcome, intensive or critical care were small, single centre, retrospective reports; the majority from European or North American specialist centres.
Many described a heterogeneous group of patients with various primary haematological diagnoses. Some reports focused on stem cell transplant patients (autologous, allogeneic or both). In some studies, haematology patients formed a sub-group of all admissions with cancer, and it was not always possible to extract outcome data from the data for the rest of the group.

The most relevant report for United Kingdom practice is a retrospective analysis of the Intensive Care National Audit and Research Centre (ICNARC) Case Mix Programme database, published in 2009 [Hampshire et al, 2009]. Over 94% of ICUs in the UK take part in the ICNARC Case Mix Programme. ICNARC systematically and prospectively collects individual patient data on all ICU admissions, including demographics, severity of illness and outcome information. This report extracted data from 7689 HM admissions to critical care between 1995 and 2007. Overall ICU mortality was 43.1% and in-hospital mortality was 59.2%.

Outcomes appear to have improved over time, probably reflecting a number of factors, including better supportive care, rather than single treatment changes. One single-centre study on critically ill patients with myeloma grouped patients into cohorts based on admission year, and reported a significant (p=0.0007) fall in mortality between the early 1990s (75% in hospital mortality, 1990-1995) and more recent admissions (40% in hospital mortality, 2002-2006) [Peigne et al, 2009]. Several other publications on ICU mortality trends also report recent improvements in outcome, suggesting that there has been an improvement in the process of care for different forms of critical illness and not just HM [Martin et al, 2003; Li et al, 2011; Zambon & Vincent, 2008].

The volume of cases also appears important: Lecuyer et al [2008] demonstrated, in a regional database of 28 ICUs admitting 1753 patients with HM and acute respiratory failure, that high volume centres with critical care units admitting more than 30 patients a year had improved survival compared to low volume centres.

In recent years, there have been significant changes in chemotherapy protocols and transplant conditioning regimens, which have reduced treatment-related toxicities, and this is also likely to have contributed to improved ICU outcome. A recently published UK single-centre study of 164 consecutive adult allogeneic transplant recipients admitted to ICU
demonstrated a survival benefit for recipients of reduced intensity transplants compared to myeloablative transplants, despite increased age [Townsend et al, 2013]. Patients surviving to ICU discharge had a 5-year overall survival of 50%.

PREDICTORS OF POOR OUTCOME FOR HAEMATOLOGICAL MALIGNANCY PATIENTS ADMITTED TO CRITICAL CARE

Few studies have assessed predictors of outcome, and have often focussed on specific patient subsets, for example, patients with acute leukaemia admitted to ICU. Studies from the 1990s showed that acute leukaemia patients requiring ventilatory support rarely survived ICU admission, and aggressive therapy was regarded as futile. A 2004 study of patients with acute myeloid leukaemia (AML) and pulmonary infiltrates requiring mechanical ventilation showed 87% mortality. Patient age was identified as a prognostic factor [Rabe et al, 2004]. A European study in the following year showed that not just age, but AML subtype and disease status (complete remission or not) predicted 1-year survival, and suggested that ICU admission was justified for selected patients with AML [Rabbat et al, 2005].

A retrospective study of 90 acute leukaemia patients admitted to ICU showed inferior outcome to be associated with elevated admission APACHE (Acute Physiology and Chronic Health Evaluation) II score, use of vasopressors, preparative bone marrow transplantation regimen and adverse cytogenetics. Age, new diagnosis and specific type of leukaemia did not correlate with outcome [Thakkar et al, 2008]. Perhaps most importantly, this study showed that 25% of the study cohort survived ICU admission, left hospital and were alive two months later. This led the authors to conclude that a diagnosis of acute leukaemia per se should not disqualify a patient from consideration of ICU admission.

A larger study (428 ICU admissions over an 11 year period) examined survival of cancer patients, of whom two thirds had HM, admitted to ICU with severe sepsis or septic shock, in the presence of neutropenia [Legrand et al, 2012]. Older age and need for inotropic support predicted inferior survival on multivariate analysis. Improved survival was predicted by admission after 2003 (study period 1998-2008), use of combination antibiotics including an aminoglycoside, and early removal of indwelling catheter(s).
One paper specifically examined the importance of HM as an independent predictor of poor outcome in the critically ill [Benoit et al, 2003]. Outcome of critically ill general medical patients requiring renal replacement therapy (RRT) was compared with that of patients with HM, also given RRT [Benoit et al, 2005]. The HM group had higher ICU, hospital and 6-month mortalities, but these differences were explained by a higher initial severity of illness in the HM group. The need for RRT was much higher in the HM patients (22.5% compared to 5.8%).

The largest study to date exploring prognostic factors of haematology patients on admission to critical care was a secondary analysis of the ICNARC Case Mix Programme Database [Hampshire et al, 2009]. Between 1995 and 2007 there were 7689 eligible admissions with an ICU mortality of 43.1% and a hospital mortality of 59.2%. Admission factors associated with an increased risk of death were bone marrow transplantation, Hodgkin lymphoma, severe sepsis, age, length of hospital stay prior to intensive care admission, tachycardia, low systolic blood pressure, tachypnoea, low Glasgow Coma Score, sedation, ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO2:FiO2), acidaemia, alkalaemia, oliguria, hyponatraemia, hypernatraemia, low haematocrit and uraemia.

CAN INDIVIDUAL OUTCOME BE PREDICTED IN CRITICALLY ILL HM PATIENTS?

A number of ICU outcome prediction models have been developed utilizing the APACHE [Knaus et al, 1985], SOFA (Sepsis-related Organ Failure Assessment) [Vincent et al, 1996] and SAPS (Simplified Acute Physiology Score II) [Le Gall et al, 1984] scores. All provide reasonably robust population-wide predictions of outcome, but perform poorly at an individual patient level. Several studies confirm that these models correlate with outcome in patients with HM [Hampshire et al 2009]. In practice, outcome prediction models are of limited use when making decisions on individual patients. Unless there is a clear contradiction to ICU, such as patient refusing treatment, or an individual who is clearly in the terminal phase of the disease, patients should be considered for a trial of ICU.
RECOMMENDATIONS

• The prognosis for patients with haematological malignancy who develop critical illness has improved substantially in recent years and this patient group should not be denied access to intensive care (Grade 1C)

RECOGNITION OF CRITICAL ILLNESS AND WARD-BASED ASSESSMENT OF CRITICALLY ILL HAEMATOLOGY PATIENTS

Early recognition of critical illness is required to enable prompt referral of patients who may benefit from critical care. Duration of hospitalization prior to ICU admission is an independent predictor of ICU outcome in both solid tumour and haematology patients [Hampshire et al, 2009, Goldhill et al, 2004]. Amongst hospitalized patients with HM, 7% develop critical illness, rising to 15.7% amongst recipients of a bone marrow transplant [Gordon et al, 2005; Afessa & Azoulay, 2010].

In accordance with recommendations for all acutely ill patients [NICE, 2007] Early Warning Scores (EWS) should be used routinely on the haematology ward to enable early referral. Onset of critical illness is characterized by perturbations in physiological parameters [McQuillan et al, 1998; Goldhill & McNarry, 2004] and has led to the widespread introduction of physiological track and trigger systems [Bokhari et al, 2010]. Track and trigger systems use repeated measures of physiological variables (track) and if predetermined thresholds (trigger) are reached, appropriately trained staff attend the patient. A variety of such systems are in common use and have been the subject of both systematic reviews [Smith et al, 2008; Gao et al, 2007] and a NICE Guideline [NICE, 2007]. Although robust evidence that use of EWS leads to improved survival is lacking [Hillman et al 2005, Cuthbertson & Smith, 2007], it has been shown to result in earlier intervention and referral [Hillman et al 2005].

Problems encountered by patients with HM are similar to other critically ill hospitalized patients. Sub-optimal ward care is associated with increased mortality for patients subsequently admitted to ICU, and contributes to admissions that may otherwise be avoidable [McQuillan et al, 1998; Cullinane et al 2005]. Factors identified in adverse ward
care include poor communication, lack of organization, knowledge and supervision, low staff to patient ratios, and failure to recognize critical illness and seek advice.

Systems that use a single parameter with a threshold, e.g. heart rate >140/min, to trigger a response (single parameter systems), have low sensitivity and poor positive predictive value. Multiple parameter systems require more than one criterion to be met and generate a score that in turn triggers a particular level of response [Goldhill et al, 1999]. Aggregate systems are employed most frequently in the UK and use weighted scores assigned to the level of physiological derangement and add them together [Gao et al, 2007]. Multiple parameter and aggregate track and trigger systems allow for a graded response, but documentation may be inaccurate [Prytherch et al, 2006] and both intra- and inter-rater reliability are poor in comparison to less complex single parameter systems [Subbe et al, 2007]. Guidance issued in the NICE Clinical Guideline 50 [NICE, 2007] provides an appropriate framework for the monitoring of inpatients with HM. Staff caring for HM patients should be competent in monitoring and interpreting physiological changes and in responding appropriately.

Although it is accepted that critical illness is characterized by physiological derangement, there is little data to support the contention that current track and trigger systems improve patient outcomes [Gao et al, 2007; McGaughey et al, 2007; Jansen & Cuthbertson, 2010]. It has been argued that this failure is in part, a consequence of the wrong choice and weighting of variables [Cuthbertson & Smith, 2007]. A national (UK) aggregate scoring system, the National Early Warning Score (NEWS) has been developed by the Royal College of Physicians (RCP) and aims to address these deficiencies [RCP, 2012].

Physiological track and trigger systems herald the onset of critical illness, but are without value unless appropriate action is taken. Critical care outreach teams are present in the majority of hospitals within the UK [McDonnell et al, 2007] and were identified as a strategy for preventing or enabling appropriate admission to critical care [Department of Health 2000]. Two systematic reviews [Esmonde et al, 2006; McGaughey et al, 2007] concluded, however, that there is no conclusive data indicating that outreach services improve patient outcomes.
Fifty-four per cent of patients with HM admitted to critical care have severe sepsis as a diagnosis and 55% require ventilation in the first 24 h [Hampshire et al, 2009]. These demographics must be considered when patients undergo a focussed clinical examination [Frost & Wise, 2012] with a stepwise Airway, Breathing, Circulation, Disability and Exposure (ABCDE) approach. Assessment may also include initiating treatment and investigations, and should include a call for more senior help if the patient is deviating from their expected trajectory.

HM not only increases the risk of sepsis but may also abrogate features of the Systemic Inflammatory Response Syndrome (SIRS), although one single centre nested case control study suggested these criteria may still be valid [Mato et al, 2009]. Clinicians should have a high index of suspicion for infection causing critical illness. Particular attention should be paid to indwelling devices as catheter-related blood stream infections are common [Mollee et al, 2011] and line removal may be required. If a diagnosis of sepsis is made, recommendations from the Surviving Sepsis campaign should be followed [Dellinger et al, 2013] in addition to locally agreed protocols for the management of neutropenic sepsis [NICE, 2012].

Adverse outcome in critically ill patients is more common when there is a lack of Consultant involvement [Cullinane et al 2005, NCEPOD 2007, 2008, 2009, Wise & Frost, 2010]. A discussion with or review by a Consultant should take place if patients deviate from their expected clinical course, there are end-of-life issues or referral to critical care is required.

**RECOMMENDATIONS**

- **Hospitalized patients with HM are at risk of developing critical illness.** Sub-optimal ward care is associated with adverse outcomes and it is important to maintain adequate staffing and skill mix outside routine working hours. An aggregate track and trigger system such as the National Early Warning Score (NEWS) should be in place to monitor patients (Grade 1C)

- **Severe sepsis and respiratory failure are common reasons for admission to critical care and patient assessment should focus on these.** Recommendations of the Surviving Sepsis campaign should be followed if sepsis is suspected including immediate/early removal of indwelling catheters, particularly if no alternative focus of infection is identified (Grade 1C)
REFERRAL OF PATIENTS TO ICU, INDICATIONS FOR ICU ADMISSION, ROLE OF ‘ICU TRIAL’

The decision to admit a patient to ICU should involve both the consultant caring for the patient at that time and the consultant in critical care, as recommended by NICE (2007).

Referrals to ICU should be from consultant to consultant whenever possible, as the decision to admit must be based on assessment by an experienced physician in the light of:

- status of the underlying malignancy
- treatment prior to referral
- pre-morbid performance status
- patient wishes

The following information should be clearly stated and documented at time of discussion and referral:

- haematological disease state, treatment plan and prognosis
- any treatment limitations previously agreed with patient
- special transfusion requirements (e.g. irradiated products, cytomegalovirus (CMV)-screened)
- history of bleomycin exposure/radiotherapy
- isolation needs

The objectives and likely outcome should be discussed with the patient and, if appropriate, next of kin, at the time of critical care referral. Many patients initially improve with resuscitation and organ support, but then subsequently deteriorate.

In the event of disagreement between intensivists and haematologists concerning suitability for ICU admission, admission of the patient for a limited trial of ICU should be considered. In a prospective study of outcome following referral of cancer patients to ICU (two thirds of whom suffered from HM and/or had undergone HSCT) there was disagreement in 15% of cases [Lecuyer et al, 2007].

The concept of the ‘ICU trial’ was introduced by Lecuyer et al, (2007). During a three-year period, 188 patients scheduled for further cancer treatment or with good performance status...
were admitted to ICU without restriction, and the level of care reassessed in 103 patients who survived to Day 5. It was not possible to distinguish survivors from non-survivors at admission, but requirement for ventilation, vasopressors and renal replacement therapy developing after day three were associated with a greater probability of death. Survival to hospital discharge was 21.8% in a cohort of patients who conventionally would have been denied ICU admission. The authors concluded that treatment limitations should not be imposed before Day 5 in this group of patients.

RECOMMENDATIONS

- The objectives of proposed interventions in ICU should be discussed with the patient and relatives at the time of ICU referral (Grade 1D)
- ICU referral should involve direct discussion between an ICU consultant and a haematology consultant (when this is impractical or would otherwise delay admission both consultants should be made aware) (Grade 1D)
- Patients with haematological malignancy who are clearly in the process of dying with irreversible illness or who decline treatment should not be referred to critical care (Grade 1D)
- Critical care survival is largely determined by the acute critical illness rather than the underlying haematological malignancy. Patients appropriate for further life-extending treatment or with good performance status should be considered for an unrestricted critical care ‘ICU Trial’ (Grade 1C)
- Therapy should be reviewed daily and, in survivors, it is suggested that review on day five of critical care admission is appropriate, to assess whether treatment should continue or is futile (Grade 1C)

NON-INVASIVE AND MECHANICAL VENTILATION

The level of care available on the haematology ward will partly determine the selection of patients for ICU, and this may vary between institutions [Lecuyer et al, 2008]. Non-invasive ventilation (NIV) for respiratory failure may be available on the haematology ward [Azoulay et al, 2001]. It is known that patients with HM who develop acute respiratory failure have increased mortality, and that mortality increases further if they require ICU admission and
mechanical ventilation [Mokart et al, 2012]. In a prospective single centre trial of 526 patients who underwent HSCT, 86 (16%) developed respiratory failure and were randomized to oxygen or oxygen plus NIV, administered on the haematology ward [Wermke et al, 2012]. Failure to achieve adequate oxygenation was less common in the group who received NIV (24% versus 39%), but the difference was not statistically different. There was no difference between groups for subsequent admission to ICU, need for intubation or survival. Moreover, a survey of patients successfully treated with NIV outside of ICU reported a high incidence of safety concerns [Cabrini et al, 2012], such as being unable to get help when required (50%) or not knowing how to remove the facemask when needed (22%).

A retrospective multi-centre Italian cohort study, involving 1302 patients with HM and acute respiratory failure, compared NIV and invasive mechanical ventilation at time of ICU admission [Gristina et al, 2011]. A minority of patients (21%) received NIV, which failed in 46% of these cases with the patient requiring subsequent intubation. Successful NIV treatment was associated with the lowest mortality: Mechanical ventilation after failed NIV was associated with the highest mortality. In a study by Adda et al [2008], high respiratory rate while on NIV, renal replacement therapy and vasopressor use were predictive of NIV failure and progression to mechanical ventilation. A Spanish prospective multi-centre observational study [Molina et al, 2012] on 450 patients with HM, 300 of whom required respiratory support, found that, among patients initially managed with NIV, 79 of 131 (60.3%) later required intubation; mortality in this group was 79.7%. NIV failure had an odds ratio for death of 5.74, compared to those electively intubated from the outset (odds ratio 3.13).

Surprisingly few studies have addressed the use of continuous positive airway pressure (CPAP) support in patients as a means to reduce critical care admission or endotracheal intubation. Delclaux et al [2000] randomized 123 patients admitted to six intensive care units with acute nonhypercapnic respiratory failure to CPAP or standard oxygen therapy. Despite improvements in oxygenation, CPAP did not reduce rates of intubation, intensive care length of stay or hospital mortality but was associated with significantly more adverse events. In a small multicentre randomized trial in high dependency units with continuous monitoring, 1:4 nurse/patient ratios and an on-site treating physician 24/7, 81 patients with hypoxaemic respiratory failure due to pneumonia were randomized to helmet CPAP or oxygen therapy [Brambilla et al 2014]. Although CPAP significantly reduced the indications for endotracheal intubation, only two in the CPAP and one in the oxygen therapy group
were actually intubated. In a smaller single centre study Squadrone et al [2010] examined the use of CPAP in 40 patients with HM developing acute respiratory distress syndrome and found that CPAP reduced ICU admissions and intubation rates. However patients with pneumonia, infection or sepsis, which make up the majority of critically ill patients with HM, were excluded from this study.

RECOMMENDATIONS

• Use of NIV or CPAP in the ward setting should not normally be undertaken in patients with haematological malignancy (Grade 1C)
• Treatment failure in patients receiving NIV is common (50%) and patients should be carefully selected. Mortality is higher than for elective intubation, and intubation should not be delayed in those deteriorating on NIV (Grade 1B)

INTRA- AND INTER-HOSPITAL TRANSFER OF CRITICALLY ILL PATIENTS

Critically ill patients are at high risk of adverse events during times of transfer and transport [Warren et al, 2004]. Inter-hospital transfer may be necessary due to a lack of ICU capacity, or because it is necessary to access more specialized ICU and other facilities. It is recommended that admitted patients who have undergone recent allogeneic HSCT should be considered for transfer to an ICU attached to a level 3 Haematology transplant unit [Matthey et al, 2010], subject to careful assessment of the risk: benefit of transfer. The process of intra- and inter-hospital transfer should follow recommendations in the ICS Guidelines for the Transport of the Critically Ill Adult (Whitely et al 2011). The following specific recommendations are highlighted:
(i) All acute hospitals should have adequately trained, resourced and supervised hospital transport teams
(ii) Patients should normally be accompanied by two suitably trained, experienced and competent attendants
(iii) The decision to transfer to another hospital must be made by a consultant in intensive care in discussion with consultant colleagues from the referring and receiving units
Upon arrival at the receiving unit, there should be verbal and written handover to the receiving medical and nursing teams.

Adverse events during transfer occur in over 20% of transfers [Gillman et al, 2006] and are caused by equipment problems and human error [Beckmann et al, 2004]. Local written policies and procedures should be in place for inter-hospital transfer, in particular addressing issues of coordination and communication, accompanying personnel, equipment and monitoring [Warren et al, 2004].

RECOMMENDATIONS

• Patients who have undergone allogeneic HSCT should be transferred where feasible to an ICU attached to a level 3 BCSH unit (Grade 1D)
• Inter-hospital and intra-hospital transfer should follow the procedures recommended in the ICS 2011 Guidelines for the Transport of the Critically Ill Adult (Grade 1C)

DELIVERY OF CHEMOTHERAPY TO PATIENTS WITH HAEMATOLOGICAL MALIGNANCY ON ICU

Historical studies suggested that administration of chemotherapy to patients with HM while in ICU was not indicated. A study in 2006, however, in which severely ill patients with HM received intravenous chemotherapy, showed that chemotherapy for a life-threatening malignancy-related complication could be lifesaving, even when infection or organ failure was also present [Benoit et al, 2006]. Another retrospective study showed that, among 62 critically ill cancer patients (46 of whom had HM) who received chemotherapy while in ICU, 60% survived to ICU discharge [Song et al, 2011]. Commonest causes of death in ICU were septic shock, disease progression and bleeding. ICU mortality post-chemotherapy correlated with mechanical ventilation and high SOFA score at initiation.

RECOGNITION OF FUTILITY AND PALLIATIVE CARE
Despite the improvement in outcome for critically ill patients with haematological malignancies, the result in many cases is death [Hampshire et al, 2009]. In some patients there will be a clear expectation of recovery from critical care, whilst in others it may not be possible to predict outcome at the onset of critical illness [Lecuyer et al, 2007]. Recognition of futility, when therapy is only delaying inevitable death, is important. Critical care is likely to be futile in a patient who has a poor performance status and is unsuitable for life-prolonging therapy of their malignancy. This decision should involve the haematology consultant and, once agreed, care should involve palliative care services [Ellershaw, 2007]. Discussion with patient and family should occur in advance of critical illness developing, whenever possible.

Death in critical care is common. In the USA, one fifth of deaths occur in this environment [Angus et al, 2004] and >40% of patients with HM admitted to critical care in the UK die while in the ICU [Hampshire et al, 2009]. Recognition of futility and end-of-life management are therefore core skills for both critical care physicians [Siegel, 2009] and haematologists [Buss et al, 2011].

End-of-life management requires effective communication between the patient (where possible), next of kin and clinical team. The plan for treatment change to palliative care should be documented and may follow a protocol [Brody et al, 1997; Shanawani et al, 2008].

**RECOMMENDATIONS**

- Recognition of futility in a ward patient should be made by the responsible haematology consultant (Grade 1D)
- Palliative care services and/or an end-of-life pathway should guide patient care when active medical treatment is futile (Grade 1D)

**Summary**

Outcome for patients with HM admitted to an ICU has improved in recent years. The BCSH and ICS recommend that data for outcome of patients with HM should be regularly updated using the ICNARC case-mix programme.
Carefully selected patients, receiving active treatment for their HM and with a reasonable expectation of life prolonging treatment, should be considered for critical care in the same way as other severely ill patients: The severity of acute illness appears more important than the underlying haematological disorder.

Use of appropriate early warning systems is recommended, allowing early identification and referral of patients. Communication between clinical teams is key and ICU referral should be from consultant to consultant. Expectations and objectives of critical care admission should be agreed from the outset. There is some evidence that a 5-day ‘trial’ of critical care should be considered in suitable patients.

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Simon V Baudouin, David Howell, David I Marks and Nilima Parry-Jones have no conflicts of interests to declare.

Disclaimer
While the advice and information in this guidance is believed to be true and accurate at the time of going to press, neither the authors, the British Committee for Standards in
Haematology nor the publishers accept any legal responsibility for the content of this guidance.
References


### Appendix S1: Manuscripts related to outcome during critical illness in patients with haematological malignancy

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<td>Azoulay, E., Mokart, D., Pène, F., Lambert, J., Kouatchet, A., Mayaux, J., Vincent, F., Nyunga, M., Bruneel, F., Laïne, L.M., Rabbat, A., Lebert, C., Perez, P., Chaize, M., Renault, A., Meert, A.P., Benoit, D., Hamidfar, R., Jourdain, M., Darmon, M., Schlemmer, B., Chevret, S. &amp; Lemiale, V. (2013) <em>Journal of Clinical Oncology</em>, 31, 2810–2818.</td>
<td>Outcomes of critically ill patients with hematologic malignancies: prospective multicenter data from France and Belgium: a groupe de recherche respiratoire en réanimation onc-hémato logique study.</td>
<td>Prospective, multicentre cohort study of critically ill patients with haematological malignancy</td>
<td>1,011 patients, 38.2% newly diagnosed malignancy, 23.1% in remission, and 24.9% post-HSCT (145 allogeneic)</td>
<td>Hospital, day-90, and 1-year survival rates 60.7%, 52.5%, and 43.3%</td>
<td>Poor performance status, Charlson comorbidity index, allogeneic HSCT, organ dysfunction score, cardiac arrest, acute respiratory failure, malignant organ infiltration, invasive aspergillosis associated with hospital mortality</td>
<td>Moderate</td>
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<tr>
<td>Authors</td>
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<td>Benoit, D.D., Depuydt, P.O., Vandewoude, K.H., Offner, F.C., Boterberg, T., De Cock, C.A., Noens, L.A., Janssens, A.M. &amp; Decruyenaere, J.M. (2006)</td>
<td>Intensive Care Medicine, 32, 93–99.</td>
<td>Outcome in severely ill patients with hematological malignancy who received intravenous chemotherapy in the intensive care unit.</td>
<td>37 ICU patients receiving chemotherapy</td>
<td>ICU, hospital &amp; 6-month mortality rates in non-ventilated vs. ventilated patients were 7% and 48%, 14% and 61%, and 54% and 74%, respectively</td>
<td>Mechanical ventilation associated with mortality</td>
<td>Low</td>
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<td>Benz, R., Schanz, U., Maggiorini, M., Seebach, J.D. &amp; Stussi, G. (2014)</td>
<td>Bone Marrow Transplant, 49, 62–65.</td>
<td>Risk factors for ICU admission and ICU survival after allogeneic hematopoietic SCT.</td>
<td>33 (of 250 HSCT patients) admitted to ICU</td>
<td>64% ICU mortality, 85% at six months</td>
<td>Organ failures</td>
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<tr>
<td>Authors</td>
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<td>Darmon, M., Azoulay, E., Alberti, C., Fieux, F., Moreau, D., Le Gall, J.R. &amp; Schlemmer, B.</td>
<td>Impact of neutropenia duration on short-term mortality in neutropenic critically ill cancer patients.</td>
<td>2002</td>
<td>Intensive Care Medicine</td>
<td>28, 1775–1780.</td>
<td>Single centre retrospective cohort study</td>
<td>102 neutropenic patients (91.2% had haematological malignancy)</td>
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<tr>
<td>Depuydt, P.O., Benoit, D.D., Vandewoude, K.H., Decruyenaere, J.M. &amp; Colardyn, F.A.</td>
<td>Outcome in noninvasively and invasively ventilated hematologic patients with acute respiratory failure.</td>
<td>2004</td>
<td>Chest</td>
<td>126, 1299–1306.</td>
<td>Single centre retrospective cohort study</td>
<td>166 patients requiring ventilation</td>
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<tr>
<td>Evison, J., Rickenbacher, P., Ritz, R., Gratwohl, A., Haberthür, C., Elsasser, S. &amp; Passweg, J.R.</td>
<td>Intensive care unit admission in patients with haematological disease: Incidence, outcome and prognostic factors.</td>
<td>2001</td>
<td>Swiss Medical Weekly</td>
<td>131, 681–686.</td>
<td>Single centre retrospective cohort study 1990-1997</td>
<td>78 patients</td>
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<td>Author(s)</td>
<td>Title</td>
<td>Journal</td>
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<td>Jackson, K., Mollee, P., Morris, K., Butler, J., Jackson, D., Kruger, P., Klein, K. &amp; Kennedy, G. (2014)</td>
<td>Outcomes and prognostic factors for patients with acute myeloid leukemia admitted to the intensive care unit.</td>
<td>Leukemia &amp; Lymphoma, 55, 97–104.</td>
<td>2014</td>
<td>Single centre retrospective observational cohort study of newly diagnosed AML</td>
<td>83 patients with AML (out of 505) admitted to ICU</td>
<td>Survival to hospital discharge or 1 year – 59% &amp; 41.3%</td>
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<td>Lengliné, E., Raffoux, E., Lemiale, V., Darmon, M., Canet, E., Boissel, N., Schlemmer, B., Dombret, H. &amp; Azoulay, E. (2012) Leukemia &amp; Lymphoma, 53, 1352–1359.</td>
<td>Intensive care unit management of patients with newly diagnosed acute myeloid leukemia with no organ failure</td>
<td>Single centre study</td>
<td>42 AML patients with abnormal physiology admitted early to ICU &amp; 42 matched AML patients initially admitted to a ward</td>
<td>Early ICU admission 79% survival compared to 65% in 20 (out of 42) patients admitted late</td>
<td>Early ICU admission of AML patients without organ dysfunction improves survival</td>
<td>Low</td>
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<tr>
<td>Moran, J.L., Solomon, P.J. &amp; Williams, P.J. (2005) Anaesthesia and Intensive Care, 33, 26–35.</td>
<td>Assessment of outcome over a 10-year period of patients admitted to a multidisciplinary adult intensive care unit with haematological and solid tumours.</td>
<td>Single centre retrospective cohort study 1989-99</td>
<td>87 patients (73% HM)</td>
<td>ICU &amp; 30-day mortality 39% and 54%</td>
<td>APACHE II, mechanical ventilation, delayed ICU admission</td>
<td>Low</td>
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<tr>
<td>Authors</td>
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<td>Study Population</td>
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<td>Namendys-Silva, S.A., ...</td>
<td>Outcome of critically ill patients with hematological malignancies.</td>
<td>Single centre prospective observational cohort study 2008-11</td>
<td>102 patients</td>
<td>ICU &amp; hospital mortality 46.1% and 57.8 %</td>
<td>Mechanical ventilation, vasopressors, neutropenia, serum creatinine &gt;106 µmol/L</td>
<td>Low</td>
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<td>Neumann, F., ...</td>
<td>The sepsis-related Organ Failure Assessment (SOFA) score is predictive for survival of patients admitted to the intensive care unit following allogeneic blood stem cell transplantation.</td>
<td>Single centre retrospective cohort study 1999-2006</td>
<td>64 (out of 319) patients following allogeneic peripheral blood SCT</td>
<td>ICU survival 28.1%</td>
<td>SOFA score on day of ICU admission predicts survival</td>
<td>Low</td>
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<td>Owczuk, R., ...</td>
<td>Patients with haematological malignancies requiring invasive mechanical ventilation: Differences between survivors and non-survivors in intensive care unit.</td>
<td>Single centre cohort study</td>
<td>40 patients</td>
<td>ICU mortality 65%</td>
<td>SAPS II score</td>
<td>Low</td>
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<tr>
<td>Park, M.R., ...</td>
<td>Outcomes in critically ill patients with hematologic malignancies who received renal replacement therapy for acute kidney injury in an intensive care unit.</td>
<td>Single centre retrospective cohort study</td>
<td>94 HM ICU patients with AKI and RRT</td>
<td>ICU mortality 77%</td>
<td>Modified SOFA score at initiation of RRT</td>
<td>Low</td>
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<tr>
<td>Park, H.Y., ...</td>
<td>Outcome and prognostic factors of patients with acute leukemia admitted to the intensive care unit for septic shock.</td>
<td>Single centre retrospective cohort study 2001-6</td>
<td>50 patients with acute leukaemia and septic shock</td>
<td>ICU &amp; hospital mortality 60% &amp; 68%</td>
<td>SOFA score, relapse/refractory leukaemia</td>
<td>Low</td>
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<td>Reference</td>
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<td>Survival and Predictors of Outcome</td>
<td>Predictors of Mortality</td>
<td>Improved Intensive Care Unit Survival</td>
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APACHEII  Acute Physiology and Chronic Health Evaluation II  
AKI  Acute Kidney Injury  
ARDS  Adult Respiratory Distress Syndrome  
GVHD  Graft Versus Host Disease  
HM  Haematological Malignancy  
HSCT  Haemopoietic Stem Cell Transplant  
ICU  Intensive Care Unit  
RCT  Randomised Controlled Trial  
RRT  Renal Replacement Therapy
SAPS2  Simplified Acute Physiology Score 2
SOFA  Sequential Organ Failure Score