Dealing with the haemato-oncology patient in intensive care

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The Royal Marsden

Our old ICU….

ICM at the Marsden

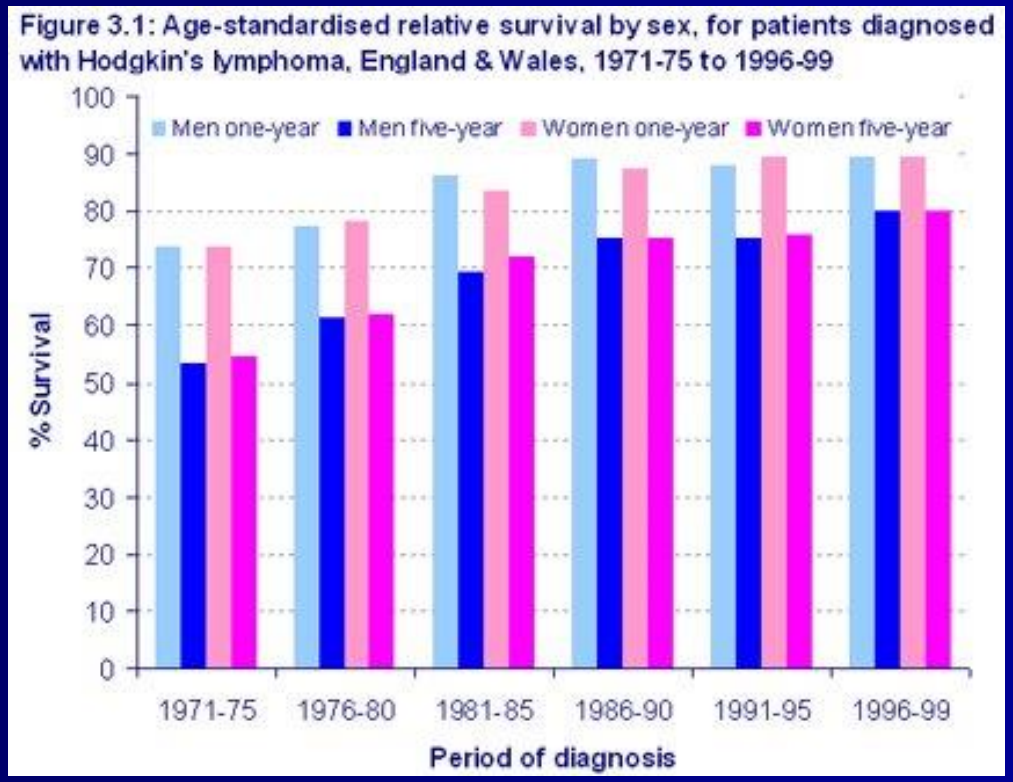
- 11 Level 3 beds in Chelsea
- 2 HDU beds in Sutton
- 900 admissions per year
  - 70% elective/emergency surgical
  - 30% mix of various medical oncology
  - 5-6% Haemato-oncology

- Outcomes for Haemato-oncology patients
- Prognostic indicators
- General Admission strategy
- Bone Marrow Transplant patients
- Prognostic indicators
- Common problems with BMTs
- Admission strategy for BMTs

Improving outcomes

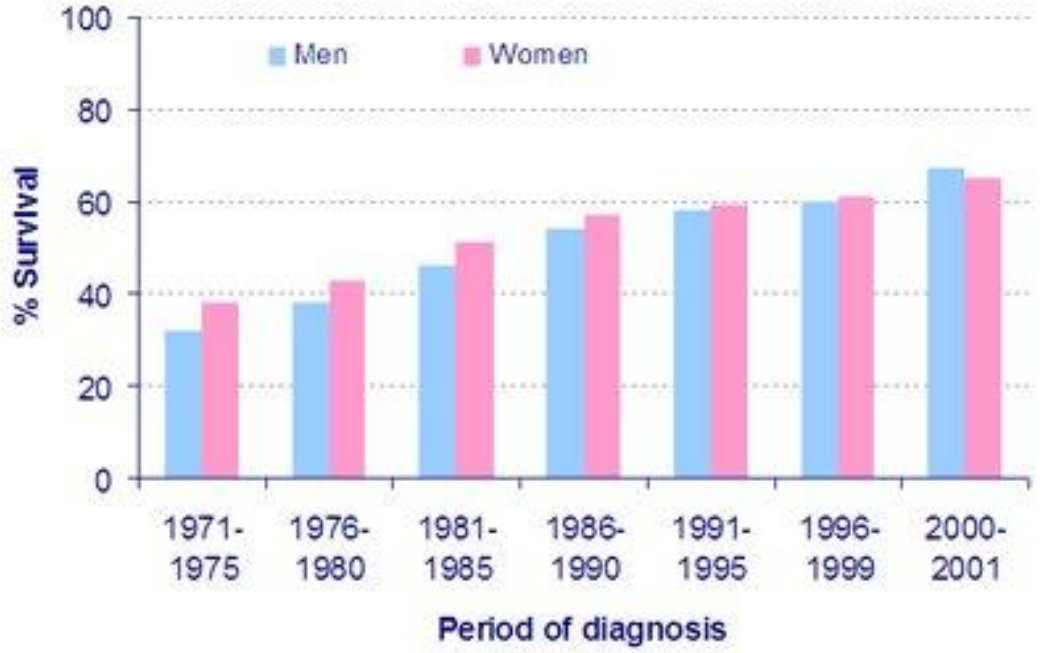
- General trends for the haemato-oncology patient
- ICU Mortality

Relative survival from NHL



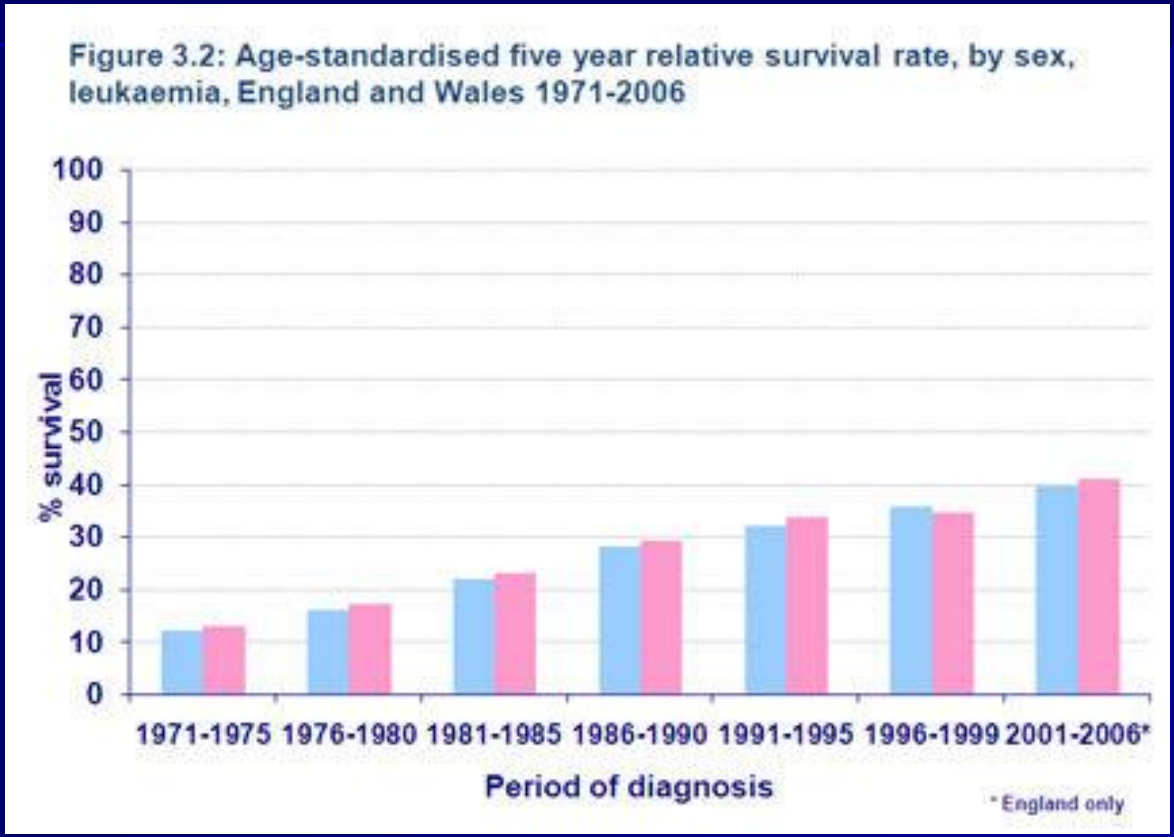
Relative survival from multiple myeloma

Figure 3.1: One-year age-standardised survival for multiple myeloma by sex for patients diagnosed in England and Wales during 1971-2001



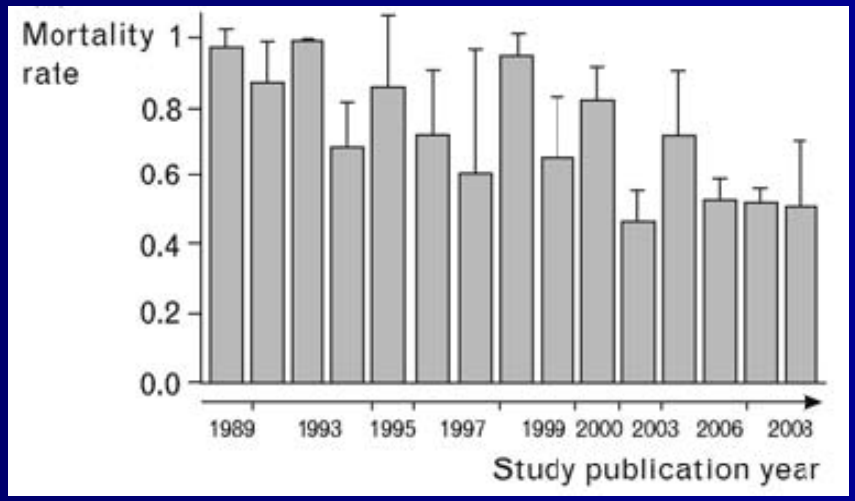
Source :CR-UK

Relative survival from leukamia



Source :CR-UK

ICU Mortality – Bone Marrow Transplants



Azoulay 2009

RMH ICU Haemato-oncology data 2005-2009

- 1 in 4 Haem-Onc Patients need ICU
- n=199
- 43% (n=87) post bone marrow transplant
- Apache 24.7 +/-7.6
- Mortality 38.2% (ICU)
  51.4% (Hospital)

ICNARC data for Haem-Onc patients 1995-2007

Case mix for admissions with haematological malignancy

	All admissions (n = 7,689)
Age, mean (SD)	57.5 (17.6)
Male, *n* (%)	4,638 (60.3)
APACHE II Acute Physiology Score, mean (SD)	17.1 (7.4)
APACHE II score, mean (SD)	24.4 (7.9)
ICNARC physiology score, mean (SD)	23.7 (11.4)
Number of organ system failures, mean (SD)	1.5 (1.2)

Mortality, *n* (%)	
Unit	3,312 (43.1)
Hospital[a]	4,239 (59.2)

Comparative Haem-Onc Mortality

	APACHE II	ICU MR
All comers	16.5	21.5
Chronic Dialysis	24.7	26.5
Acute kidney injury	20.2	58.6
Sepsis (SOAP study)		27.0
Acute pancreatitis	17.0	30.6
COPD	13.4	23.1
Haem-onc	24.4	43.1

All data from ICNARC with the exception of the Sepsis data (taken from the SOAP study)

What has changed

- New drugs
  - GCSF
  - New antibiotics and antifungals
- New techniques
  - Less myeloablative techniques
  - More autologous transplants
- Changes in ICU care
  - Early ICU admission
  - GDT
  - Less therapeutic nihilism

Debunking the myths

- Disease status
- Neutropenia
- Sepsis
- Recent chemotherapy
- Mechanical Ventilation

Disease prognosis does not affect ICU survival

Variable	Mortality			
	ICU	Hospital	6-Month	Long Term
Univariate analysis				
Age	—	—	—	0.065
Sex	0.058	—	—	—
BMI	—	—	0.046	—
Creatinine	0.024	—	—	—
APACHE II	—	—	—	—
SAPS II	0.027	—	—	—
LODS	0.043	—	—	—
MODS	0.002	0.062	—	—
Respiratory	<0.001	0.018	—	—
Cardiovascular	—	—	—	—
Renal	0.055	—	—	—
Hepatic	—	—	—	—
Neurologic	—	—	—	—
Hematologic	—	—	—	—
OSF	0.005	0.009	—	—
Aplasia	—	—	—	—
Respiratory culture	0.032	0.035	—	—
Fungal infection	0.085	0.009	0.050	0.033
Transplant status	—	—	0.046	0.013
Hemopathy disease	0.067	0.035	0.017	0.080
Tumor progression	—	0.053	0.023	0.002
Hematologic prognosis	—	0.089	0.058	0.002
Multivariate analysis[a]				
Age	—	—	—	0.014
MODS	—	—	0.057	—
Respiratory	0.001	—	—	—
Renal	0.073	—	—	—
OSF	—	0.005	—	—
Fungal infection	0.053	0.009	0.076	—
Transplant status	—	0.018	0.003	<0.001
Hemopathy disease	—	—	0.044	—
Tumor progression	—	0.067	0.004	0.020
Hematologic prognosis	—	—	—	0.004

Massion et al, CCM 2002

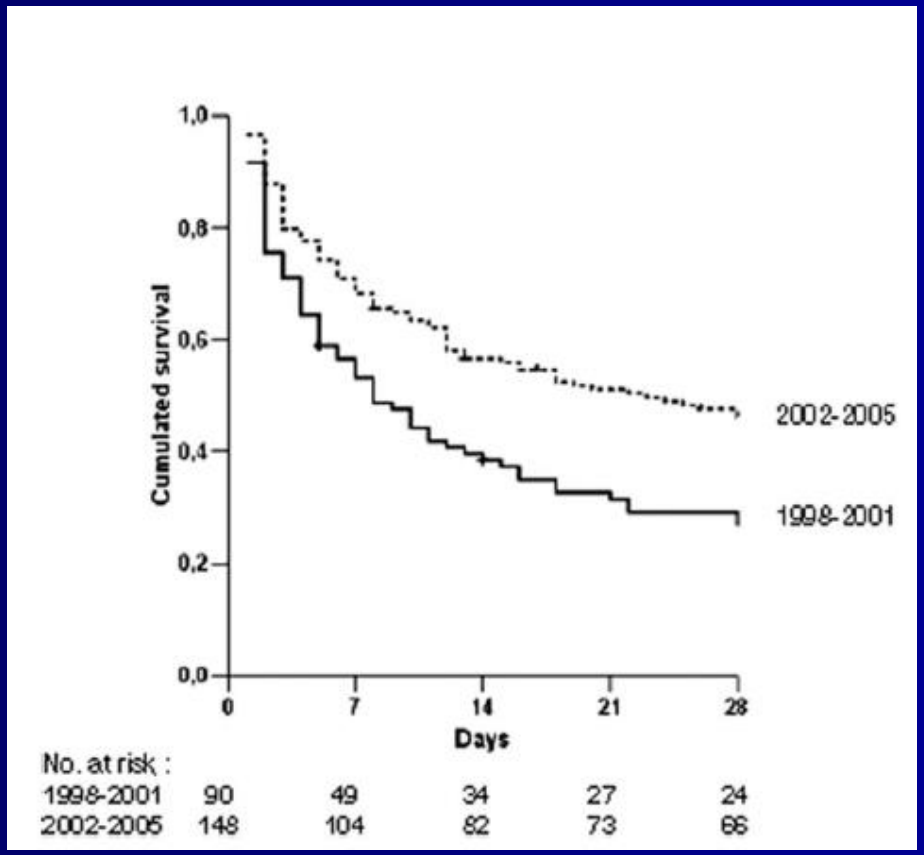
Neutropenia does not affect ICU survival

Table 2 Predictors of 30-day mortality in bivariate analyses using a logistic regression model and a Cox model

Parameters	Logistic model		Cox model	
	Odd-ratio (95% CI)	*P* value	Hazard-ratio (95% CI)	*P* value
Patient characteristics				
Age >60	1.03 (1.00–1.06)	0.05	1.02 (1.00–1.05)	0.03
Female gender	1.63 (0.73–3.64)	0.23	1.43 (0.85–2.41)	0.18
Knaus scale C or D	1.02 (0.35–2.98)	0.97	1.07 (0.53–2.19)	0.84
Malignancy characteristics				
Solid tumor	1.00		1.00	
Leukemia	1.34 (0.49–4.00)	0.54	1.43 (0.72–2.85)	0.30
Lymphoma	2.01 (0.75–5.44)	0.17	1.40 (0.76–2.60)	0.28
Myeloma	0.48 (0.11–2.16)	0.34	0.67 (0.20–2.45)	0.52
Radiation therapy	1.23 (0.46–3.33)	0.68	1.08 (0.57–2.04)	0.82
Methotrexate	0.30 (0.09–0.93)	0.04	0.45 (0.18–1.14)	0.09
Cyclophosphamide	1.79 (0.81–3.95)	0.15	1.40 (0.83–2.36)	0.21
Complete remission	0.75 (0.28–1.98)	0.55	0.76 (0.39–1.51)	0.44
Reason for admission				
Acute respiratory failure	2.49 (0.93–6.68)	0.07	1.96 (0.93–4.14)	0.08
Shock	1.96 (0.88–4.34)	0.10	1.71 (1.00–2.94)	0.05
Acute renal failure	2.20 (0.91–5.31)	0.08	1.69 (0.99–2.88)	0.05
Neurological failure (coma)	1.92 (0.55–6.70)	0.31	1.57 (0.77–3.20)	0.21
Clinical sepsis	1.52 (0.58–3.98)	0.40	1.33 (0.67–2.62)	0.41
SAPS II score	1.06 (1.03–1.09)	$<10^{-4}$	1.04 (1.03–1.05)	$<10^{-4}$
Neutropenia				
Neutropenia recovery	0.06 (0.01–0.52)	0.01	1.30 (0.69–2.44)	0.42
In-ICU neutropenia	0.98 (0.90–1.02)	0.6		
Treatments				
Vasopressor agents	7.30 (2.89–18.42)	$<10^{-4}$	3.92 (1.92–8.00)	$<10^{-4}$
Invasive mechanical ventilation	32.62 (8.78–121.28)	$<10^{-4}$	13.98 (4.35–44.91)	$2.\ 10^{-4}$
Noninvasive mechanical ventilation	0.40 (0.18–0.91)	0.03	0.49 (0.28–0.86)	0.01
G-CSF	1.60 (0.73–3.51)	0.24	1.35 (0.80–2.28)	0.26
Dialysis	3.17 (1.20–8.35)	0.02	1.51 (0.88–2.59)	0.13

Darmon et al , ICM 2002

Sepsis has a similar ICU outcome in Cancer and non-Cancer patients



Pene et al, CCM 2008

Use of chemotherapy prior to admission does not affect ICU survival

	OR	95% CI	*p*
Unadjusted			
Intravenous chemotherapy	0.51	0.28–0.911	0.023
Adjusted for variables before ICU admission[a]			
Intravenous chemotherapy	0.35	0.16–0.75	0.007
Age (per year)	1.01	0.99–1.03	0.295
High-grade malignancy	1.22	0.60–2.51	0.586
Active disease	2.11	1.09–4.06	0.026
Combination antibiotic therapy	2.54	1.24–5.22	0.011
Neutropenia	1.09	0.53–2.25	0.812
Days of hospitalization (per day)	0.99	0.97–1.01	0.432
Adjusted for variables upon ICU admission and the most important variables before admission[b]			
Intravenous chemotherapy	0.48	0.23–1.00	0.049
Active disease	1.98	0.95–4.14	0.069
Combination of antibiotic therapy	1.52	0.71–3.23	0.280
Pulmonary site of infection	2.84	1.38–5.84	0.005
Fungal infection	4.18	1.61–10.87	0.003
SOFA (per point)	1.26	1.14–1.39	< 0.001
Additionally adjusted for propensity score[c]			
Intravenous chemotherapy	0.50	0.23–1.08	0.079
Active disease	1.76	0.80–3.84	0.158
Combination of antibiotic therapy	1.51	0.65–3.49	0.341
Pulmonary site of infection	2.85	1.39–7.57	0.009
Fungal infection	4.04	1.50–10.83	0.006
SOFA (per point)	1.28	1.15–1.42	< 0.001
Propensity score	1.52	0.18–12.68	0.697

[a]Hosmer and Lemeshow: $\chi^2 = 9.04$, df 8, $p = 0.34$, ROC 0.68 (0.60–0.75), SE = 0.039; [b]Hosmer and Lemeshow: $\chi^2 = 6.07$, df 8, $p = 0.64$, ROC 0.82 (0.74–0.87), SE = 0.032; [c]Hosmer and Lemeshow: $\chi^2 = 3.42$, df 8, $p = 0.91$, ROC 0.81 (0.75–0.87), SE = 0.032

Vandijck et al, ICM 2008

Ventilation *in the first 24hrs* does not affect survival in ICU

- ICNARC review of haemato-oncology ICU admissions
  - IMV within 24 hours of admission not associated with **increased mortality after adjustment for other prognostic factors**
  - 70.2% of intubated patients died in hospital
  - 45.3% of non-intubated died in hospital

RMH ICU results for patients ventilated in the first 24 hours

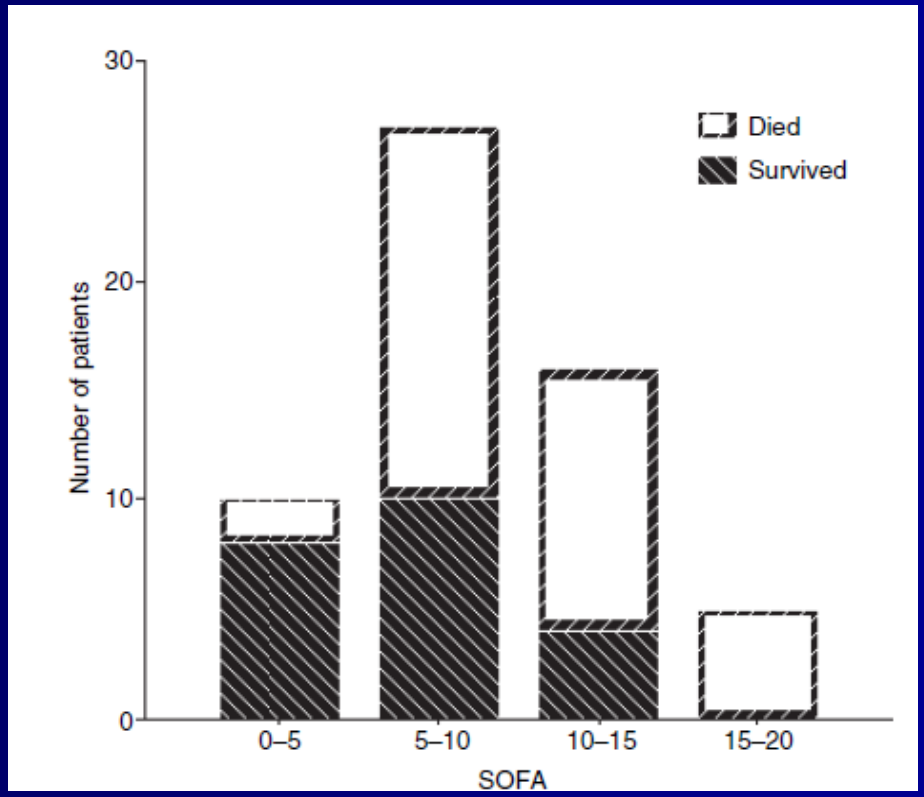
- N=81
- ICU mortality 58.8%
- Hospital mortality 64.7%
- 6 month mortality 72.5%.

What *does* predict outcomes ?

- Organ failure √
- Progression of organ failure √

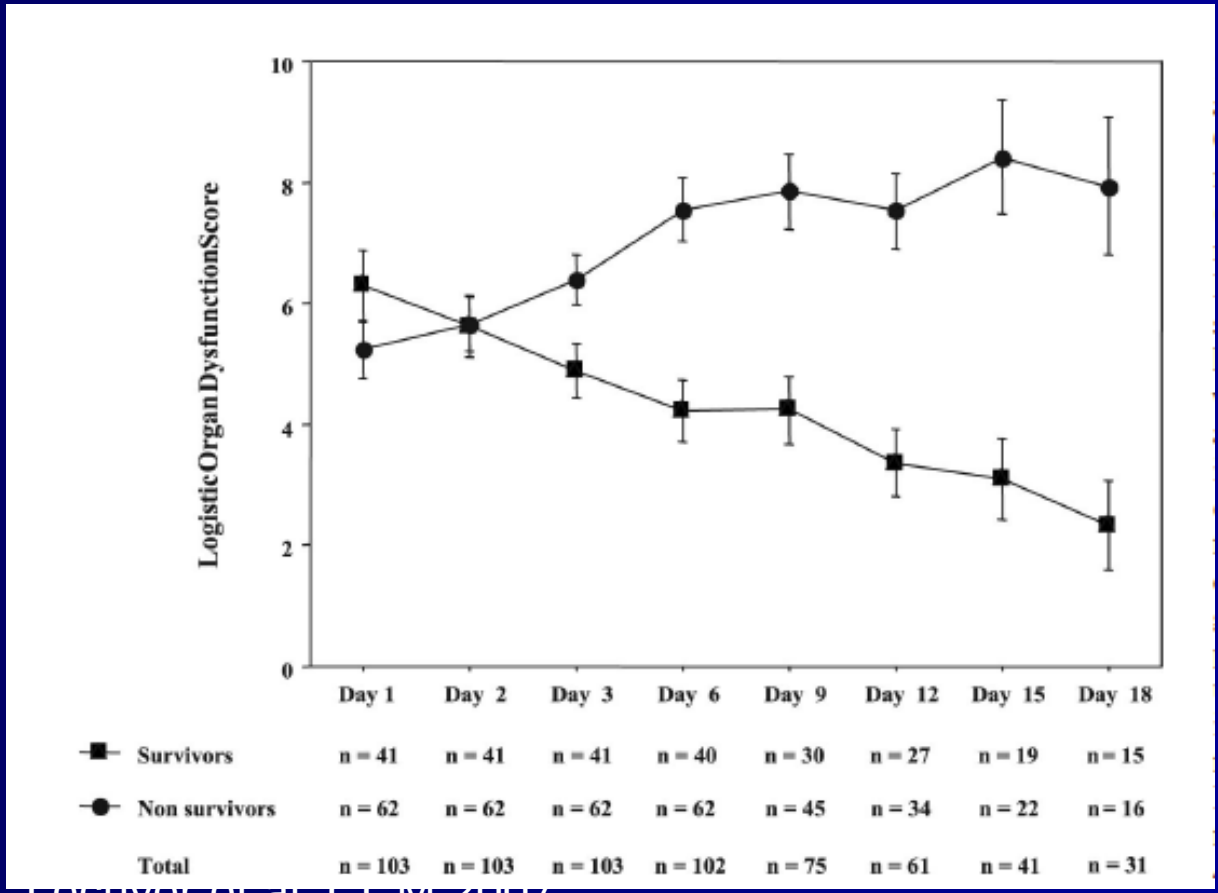
- Organ failure
  - High initial organ failure score
  - Progress of organ dysfunction
  - Development of OF post admission

Initial SOFA scores predict survival



Cornet et al, Eur J Haematol 2005

Progress of OF predicts survival

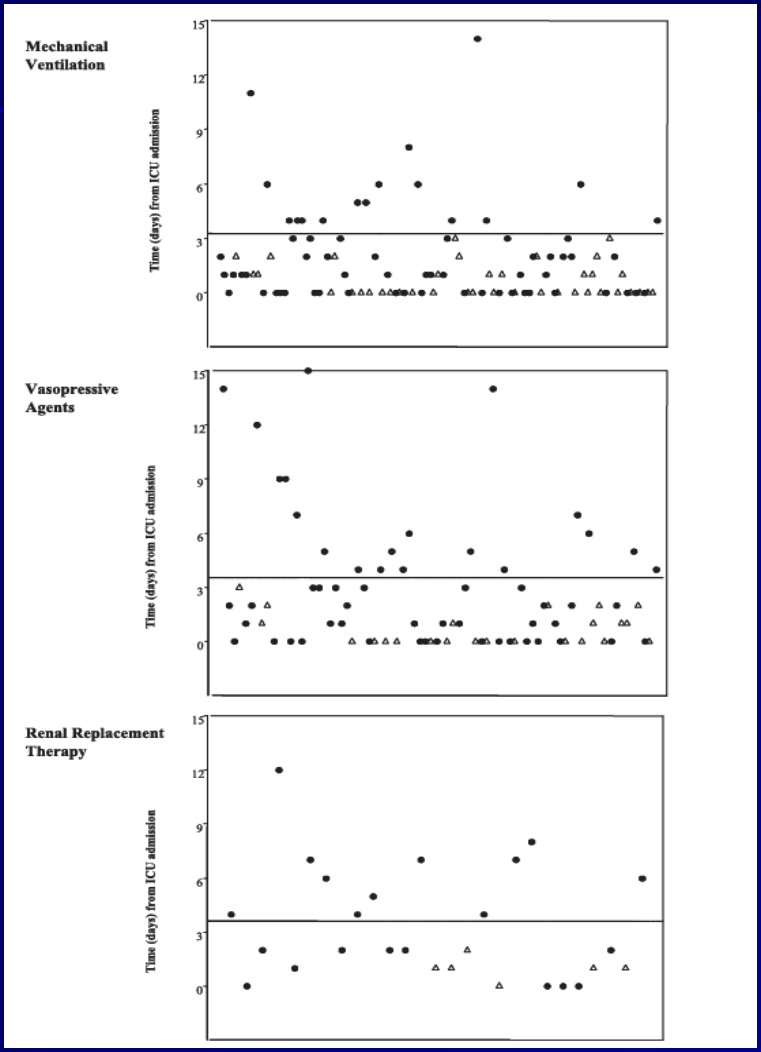


Lecuyer et al, CCM 2007

Development of *late* Organ Failures predicts death

Black dot = Non survivor

Open triangle = survivor



Time refers to time from admission to development of organ failure

OF progression predicts death but not foolproof !

Above the line = Deteriorating organ status
Black dot = Survivor
Clear dot = Non survivor

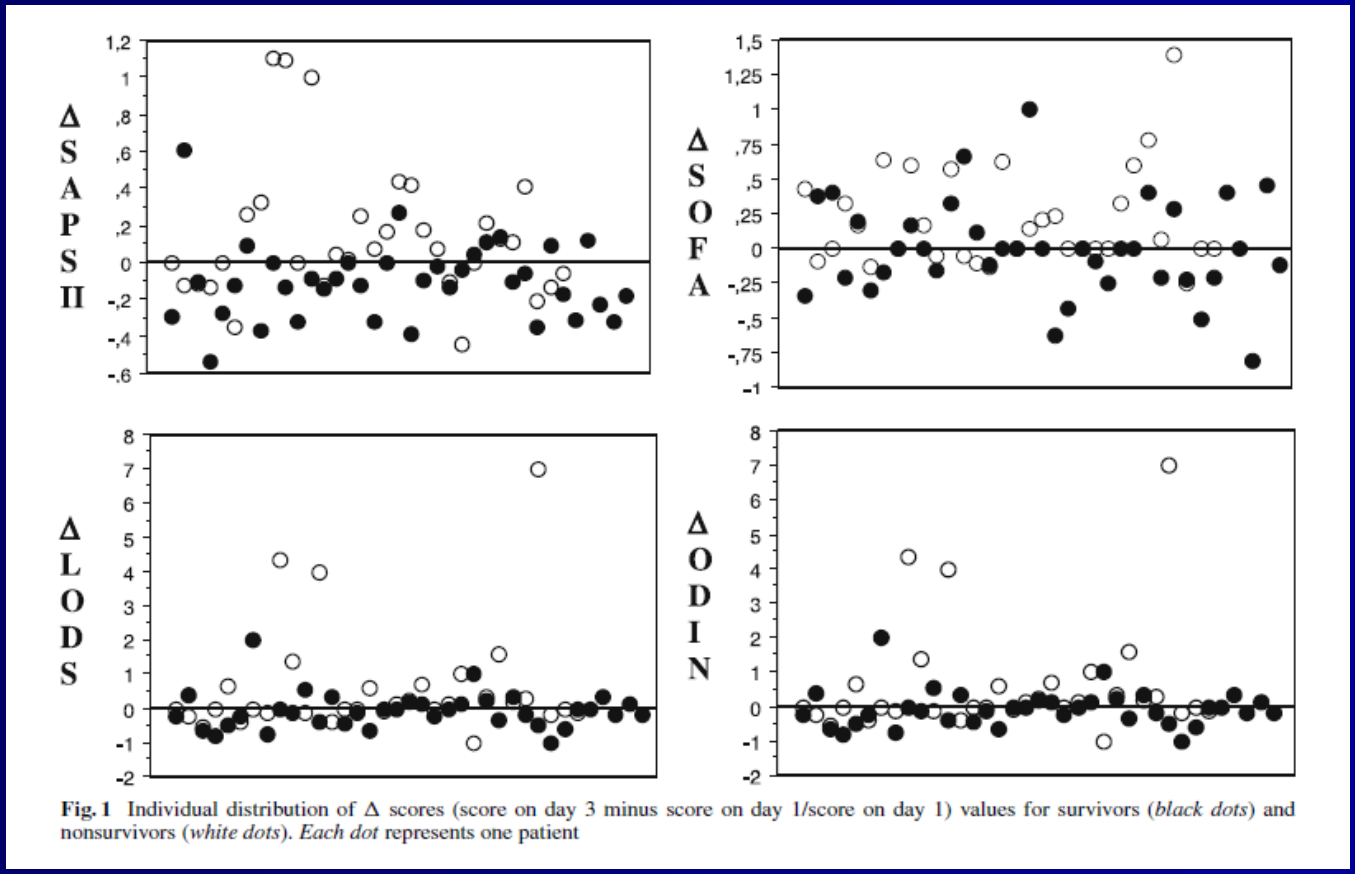


Fig. 1 Individual distribution of Δ scores (score on day 3 minus score on day 1/score on day 1) values for survivors (*black dots*) and nonsurvivors (*white dots*). *Each dot* represents one patient

Lamia et al ICM Oct 2006

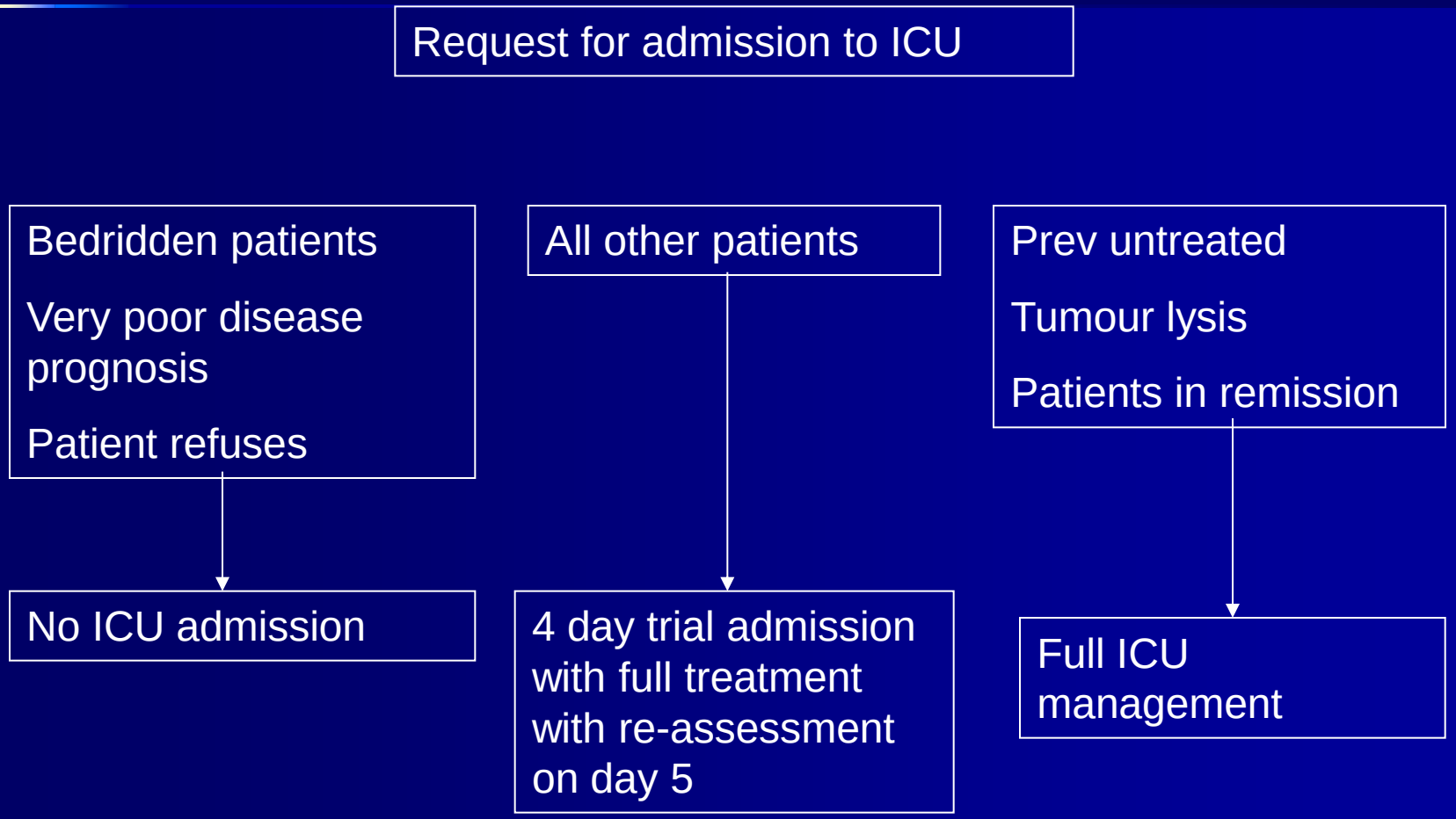
Scoring systems

- Most scoring systems fare badly
- Tendency to underestimate mortality
- Accurate at extremes
- ICMM designed specifically for cancer patients

So…who should I admit to ICU ?

- Survival has improved for critically ill cancer patients
- Classic predictors of mortality have lost much of their value
- The characteristics of the malignancy are not associated with ICU mortality
- Scoring systems do not perform well
- Mortality depends on organ failures at presentation and at 3 days

So…who should I admit to ICU ?



Bone marrow transplantation

- 50-60,000/yr – Most autologous
- Most common
  - Multiple myeloma
  - NHL
  - AML
  - Hodgkins

  Approx 15% end up in ICU

Bone marrow Transplantation

- Preconditioning
  - Chemotherapy
  - Radiotherapy
  - Ablative vs non-ablative
- Stem cell source
  - Autologous
  - Allogeneic
    - Cord
    - Matched related
    - Matched unrelated

Reasons for admission to ICU

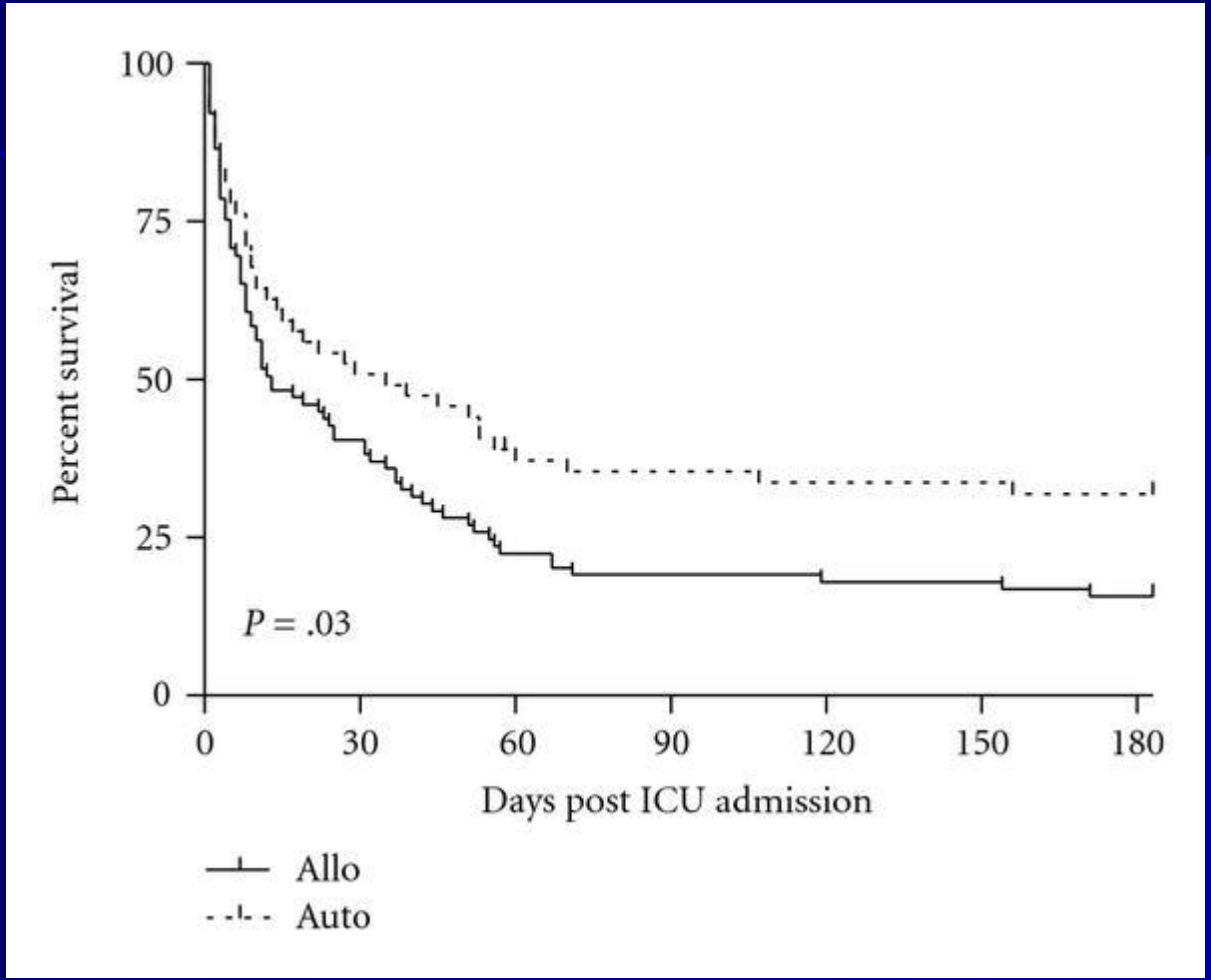
- Respiratory system
  - Airway
  - Pneumonia
  - Pulmonary edema
  - Acute respiratory distress syndrome (ARDS)
  - Idiopathic pneumonia syndrome (IPS)
  - Diffuse alveolar hemorrhage (DAH)
  - Per-engraftment respiratory distress syndrome (PERDS)
- Cardiovascular system
  - Septic shock
  - Hypovolemic shock (dehydration and bleeding)
  - Cardiogenic shock
  - Obstructive shock
- Central nervous system
  - Seizure
  - Intracranial bleeding
- Gastrointestinal system
  - Gastrointestinal bleeding
  - Hepatic failure
  - Neutropenic colitis
- Renal failure

RMH ICU BMT data

- N=87
- ICU mortality 36.8%
- Hospital mortality 49.4%
- 6-month mortality 63.2%

BMT prognosis in ICU

- Predictors of good outcome
  - **Autograft**
  - Younger age
  - Resp failure
    - Pulmonary Oedema
    - Bacterial Pneumonia
  - Ventilation for less than 7 days
- Predictors of poor outcome
  - **Allograft**
    - GVHD
    - Increasing HLA mismatch
  - Increasing Age
  - Recurrent malignancy
  - Resp failure
    - DAH
    - IPS
    - BOOP
    - CMV, RSV
    - Aspergillosis
  - Ventilation for more than 7 days



Huynh et al. Outcome and Prognostic Indicators of Patients with Hematopoietic Stem Cell Transplants Admitted to the Intensive Care Unit

Invasive Ventilation and mortality for BMT recipients

Table 1
Rate of invasive MV and associated mortality in HSCT recipients admitted to the ICU

Study	Years	Total	Invasive MV	Mortality of Invasive MV
Torrecilla[14]	1981–1987	25	16 (64%)	15 (94%)
Denardo[6]	1979–1984	50	44 (88%)	40 (91%)
Faber-Langendoen[48]	1978–1990		191	173 (91%)
Afessa[5]	1982–1990	35	27 (77%)	25 (93%)
Crawford[46]	1986–1990		348	333 (96%)
Paz[12]	1984–1991	36	28 (78%)	27 (96%)
Epler[47]	1985–1991		71	64 (90%)
Paz[16]	1984–1993		25	24 (96%)
Jackson[7]	1988–1993	116	92 (79%)	76 (83%)
Huaringa[49]	1992–1993		60	55 (92%)
Kress[51]	1993–1996		20	11 (55%)
Price[21]	1994–1996	115	48 (42%)	39 (81%)
Khassawneh[30]	1991–1999		78	58 (74%)
Afessa[19]	1996–2000	112	62 (55%)	32 (52%)
Kew[8]	1992–2001	37	25 (68%)	20 (80%)
Soubani[18]	1998–2001	85	51 (60%)	41 (80%)
Scales[13]	1992–2002	504	258 (51%)	224 (87%)
Naeem[11]	1998–2003	25	12 (48%)	10 (83%)
Pene[17]	1997–2003	209	122 (58%)	103 (84%)
Trinkaus[15]	2001–2006	34	20 (59%)	11 (55%)
Total			805/1383 (58.2%)	1381/1598 (86.4%)

Afessa, and Azoulay, Crit Care Clinics Jan 2010

So…which BMT do I admit to ICU ?

- ICU admission
  - Pre-engraftment
  - No recurrence
- ICU trial
  - Unknown disease status
  - Recurrence with available treatment options
- Refusal
  - Disease recurrence with no treatment options
  - Bedridden
  - Severe GVHD

Infection

- Pre-engraftment (0-30 days)
  - Neutropenia and breaks in mucocutaneous barriers
    - Bacteria
    - Candida
    - Aspergillus
- Early post engraftment
  - Impaired cell mediated immunity
    - CMV
    - PCP
    - Aspergillus
- Late post engraftment
  - Impaired cell mediated and humoral immunity (partic in allogeneic)
    - Viruses
    - Haemophilus
    - Strep
    - TB

CXR clues

Lobar	Bacterial
Diffuse	Opportunistic
Acute intersititial	Viral
Cavitating	TB, Klebsiella, Staph, Nocardia
Upper lobes	TB, Klebsiella, Meliodosis, Aspergillus, Pneumocystis, CMV

Investigation of Respiratory failure

Radiography			**Tick**
Chest Xray			
CT Scan			
Pleural USS/ Echocardiography			
Microbiology	**Container**	**Forms**	**Tick**
Sputum +/- Bronchial Alveolar Lavage (BAL)	(in line) sputum pots	yellow	
MC and S	II	II	
Acid Fast Bacilli (AFB)	II	II	
Fungi (Aspergillus)	II	II	
Nasopharyngeal aspiration	II	II	
Tests for viruses (viral and immunofluoresence)	II	II	
Blood Cultures	Blood culture bottles	II	
Serum tests, serology			
Chlamydia	Red top	yellow	
Mycoplasma	Red top	same	
Legionella	Red top	same	
CMV/EBV PCR	Purple (edta)	yellow	
Urine			
MC and S	30 mls urine	yellow	
Legionella	30 mls urine	yellow	
Cytology			
Urine	30 mls urine	Orange/ Cytology	
Biological marker			
CRP	Red top	Biochemistry	
Procalctonin	Green top	CCU	
Haematology			
Fibrinogen/clotting	Blue top	Haematology	

Respiratory failure in the BMT patient

Infectious

Virus — CMV, RSV, Adenovirus, VZV, EBV

Bacteria — Gram +ve or -ve — Intracellular, Encapsulated

Fungi — Candida — Aspergillus, PCP — Emerging fungal infections

Non- infectious

Pulm Oedema

DAH

Engraftment synd — IPS — COP, BO, Pulm GVHD

NPPV in BMT

- Possibly decreases mortality
  - Azoulay et al CCM 2001
  - Afessa et al CCM 2003
  - Pene et al J Clin Oncol 06
- Small numbers in the trials
- Requires early intervention and acutely reversible cause
- Anecdotal experience at RMH

Other potential problems

- GvHD
- Tumour Lysis
- Veno-occlusive disease (VOD)
- Blood product support

GvHD

- Classic Triad
- Can affect lung also
- Management via (more) immunosuppression

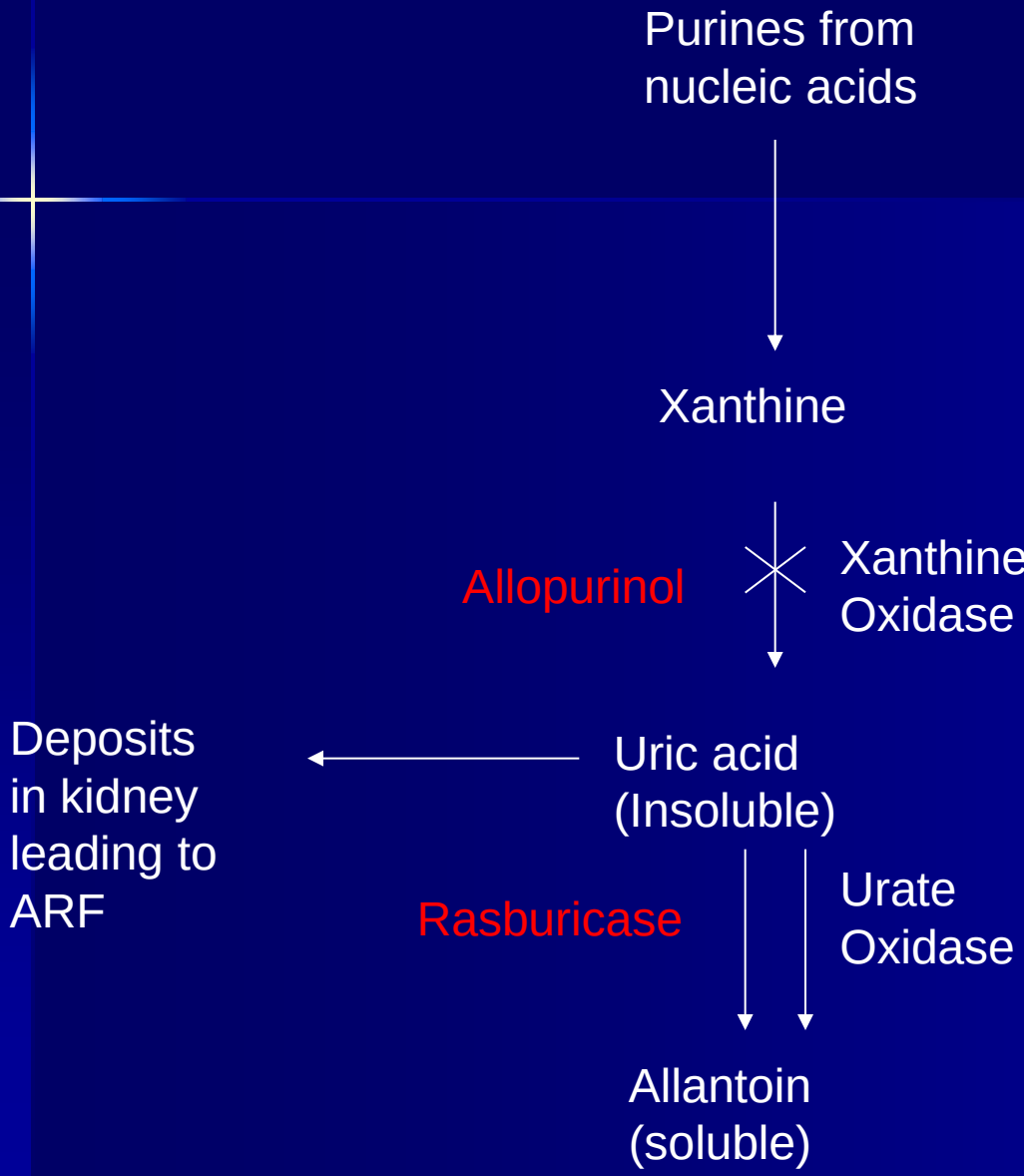
Veno-occlusive disease

- Occurs in first 21 days post Tx
- Due to Hepatic endothelial damage from pre-conditioning
- Thrombosis leads to
  - Weight gain
  - Hepatomegaly
  - Hyperbilirubinaemia
  - Ascites
- Diagnosis with Doppler
- Defibrotide has drastically reduced incidence and mortality

Tumour Lysis

- Typically following induction chemotherapy for leukaemia or lymphoma
- Predicted by an LDH>1500
- Up to a third occur spontaneously

- Causes release of purines, potassium and phosphate
- Consequent
  - Life threatening arrhythmias
  - ARF (uric acid and calcium phosphate deposition)


Purines from nucleic acids
Xanthine
Allopurinol
Xanthine Oxidase
Deposits in kidney leading to ARF
Uric acid (Insoluble)
Rasburicase
Urate Oxidase
Allantoin (soluble)

- Prophylaxis
  - Hydration
  - Allopurinol or rapspuricase
  - Avoid urine alkalinization (xanthines more insoluble in alkaline urine)
- Treatment
  - Symptomatic
  - Avoid correcting hypocalcaemia unless ECG changes
  - Rasburicase
  - Filtration

Blood product support

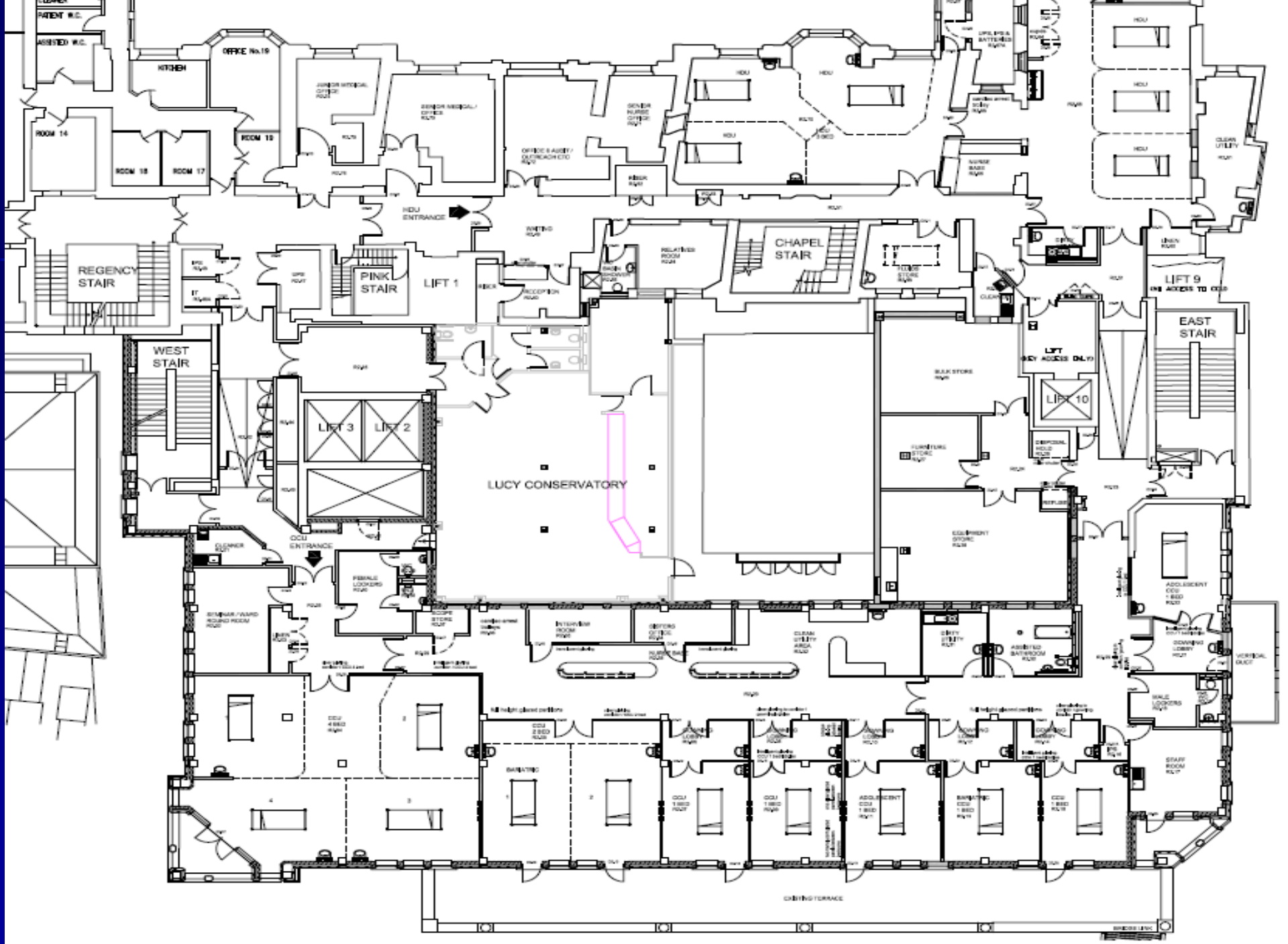
- All products must be irradiated
  - Risk of fatal GvHD from Tx T lymphocytes
- All patients should have CMV –ve products (even if CMV +ve preTx)
  - If non available, leucodepleted red cells of platelets can be used in prev CMV +ve pts

In conclusion

- Outcomes are improving
- Therapeutic nihilism is self fulfilling

BUT….

- Heavy users of resource
- Trials of admission require a clear understanding and a close relationship with the relatives and haematologists !


KITCHEN
OFFICE No.19
ROOM 14
ROOM 18
ROOM 17
ROOM 16
HDU ENTRANCE
REGENCY STAIR
PINK STAIR
LIFT 1
CHAPEL STAIR
LIFT 9
EAST STAIR
WEST STAIR
LIFT 3
LIFT 2
LUCY CONSERVATORY
LIFT 10
OCU ENTRANCE
CABLING TERRACE

Early versus late admission to ICU

Table 4 Multivariable analysis to identify independent risk factors of 30-day mortality. Goodness-of-fit chi-square *P* value >0.05. {*DLOD* [(LOD score on day 3–day 1)/LOD score on day 3]}

	Odds ratio	95% CI	*P* value
ICU admission between 1998 and 2000	0.231	0.054–0.988	0.04
Lymphoma	5.6	0.40–16.60	0.07
Time to antibiotic administration >2 h	7.05	1.17–42.21	0.03
DLOD ratio	3.47	1.44–8.39	0.005
Colloid on day 1	3.43	0.63–18–69	0.15
Antibiotic adaptation	0.245	0.06–0.95	0.04

Larche et al ICM 2003

Bigger units get better results

- Lecuyer et al, euro resp journal 2008